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NOVEL METHODOLOGY TO CHARACTERISE HOW ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS USE THEIR INHALERS AND METHODS TO IMPROVE THEIR INHALER TECHNIQUE

Objective assessment of how patients use inhalers

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Copyright Statement

Abstract

KEY WORDS: *Pressurised Metered Dose Inhalers, Dry Powder Inhalers, Inhalation Characteristics, Inhalation Profiles, Asthma, COPD*

Inhaled administration is the mainstay of asthma and chronic obstructive pulmonary disease (COPD) management using either a pressurised metered dose inhaler (pMDI) or a dry powder inhaler (DPI). Poor disease control and increased hospitalisations is linked to poor inhaler technique. Previous studies to assess inhaler technique have used subjective measures and there is very limited data about the inhalation characteristics used by patients when they use their inhalers.

Inhalation flow profiles when patients use their pMDI and inhalation pressure profiles when they use DPIs have been measured using 659 subjects (106 children with asthma [CHILD], 361 adults with asthma [ADULT], 142 COPD [COPD] and 50 healthy volunteers [HEALTHY]) in 5 separate studies. All patient studies used their real life inhaler technique. One of the studies also evaluated the value of using a pMDI co-ordination aid and training these patients to prolong their inhalation whilst a different one investigated the impact of using enhanced training when using a DPI.

The first study, 20 CHILD, 57 ADULT and 32 COPD subjects, revealed that the mean (SD) inhalation flows through a pMDI were 108.9 (40.4), 146.0 (58.8) and 107 (50.6) L/min, respectively and only 7, 10 and 10 used a slow flow. In the second pMDI study involving, 20 CHILD, 130 ADULTS, 31 COPD patients, their flows were 70.5 (36.4), 131.4 (60.8) and 70.9 (28.1) L/min and 5, 53 and 10 used their pMDI with good co-ordination. However only 3, 6 and 9 patients had good co-ordination and slow flow. In the third study, 71 ADULT patients, the mean (SD) pMDI inhalation flow was 155.6 (61.5) L/min which decreased ($p<0.001$) to 112.3 (48.4) when the pMDI was fitted with a co-ordination aid. This was due to the increased resistance to airflow from the aid. Inhalation flow further reduced ($p<0.001$) to 73.9 (34.9) L/min when patients were trained to prolong their inhalations. Their inhaled volumes did not change whereas mean (SD) inhalation times were 1.60 (0.21), 1.92 (0.80) and 2.66 (1.03) seconds ($p<0.001$) respectively. There was a good correlation between their inhaled volume and forced vital capacity with a ratio of 0.7 suggesting that the patient used a full inhalation.

A DPI study, involving 16 CHILD, 53 ADULT and 29 COPD patients, measured inhalation characteristics through different DPIs (low to high resistance) when patients used their real life DPI inhalation manoeuvres. The inhalation characteristics were lower in CHILD and highest in ADULT. Overall flows were higher when using low resistance DPIs but the pressure changes and the acceleration of the inhalation flow were significantly higher with high resistance DPIs which suggest more efficient de-aggregation of the formulation. There was a tendency for more problems with low resistance DPIs than high resistance DPIs. The last study involved CHILD, ADULT, COPD and HEALTHY subjects (50 of each) when they inhaled through a Spiromax and a Turbuhaler (similar resistance) after standard verbal inhalation technique training and when using enhanced training with an IN-Check Dial. The order of inhalation characteristics was HEALTHY > ADULT > COPD > CHILD. Significant ($p<0.001$) improvements in the inhalation flows, pressure changes and acceleration of the flow were achieved in all groups after the enhanced training.

The studies provide an insight into the inhalation characteristics of patients when they use different inhalers. The main problem with pMDI use was short inhalation times and when patients were trained to prolong their inhalation then flows reduced. Enhanced training when using a DPI significantly improved the technique of all patients.

Parts of this PhD thesis have been already published or submitted for publication as follows:

1. Azouz W, Campbell J and Chrystyn H. Training tools for inhalation devices: the need for more sophistication. Prim Care Respir J 2011; 20(2): 221.

2. Azouz W and Chrystyn H. Clarifying the dilemmas about inhalation techniques for dry powder inhalers: integrating science with clinical practice. Primary Care Respiratory Journal. 2012 (in press)

3. Azouz W, Chetcuti P, Hosker H, Saralaya D, and Chrystyn H. Objective measurement of inhalation profiles in patients using metered dose inhalers (MDIs). University of Huddersfield, Paediatrics, Leeds General Infirmary, Leeds, Airedale General Hospital, Steeton, Bradford Royal Infirmary, Bradford, United Kingdom. The European Respiratory Society (ERS), 21st Annual Congress, 24–28 September 2011, The Netherlands, Amsterdam. (Abstract p838 and poster).

4. Azouz W, Chetcuti P, Hosker H, Saralaya D and Chrystyn H. Inhalation Characteristics of Asthmatic Children (CHILD), Adult Asthmatics (ADULT) and Chronic Obstructive Pulmonary Disease Patients with a pressurised Metered Dose Inhaler (pMDI). Presented at the 18th International Society of Aerosols in Medicine Annual Congress June (2011), Rotterdam, The Netherlands.

Paper submitted

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Abstract Submitted

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Dedicated to my beloved parents and family husband and daughters, who scarified and supported me very much towards this achievement

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List of Abbreviations

Abbreviation	Definition
ACQ:	The Asthma Control Questionnaire
ACT:	The Asthma Control Test
AQLQ:	The Asthma Quality of Life Questionnaire
BTS/SIGN:	The British Thoracic Society Guidelines for Asthma Management
C-ACT:	The Childhood Asthma Control Test
CFC:	Chlorofluorocarbon(s)
CI:	Confidence Intervals
COPD:	Chronic Obstructive Lung Disease
DPI or DPIs:	Dry Powder Inhaler(s)
FEV$_1$:	Forced Expiratory Volume in One Second
FVC:	Forced Vital Capacity
GINA:	The Global Initiative for Asthma Management
GOLD:	The Global Initiative for COPD Management
HFA:	Hydrofluoroalkane
HRQL:	Health-Related Quality of Life
ICS:	Inhaled Corticosteroid(s)
IFR:	Inhalation Flow Rate
IP:	Inhalation Profile
IV:	Inhalation Volume
LABA:	Long Acting ß2-Agonist
MDI or pMDI	Pressurized Metered Dose Inhaler(s)
MHRA	Medicines And Healthcare Products Regulatory Agency
Mini-AQLQ:	The Mini- Asthma Quality of Life Questionnaire
MRC:	The Medical Research Counsel
NICE:	National Institute for Clinical Excellence
PACQLQ:	The Paediatric Asthma Caregiver's Quality of Life Questionnaire
PAQLQ:	The Paediatric Asthma Quality of Life Questionnaire
PEF:	Peak Expiratory Flow
PIF:	Peak Inhalation Flow
RCP:	The Royal College of Physicians
PIF:	Patient Information Leaflet
SABA:	Short Acting ß2-Agonist
SGRQ:	The St. George's Respiratory Questionnaire

Abbreviation	Definition
SD:	Standard Deviation
SPSS	Statistical package for Social Sciences
TLC:	Total Lung Capacity
TV:	Tidal Volume
Vin:	Total Inhaled Volume (L)
TsIn:	Actuation time after start of inhalation (sec)
Ti:	Total Inhalation time (sec)

Chapter 1: Introduction

1.0 Introduction

Respiratory disorders are steadily increasing in prevalence, and impose a significant economic burden all over the world. Asthma and chronic obstructive pulmonary disease (COPD) are obstructive lung diseases and are two of the most common healthcare burdens worldwide. According to mortality statistics COPD is the fifth leading cause of death and the latest WHO estimates have predicted it to become the third leading cause of death by the year 2020 (Stockley et al., 2006). On the international scale, the prevalence of asthma is between one percent and 18 percent of the population in different countries according to the Global Initiative for the Asthma Management (GINA, 2008) report. There are approximately 3 deaths per day in the UK that are attributed to asthma and these are mostly in children and young adults and most of these are preventable.

The inhaled route of administration is the optimal method of drug delivery for the treatment of patients with obstructive airway diseases (Pauwels et al., 1997). The most important advantage of inhaled therapy is that drugs are delivered directly onto the sites of action producing higher local concentrations for better efficacy and with significantly less systemic exposure hence a reduced of risk of side effects (Toogood, 1989; Lipworth, 1999; Broeders et al., 2009). The therapeutic drugs used in the treatment of asthma and COPD, mostly bronchodilators and corticosteroid anti-inflammatory agents, therefore have been formulated as inhaled aerosols. Consequently, a wide array of inhalation devices have been introduced to the market and have become the prime methods for drug administration in the treatment of patients with obstructive pulmonary diseases (van Beerendonk et al., 1998).

The pressurised metered dose inhaler (pMDI) is presently the most commonly used inhaler. Alternatively, drugs can be administrated by a dry powder inhaler (DPI) or a

nebuliser. Nebulisation is not routinely used and usually reserved for administering large doses especially during acute exacerbations, antibiotics or drugs that are difficult to formulate in a pMDI or DPI. Each class of inhaler device has its pros as well as cons. Despite the pressurised metered dose inhaler (pMDI) being widely prescribed, many patients do not obtain the full therapeutic benefit because their inhalation technique is poor (Paterson and Crompton, 1976; Crompton, 1982b; Pedersen et al., 1986; Larsen et al., 1994; Lenney et al., 2000). Thus the benefits of inhaled therapy are accompanied by the drawbacks, particularly the challenges patients face when using their inhaler devices. Although inhaled therapy has revolutionised the management of patients with obstructive lung disease, it is well known that the inhalation technique used with pMDIs can substantially influence the clinical response to inhaled medications.

Several studies have highlighted inhaler technique problems; 14% to 89% of the patients using their pMDI have either made at least one technique error or completely misused their inhaler (Paterson and Crompton, 1976; Epstein et al., 1979; Larsen et al., 1994). Frequent misuse of inhaler devices has been documented for patients prescribed pMDIs as well as those using dry powder inhalers (Liard et al., 1995; Cochrane et al., 2000; Molimard et al., 2003; Molimard and Le Gros, 2008; Giraud et al., 2011). Despite the availability of efficacious therapies, asthma control is often poor (Chapman et al., 2008; Giraud et al., 2011) and the improper use of inhaler devices is one major cause of poor disease control (Crompton, 2006; Molimard and Le Gros, 2008; Virchow et al., 2008). It has been suggested that approximately 50% of patients do not obtain sufficient benefit from their inhalers because of poor inhaler technique (Crompton and Duncan, 1989). A correct inhaler technique by the patient is crucial for the success of the therapy (Horsley and Bailie, 1988; Larsen et al.,

1994; Virchow et al., 2008). It has been acknowledged that the most commonly encountered pMDI technique problems by patients are; poor coordination of inhalation with inhaler actuation, stopping to inhale shortly after activating the pMDI and inspiration through the nose (Crompton, 1982b). It has also been demonstrated that many patients fail to inhale slowly and deeply through their MDI to achieve the desirable flow rate of < 90 l/min for sufficient lung deposition (Al-Showair et al., 2007a). Only 8% of patients use a slow inhalation with good co-ordination (Al-Showair et al., 2007a). Studies have shown that poor inhaler technique is linked to poor disease control (Giraud & Roche, 2002) and increased hospitalisation (Melani et al., 2011).

Frequent inhaler training technique and proper inhaler handling are recommended particularly by asthma management guidelines, and that inhaler technique should be checked regularly during follow-up (Newman et al., 1980; Broeders et al., 2003a). However, the provision of inhaler technique training remains irregular. The majority of studies suggested that a large proportion of patients do have problems using their inhalers but they are subjective assessments. The studies of this thesis have been designed to provide objective assessments of inhaler technique by measuring inhalation profiles when the patients use their inhalers and at the same time to quantify how patients use their inhalers. The studies have been designed to measure the inhalation flow rate, the time between the start of an inhalation and the pressing of the canister (co-ordination) and inhaled volume when patients inhale through an empty pMDI. In addition the inhalation profiles of patients have been used to solve inhalation technique problems through pMDIs.

Dry powder inhalers (DPIs) were introduced to the market to overcome the problems associated with the use of pMDI and to solve the problems caused by the damage to

the ozone layer by the propellants in pMDIs (Keating and Faulds, 2002; Lavorini et al., 2008b). All DPIs are classified as passive devices because the patient's inhalation reacts with the resistance inside the inhalation channel of a DPI to provide a turbulent force that de-aggregates the formulation. The drug particles that are emitted, after the de-aggregation, have the greatest likelihood for deposition in the airways. It is now recognized that inhalers differ in their efficiency of drug delivery to the lungs, depending on the form of the device, its internal resistance, formulation of the medication, particle size, velocity of the aerosol cloud and ease with which patients can use the device (Bisgaard et al., 2002).

Due to the de-aggregation process all DPIs currently available have a flow dependent dose emission property. Different studies have demonstrated that there is a relationship between the DPI's resistance and the inspiratory flows achieved by the patient through each DPI and also the amount of the drug emitted and hence deposited in the lung (Clark and Hollingworth, 1993; Pauwels, 1997; Al-Showair et al., 2007a; Chrystyn, 2009). Generally, patients using DPIs are required to inhale as hard and deep as they can for as long as they can and that this fast inhalation should begin to create a sufficient acceleration rate in order to maximise de-aggregation of the emitted dose and drug delivery to lung (Chege and Chrystyn, 1994; Borgstrom, 2001; Van der Palen, 2003). It is normally accepted that a minimum peak inhalation flow (PIF) of 30 l/min is required through the inhaler to provide sufficient de-aggregation to create a total emitted dose with fine drug particles able to deposit in the lung (Chrystyn, 2009). However, not all patients are able to achieve a sufficient inhalation flow through their device (Al-Showair et al., 2007). Therefore, instructing and training the patients on the correct inhalation technique to improve their inhaler

use is required (Newman et al., 1980; Horsley and Bailie, 1988; Broeders et al., 2003a).

Methods of assessing a patient's DPI inhalation technique are mostly subjective whereas it is possible to measure their inhalation flow with respect to time (Bisgaard et al., 1998; Broeders et al., 2003a; Chrystyn and Price, 2009a). These inhalation profiles through a DPI would provide objective data such as the peak inhalation flow, the time to the peak inhalation flow, the duration of the inhalation, the inhalation volume and the acceleration of the inhalation flow. These can be designed as simple methods that can be used in the clinic with the inhaler that the patient uses. Using this simple method patient inhalation profiles can be electronically captured using their untrained technique when they visit the clinic. Hence information about their real life inhalation technique can be obtained. These methods would objectively highlight the scale of the problem with respect to inhalation technique. Linked to this methodology, simple and novel solutions to improve inhaler technique can be indentified and validated. Since these electronic methods are simple and non-invasive and patients inhale through empty inhalers then it is convenient to measure inhalation profiles of children with asthma, adults with asthma and patients with COPD.

The inhalation profile of patients using their real life inhaler technique can be captured using simple electronic methods. The captured inhalation characteristics can be used to highlight the problems made by patients and also to identify simple methods to implement during the inhaler technique training of patient.

The work in this thesis has identified and designed electronic methodology to capture inhalation profiles during inhalation use and demonstrate the problems faced by patients (including children with asthma, adults with asthma and COPD) when they

use their inhalers (pMDIs and DPIs). Using these objective methods (scale measurements) the errors made by patients can be identified. From those measurements simple training methods have been implemented to solve the critical errors that the profiles have identified. The values of these have been evaluated by measuring further inhalation profiles.

The results drawn from these research studies may have future implications on the improvement on pMDI and DPI development as well as on clinical and pharmaceutical practice.

Following this introduction (Chapter 1) there is a literature review in Chapter 2. The review briefly explains the management of asthma and COPD to highlight that inhaled therapy is the major route of administration. The chapter describes particle deposition in the lungs and the importance of using the correct inhalation technique with each device. It also includes a review of the problem patients have using the different type of inhalers. Chapter 3 is a pilot study including children with asthma, adults with asthma and COPD patients, when they use their pMDI, a pMDI attached to Volumatic and when attached to an AeroChamber spacer and also through an EasiBreathe. This pilot study was carried out to pilot the requirement and value of using sophisticated electronic methodology to measure inhalation profiles. Chapter 4 extends Chapter 3 by measuring electronic inhalation profiles using sophisticated methodology. This study looks at pMDI use in children with asthma, adults with asthma and COPD patients. Measurements include the inhalation time of co-ordination, peak inhalation flow, inhaled volume and duration of inhalation.

Chapter 5 also uses the measurement of inhalation profiles in adult patients with asthma. The focus of study in this chapter is to investigate the value of using a simple co-ordination aid and a simple instruction to increase inhalation time. It is intended

that these will cause the peak inhalation flow to decrease and that the co-ordination problems are solved.

Chapter 6 is similar to Chapter 3 except that DPIs are used. This study includes children with asthma, adults with asthma and COPD patients when they inhale through different DPIs. Peak inhalation flow (PIF), the maximum pressure change inside the DPI, time to peak flow, the acceleration rate, inhalation volume and duration of the inhalation are measured.

Chapter 7 concludes the studies. This Chapter measure inhalation profiles and hence the inhalation parameters when children with asthma, adults with asthma, COPD patients and healthy volunteers inhale through a Spiromax and a Turbuhaler DPI. This study includes an assessment of training subjects to inhale faster using the In-Check Dial.

The thesis concludes with a summary of the work in chapter 8 and some recommendations for future work.

Chapter 2: Literature Review

2.1 Respiratory System

The respiratory system is a complex structure responsible for the delivery of oxygen (O_2) to the body and the elimination of carbon dioxide (CO_2). The respiratory system, in Figure 2.1 is a series of branching tubes called bronchi and bronchioles and this branching in the human lung represents an inverted tree without the leaves. The airways branch 23 times from the trachea down to the terminal alveoli. Figure 2.1 shows that the respiratory system is divided into three-compartments (Hinds, 1999). The head region that is referred to as the "upper respiratory tract" includes the nose, nasal cavity, mouth, pharynx and larynx.
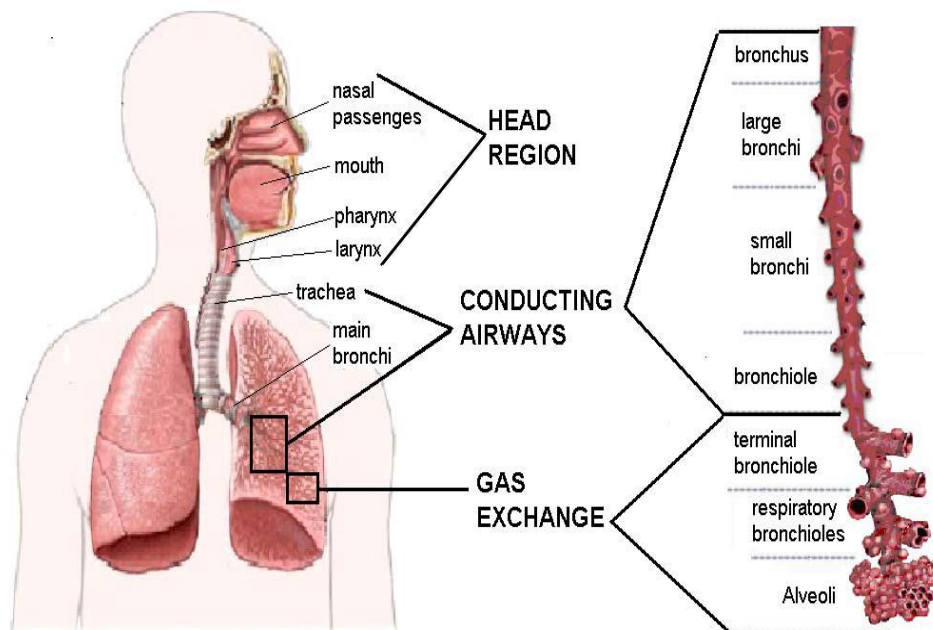
Figure 2.1. The major features of the lungs include the bronchi, the bronchioles, and the alveoli. http://www.mcgill.ca/mmimediasampler2002/images/eidelman-12no3.gif.

The second compartment, down to branch 16, is known as the conducting airways and includes the trachea, bronchi, and bronchioles. The trachea (windpipe) extends the larynx directly into the lower respiratory tract. The trachea or windpipe is about 10-12 cm long and 2 cm in diameter with C-shaped cartilages. The entry point to the

lung, where the trachea branches into the 2 main bronchi, is called the "hilum" or the root. Each bronchus divides again forming the bronchial tubes. Branching becomes more numerous with tiny sub-segmental bronchi and bronchioles (Marieb and & Hoehn, 2010). Smooth muscle surrounds the bronchi and bronchioles and is inverted by the autonomic nerve system (autonomic receptor), receiving both cholinergic and adrenergic stimuli. Sympathetic stimulation leads to a relaxation of smooth muscle in the wall of the bronchioles, and this leads to the bronchodilation of the respiratory passageways. In contrast parasympathetic activation leads to constriction of the smooth muscle which leads to a narrowing of the passage airways. Thus using an anti-cholinergic agent blocks the constriction thereby facilitating a dilation of the airways.

The third compartment, shown in Figure 2.1 from branch 16-23, represents the respiratory zone of the lungs where the terminal bronchioles connect to tiny sacs called alveoli (alveolar sac). Table 2.1 describes how the airways get narrower with each branch and the surface area increases exponentially.

The alveolar region contains approximately 300 to 600 million sacs providing a very large surface area for the process of gaseous exchange. All the alveoli have very thin membranes, and are close to each other and are surrounded by numerous pulmonary capillaries. Venous blood delivered to the lungs by the pulmonary vein is pumped through these capillaries. This blood takes up oxygen and expels carbon dioxide and leaves the pulmonary artery to the heart and is then pumped round the body. In adults, the total surface area of the respiratory membrane is about 70 m^2 which is about the size of half a tennis court (Colbert et al., 2009).

Table 2.1. A schematic representation of airway branching in the human lungs (Weibel, 1963).

	Generation		Diameter (cm)	Length (cm)	Number	Total cross sectional area (cm²)	Powder deposition by particle diameter
Conducting Zone	*Trachea*	0	1.80	12.0	1	2.54	7-10 μm
	Bronchi	1	1.22	4.8	2	2.33	2-10 μm
		2	0.83	1.9	4	2.13	
		3	0.56	0.8	8	2.00	
	Bornchioles ↓	4	0.45	1.3	16	2.48	
		5	0.35	1.07	32	3.11	
	Terminal bronchioles ↓	↓ 16	↓ 0.06	↓ 0.10	↓ 6×10^4	↓ 180	
Transitional Respiratory Zones	*Respiratory bronchioles*	17	↓	↓	↓	↓	0.5 – 2 μm and < 0.25 μm
		18					
		19	0.05	0.10	5×10^5	10^3	
	Alveolar Ducts	20	↓	↓	↓	↓	
		21					
		22					
	Alveolar sacs	23	0.04	0.05	8×10^6	10^4	

The receptors for inhaled bronchodilators are distributed throughout the lungs (Carstairs et al., 1985; Mak and Barnes, 1990), but they have the greatest effect on the receptors of the airways where smooth muscle is located, hence in the conducting airways. Therefore, by targeting these receptors dilates the airways. Corticosteroids receptors are also present throughout the airways (Adcock et al., 1996) and inflammation has been shown to exist in all regions of the lungs (Hogg et al., 2004). Hence for inhaled anti-inflammatory agents it is beneficial for the inhaled dose to be spread throughout the airways.

2.1.1 The Lungs

The lungs are the principle organ of respiration and considered as the largest organ in the body with respect to volume. Each lung is soft, spongy, elastic and is conical in shape and surrounded by the pleural cavity. The right lung, which weighs approximately 620 gm, is larger and situated a little higher than the left lung. It is divided into three lobes. The left one weighs about 520 gm and is divided into two lobes. It is smaller because the heart is accommodated in the medial aspect of the lung. Table 2.1 shows that the structure of the lungs provides a large surface area for gas exchange and presents minimal resistance to airflow and gas diffusion. The lungs can be damaged by dust, gases, the response to allergens and by infective agents (Kumar and Clark, 2002). The lungs, heart and vessels are protected by the chest frame. This frame is a bony and cartilaginous structure to provide protection and also facilities the movement of the thoracic cage to accommodate breathing. The breathing or ventilation of the air into and out of the lungs takes place when air is inhaled and exhaled.

During inhalation the diaphragm contracts and flattens. The intercostals muscles between the ribs contract thereby pulling the ribcage upward and outward. During exhalation, the intercostals muscles and the diaphragm relax, pulling the ribcage down and contracting the lungs. Inspiration occurs when the intrapulmonary pressure is negative which facilitates the contraction of intercostals muscles and the diaphragm. This results in an increase in the volume of the thoracic cavity and promotes the flow of air into the lungs.

An abnormality of breathing (inspiration or expiration) such as shortness of breaths breathlessness or wheezing may indicate a lung function disorder and significantly affects a subject's breathing pattern. The two main types of disorders that impair

ventilation or breathing are either restrictive (e.g. pulmonary fibrosis and sarcoidosis) or obstructive (asthma, chronic obstructive disease) disorders. In restrictive disorders, the normal lung expansion is restricted and there is a decrease of the inhaled volume. In obstructive lung disease the airway becomes narrow with an increase in resistance to airflow, such as asthma and COPD.

2.1.2 Lung Function Test and Spirometry

Spirometry is a pulmonary function test (PFTs) that is a useful screening test, which measures various aspects of the capacity of the lungs. Figure 2.2 describes the normal breathing process of an individual with respect to different lung volumes. This figure shows that the tidal volume (TV) is the amount of air moved in and out of the lung during a normal breath. The amount of air remaining in the lungs after a maximal exhalation is called the residual volume (RV). The vital capacity (VC) is the maximum volume of air that can be exhaled after the lungs are filled by a maximum inhalation and then exhaled as much as possible. This vital capacity manoeuvre can be done with an exhalation that is as fast as the subject can achieve and continued until the subject exhales no more air. So, when the vital capacity is forcibly exhaled, the measurement is called the Forced Vital Capacity (FVC). From this manoeuvre the indices of spirometry are: Peak Expiratory Flow Rate (PEF), the Forced Expiratory Volume in one second (FEV_1) and Forced Vital Capacity (FVC) (Ward, 2006). Sophisticated measurements that make very frequent measurements during the time of this forced manoeuvre provide a variety of other indices with respect to flow and volume.
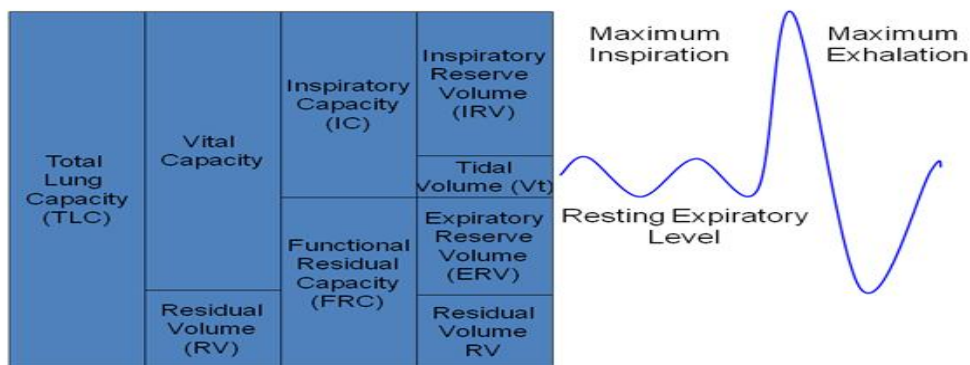
Figure 2.2. Lung Volumes.

Spirometry is considered as the preferred method to measure airflow limitation and used to confirm diagnosis of asthma and COPD (GINA, 2009).

- ➢ The Forced Expiratory Volume in one second (FEV_1) is reported in litres. It is the volume of air that is exhaled during the first second of a forced expiratory manoeuvre. The FEV_1 is the most frequently used parameter as an index for assessing airway obstruction, bronchoconstriction or bronchodilatation and it is considered as the standard index for assessing and quantifying airflow limitation. It can be further expressed as a percentage of the Forced Vital Capacity (FVC). When the lungs are normal this ratio is normally 80%.

- ➢ Peak Expiratory Flow (PEF) is generally reported in litres/minute. It is the maximal flow rate (or speed) achieved during a maximal forced expiration.

- ➢ Forced Expiratory Vital Capacity (FVC) is reported in litres. This is the volume of air that can be forcibly blown out (exhalation) after a full inspiration and continued with as much force as possible until the subject can expel no more air.

Spirometry measurements are frequent expressed as predicted values based on the subject's height, age and gender (Quanjer et al., 1993).

2.2 Obstructive Lung Disease

2.2.1 Asthma

Asthma originating from the Greek word for "panting" is defined as "*a chronic inflammatory disorder of the airways in susceptible individuals, inflammatory symptoms are usually associated with a widespread but variable airflow obstruction and increase in airway response to a variety of stimuli. Obstruction is often reversible, either spontaneously or with treatment*" (GINA, 2009). This inflammation is associated with airway hyper responsiveness (AHR) with recurrent episodes of symptoms such as wheezing, breathlessness, chest tightness and coughing, particularly at night or in the early morning. Sometimes these symptoms become so severe that breathing is severely impaired – in this situation the term acute exacerbation is used.

Worldwide the prevalence of asthma is increasing in the last decades despite considerable improvements in asthma pathogenesis, knowledge and in medical treatment. This poses a serious global health problem in adults and children (Chung et al., 2002). It is estimated to affect about 5-10% of the world's population (300 million people) (Lavorini and Corbetta, 2008), and is expected to increase each decade (Braman, 2006). Asthma is one of the chronic diseases that has a huge economic burden on healthcare resources in terms of cost of treatment and hospitalization. Thus, one of the main aims of the GINA guidelines is to reduce morbidity and mortality by improving asthma control (Lavorini and Corbetta, 2008). The current GINA challenge for each country is to reduce hospitalisation rates by 50% over the next 5 years (Fitzgerald et al., 2011).

2.2.1.1 Pathogenesis of Asthma

Asthma is an inflammatory lung condition in which the airways respond when exposed to inducers or triggers factors. Asthma can be categorised into two types' "extrinsic" (atopic asthma) and "intrinsic" (non- atopic asthma) (Holgate, 2008). Extrinsic or allergic asthma occurs when the subject is exposed to a specific allergen (environmental factors) such as dust, pollen or a non-specific stimulus such as a chemical irritant, cold air or exercise. This type of asthma develops in childhood and is considered to be the most common type. Intrinsic or non-atopic asthma occurs when there are no external factors associated with the disease such as mucosal inflammation, emotional stress or following a respiratory infection.

In atopic asthma, the environmental stimuli or triggers (allergens) cause hypersensitivity of the airway that initiate a multi-cellular inflammatory process (Schieken, 2002) as shown in Figure 2.3. This process of inflammation leads to the activation of many different inflammatory cells in the asthmatic airways. Inflammatory cells produce a variety of chemical mediators, in particular mast cells, eosinophils and T lymphocytes, which act on the cell walls of the airways (airway epithelium) (Holgate, 2010) to produce the typical features of asthma (Barnes et al., 1996). These mediators enhance airway constriction and cause oedema of the airways and this leads to bronchial narrowing (or obstruction) and a spasm of the airways with increases of the classical symptoms of asthma (Currie et al., 2005). Figure 2.4 shows the difference between the bronchioles of a normal and an asthmatic subject.
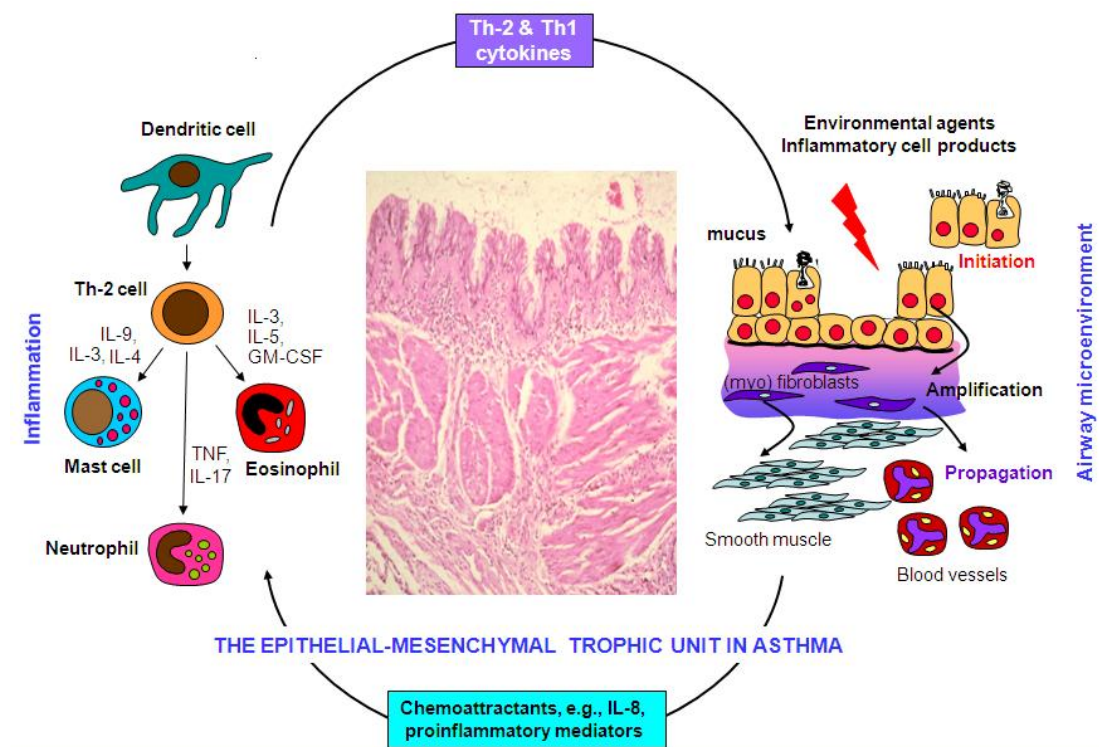
Figure 2.3. The inflammatory pathways of atopic asthma (Holgate, 2010).
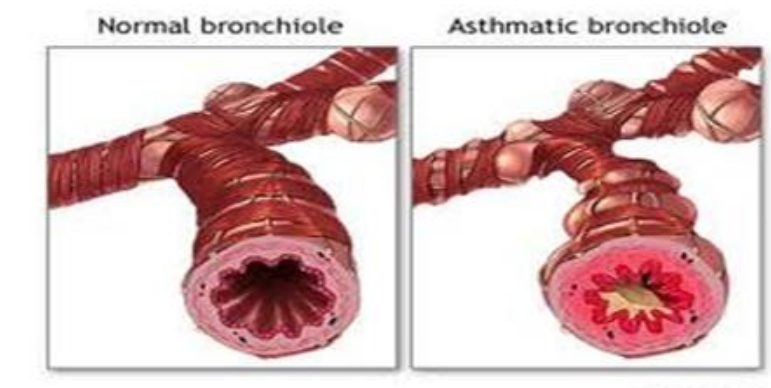
Figure 2.4. Normal and Asthmatic bronchioles (www.mywembd.com).

Symptoms of asthma

Asthma is characterized by episodes of breathlessness, chest tightness, coughing and wheezing. The characteristics of these symptoms, which are variable, are often paroxysmal and provoked by allergic or non allergic stimuli and irritants. These symptoms are useful in the diagnosis of asthma. These symptoms vary in severity

and frequency from person to person, and may occur several times in a day or a week in affected individuals. Some asthmatics become worse during physical activity or many have more symptoms at night. One of the recognised symptoms is wheezing. Wheezing symptoms heard on auscultation of the chest increases the probability of asthma (BTS/SIGN., 2009) and is more specific to asthma than other symptoms (Masoli et al., 2004).

During exacerbations of asthma, the inflammatory response increases the micro vascular permeability and thus cellular infiltration, fibro genesis and smooth muscle airway wall changes (Bradding et al., 2006; Holgate et al., 2009). This leads to a spasm and more obstruction with extra mucus secretion creating a constriction or complete blockage of the airways associated with a decline in the peak expiratory flow (PEF) and forced expiratory volume in one second (FEV_1).

2.2.1.2 Diagnosis and Classification of Asthma

The history of a patient is considered as the key factor to make a diagnosis of asthma. The GINA (2011) guidelines and the British Thoracic Society (BTS/SIGN) Guidelines (2009) have stressed that diagnosis should be based on a clinical history of subjects and consideration of the classical symptoms of asthma (wheezing, coughing, shortness of breathing and nocturnal awakening). Widespread wheezing heard on auscultation of the chest increases the probability of asthma (BTS/SIGN 2009). Moreover, objective measurements are needed to confirm the diagnosis of asthma and to assess its severity. Spirometry provides useful information about the degree of obstruction (BTS/SIGN 2009). The GINA guidelines (2008,2011) suggest that the confirmation of asthma diagnosis can be clarified by the response to inhaled β_2- agonists (bronchodilator in an acute dose situation or over time with chronic inhaled corticosteroid therapy). This is characterized by an increase of >15% in the

FEV$_1$ or an increase in the PEF by $\geq$ 20% from the baseline approximately 30 minutes after an inhaled bronchodilator. This provides evidence of reversibility (Everard, 2003). However, some patients do not show this degree of reversibility particularly those with normal or near to normal lung function which can occur either on its own or with appropriate anti-asthma therapy. The ratio of FEV$_1$/FVC is used to express the airflow limitation and it is useful for differentiating between asthma and chronic obstructive pulmonary disease (COPD).

The classification of asthma severity is based on three equally weighted domains; daytime symptoms, nocturnal symptoms and pulmonary function. According to GINA (2009) guidelines, the severity of asthma can be classified according to the degree of obstruction and its severity as described in Table 2.2. A more simple classification is to categorise asthma into mild, moderate and severe according to their predicted FEV$_1$ ($> 80\%$, 60-80% and $< 60\%$, respectively).

During an acute attack, or uncontrolled asthma, the peak expiratory flow (PEF) and forced expiratory volume in one second (FEV$_1$) can decrease to less than 30% of the subject's predicted values. This is characterised by exhaustion, cyanosis, bradycardia, hypotension and difficulty in breathing and this can lead to coma and to death. Normally people with no smoking history or never had asthma should be able to blow-out 75-80 % or more of their total lung capacity within the first second of a forced exhalation. The reduction in this ratio below 70% indicates an obstructive lung disease (Hughes and Pride, 2000).

Table 2.2. Severity Classification of asthma (GINA 2008).

Intermittent
- Symptoms < once a week   - Brief exacerbation, Nocturnal symptoms not more than twice a month FEV_1 or PEF ≥80% Predicted   - PEF or FEV_1 variability < 20%
Mild Persistent
- Symptoms more than once a week but less than once a day   - Exacerbations may affect activity and sleep, Nocturnal symptoms not more than twice a month FEV_1 or PEF ≥80% Predicted   - PEF or FEV_1 variability < 20%-30
Moderate Persistent
- Symptoms daily   - Exacerbations may affect activity and sleep, Nocturnal symptoms more than once a week and daily use of inhaled SABA FEV_1 or PEF 60-80 % Predicted   - PEF or FEV_1 variability > 30%
Persistent Severe
- Symptoms daily   - Frequently exacerbations, frequently nocturnal symptoms, Limitation of physical activity   - FEV1 or PEF < 60 Predicted   - PEF or FEV_1 variability > 30%

2.2.1.3 Pharmacotherapy of Asthma

The principles of asthma management are to improve the patient's quality of life and to provide optimal long term control of the disease. The GINA guidelines are designed to increase the awareness of asthma, reduce asthma morbidity and mortality, and improve asthma therapy. A recent initiative is to decrease hospitalisation by 50% over the next 5 years (Fitzgerald et al., 2011).

The goal of asthma management has been defined as no day or nocturnal symptoms, no limitations of daily activities, no need for reliever treatment, normal or near-normal lung function results and no exacerbations (GINA, 2011). A stepwise

approach to the pharmacological treatment is recommended by GINA guidelines (GINA, 2011) and BTS/SIGN (2009) in attempt to achieve optimal asthma control. These guidelines contain a step-up process until no disease control is achieved or as asthma worsens. Once control of asthma has been achieved and maintained for a sufficient period of time (usually at least 3 months) a gradual reduction of the maintenance therapy is recommended to identify the minimum therapy required to maintain control (BTS/SIGN., 2009).

The pharmacotherapy for the treatment of asthma is generally divided into two main categories: reliever (bronchodilators) and controllers (corticosteroids). Inhaled drug administration is used because this method delivers medication to the site of action, has a faster onset of action and minimizes systemic effects. The latter is due to the lower doses and improves the ratio of the therapeutic benefit to the potential side-effects (Pauwels et al., 1997; Lavorini and Corbetta, 2008). Figure 2.5 and 2.6 provide a summary of the BTS/SIGN guidelines for the management of chronic asthma in adults and asthmatic children.

A short course of oral prednisolone (e.g. 40 to 60 mg per day for 5 days in adults, 20 mg daily in toddlers) is effective for acute exacerbations. Tailing off the dose should be considered when a patient receives more than 2 courses in one year.
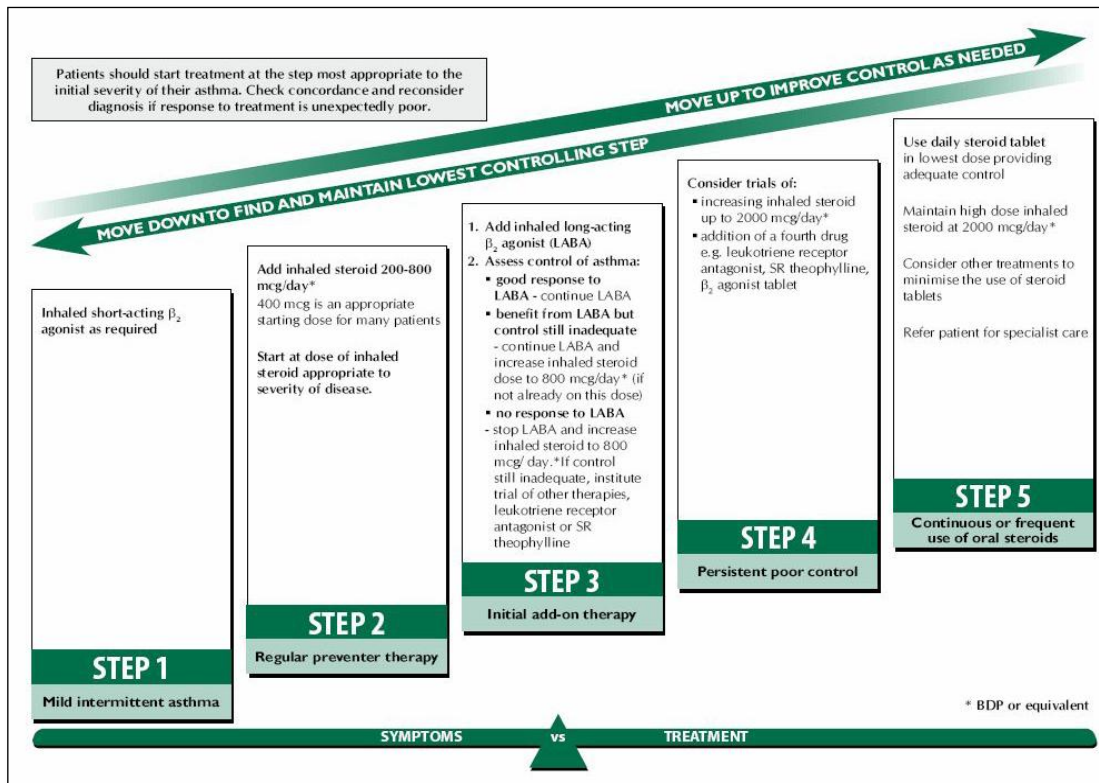
Figure 2.5. The asthma stepwise approach in adults.
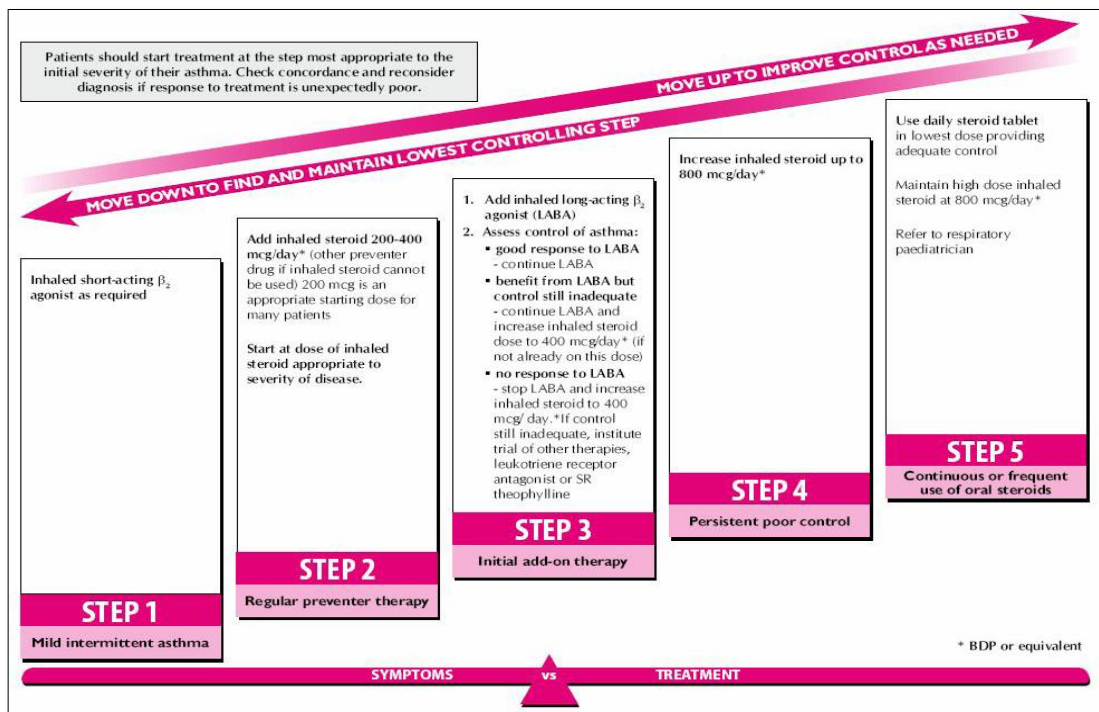
Figure 2.6. The asthma stepwise approach in children (5-12 years old).

2.2.1.4 Measuring Asthma Control

The level of a patient's asthma control can be obtained by the use of validated questionnaires. Asthma management guidelines have defined asthma control as having no or minimal daytime nocturnal symptoms, no or minimal use of rescue bronchodilators, no acute exacerbation and normal or near normal lung function (GINA, 2009). The guidelines also, stress that the objective of any asthma treatment plan is to achieve optimal asthma control and to maintain this control in the future (GINA, 2009). However, despite the availability of effective medications it is well documented that a delay in diagnosis, an under estimation of disease severity and consequently under treatment, the choice of inhaler device and insufficient patient education on correct inhaler technique and compliance may lead to poor asthma control (Horne, 2006; Laforest et al., 2006; Virchow et al., 2008). In clinical practice, patients are usually monitored by registration of their symptoms, physical examination, spirometry, and medication. The questionnaires are designed to identify which impairments are the most troublesome for patients with asthma. In many asthmatic patients, physical activity such as sports, shopping or scaling stairs induces symptoms. Other factors that may trigger symptoms are environmental stimuli, such as cigarette smoke, seasonal allergens, strong smells or weather conditions interfering with social activities.

In clinical practice, symptoms have always been evaluated through simple questions. These questions have been developed into validated and reliable questionnaires that provide insights into the patients' well-being. Such questionnaires reveal functional impairments that influence daily life. Currently, several validated, questionnaires, with strong measurement properties, are available. Some of the questionnaires are short, easily understood and in self-administrable formats (Juniper et al., 1997).

These questionnaires, referred to as instruments (questionnaires), are used to either follow up patients in clinical practice or to investigate the outcome of an intervention in clinical research. (Nantel and Newhouse, 1999; Horne et al., 2007). The ones used in asthma are

- Asthma Control Questionnaires (ACQ; Juniper et al., 1999a)
- Asthma Control Test ™ (ACT; Nathan et al., 2004)
- Childhood Asthma Control Test (C-ACT; Liu et al., 2007a)
- The RCP's "Three Key Questions" (Pearson and Bucknall, 1999; Thomas et al., 2009)
- The Asthma Quality of Life Questionnaire (AQLQ; Juniper et al., 1992)
- Mini Asthma Quality of Life Questionnaire (Mini-AQLQ; Juniper et al., 1999b)
- Paediatric Asthma Quality of Life Questionnaire (PAQLQ; Juniper et al., 1996a)
- Paediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ; (Juniper et al., 1996).

2.2.1.4. The Asthma Control Questionnaires (ACQ)

The Asthma Control Questionnaire (ACQ) was designed and validated to measure asthma control in adult asthmatics (Juniper et al., 1999a). It is simple and can be completed by patients in the clinic. The ACQ has strong measurement properties and has been fully validated for use in both clinical practice and clinical trials. For clinical practice, clinical trials and epidemiological studies, the ACQ has strong discriminative and evaluative properties which mean that it can detect small differences between patients with different levels of asthma control and it is very sensitive to within patient change in asthma control over time.

 The ACQ has 7 questions (the top scoring 5 symptoms, FEV_1% pred. and daily rescue bronchodilator use). Patients are asked to recall how their asthma has been during the previous week and to respond to the symptom and bronchodilator use

questions on a 7-point scale (0=no impairment, 6= maximum impairment). Their $FEV_1\%$ predicted is also scored using a 7-point scale. The questions are equally weighted and the ACQ score is the mean of the 7 questions and therefore between 0 (totally controlled) and 6 (severely uncontrolled).

Development and validation studies have shown that the ACQ was very responsive to change in asthma control (Juniper et al., 1999a). Cross-sectional and longitudinal validity was supported by correlations between the ACQ and other measures of asthma health status. The ACQ, therefore, has strong evaluation and discriminative properties and can be used with confidence to measure asthma control in both longitudinal research and cross-sectional surveys, respectively, as well as in clinical practice (Juniper et al., 1999a).

The ACQ is presented in Table 2.3. Many leave out the last question about the response to a bronchodilator. Several studies have shown that the measurement of validity, responsiveness and reliability of the shortened versions, 6 questions, of the ACQ are similar to those of the original 7-item ACQ. Therefore the shortened ACQ versions can be used without compromising asthma control assessment (Juniper et al., 2001; Juniper et al., 2005). In general, patients with a score below 1.0 will have adequately controlled asthma and above 1.0 their asthma will not be well controlled (Juniper et al., 2006). However, there is a very grey area between 0.75 and 1.25 where patients are on the borderline of adequate control. In general a score of < 0.75 indicates a "well-controlled" asthma, whilst a cut-point of ≥ 1.50 pinpoints an "inadequately-controlled" condition (Juniper et al., 2006). A change or difference in the ACQ score of 0.5 is the smallest that can be considered clinically important (Juniper et al., 2006).

Table 2.3. The Asthma Control Questionnaire.

---

1. On average, during the past week, how often were you **woken by your asthma** during the night?

0 Never
1 Hardy ever
2 A few minutes
3 Several times
4 Many times
5 A great many times
6 Unable to sleep because of asthma

2. On average, during the past week, how **bad were your asthma symptoms when you woke up** in the morning?

0 No symptoms
1 Very mild symptoms
2 Mild symptoms
3 Moderate symptoms
4 Quite severe symptoms
5 severe symptoms
6 Very severe symptoms

3. In general, during the past week, how **limited were you in your activities** because of your asthma?

0 Not limited at all
1 Very slightly limited
2 slightly limited
3 Moderately limited
4 Very limited
5 Extremely limited
6 Totally limited

4. In general, during the past week, how much **shortness of breath** did you experience because of your asthma?

0 None
1 A very little
2 A little
3 A moderate amount
4 Quite a lot
5 A great deal
6 A very great deal

5. In general, during the past week, how much of the time did you **wheeze**?

0 Not at all
1 Hardly any of the time
2 A little of the time
3 A moderate amount of the time
4 A lot of the time
5 Most of the time
6 All the time

6. On average, during the past week, how **many puffs of short-acting bronchodilator** (e.g. Ventolin) have you used each day?

0 None
1 1-2 puffs most days
2 3-4 puffs most days
3 5-8 puffs most days
4 9-12 puffs most days
5 13-16 puffs most days
6 More than 16 puffs most days

7. To be completed by a member of clinic staff
Pre bronchodilator FEV_1 (litres).........
Predicted FEV_1 (litres).........................
FEV_1 (% predicted).............................

0 >95%
1 90-95%
2 89-80%
3 79-70
4 69-60
5 59-50
6 <50%

2.2.2 Chronic Obstructive Pulmonary Disease (COPD)

Chronic obstructive pulmonary disease (COPD) is a progressive lung disease and worldwide is responsible for more than 3 million deaths each year. It currently ranks as the fifth leading cause of death in the UK (NICE, 2010), and is projected to become the third most common cause of mortality and the third leading burden of disease worldwide by the year 2020 (Murray and Lopez, 2000; Murray et al., 2002; NICE, 2010). COPD represents a massive and growing burden with respect to direct and indirect costs. Hence it poses economic as well as social burdens on the patients' themselves, their families and healthcare systems (GOLD-Guidelines, 2006).

COPD is a slow progressive respiratory disorder that is characterized by airflow obstruction and destruction that is not fully reversible. It varies very little from day to day and month to month until obstruction is severe and so it is relatively unnoticed until diagnosed during an acute exacerbation. The damage is due to local respiratory irritants commonly smoking. COPD is a general term for a spectrum of diseases that includes chronic bronchitis and emphysema as well as others such as small airway disease and chronic asthma that is unresponsive to therapy (Bellamy and Booker, 2004). Chronic bronchitis or emphysema can occur on their own but frequently they occur together. Several lung societies have provided statements in an attempt to define COPD and distinguish it from asthma as well as to deal with the important aspects of COPD management. The American Thoracic Society (ATS), and the European Respiratory Society (ERS) definition of COPD defines chronic bronchitis and emphysema. The Global Initiative for Chronic Obstruction Lung Disease (GOLD) proposes a definition that focuses on the progressive nature of airflow limitation and its association with abnormal inflammatory response of the lungs to various noxious particles or gases.

The National Institute for Clinical Excellence (NICE) guideline (2010) has defined COPD as "a *disease characterized by airflow obstruction. The airflow obstruction is usually progressive, not fully reversible and does not change markedly over several months. The disease is predominantly caused by smoking*". (NICE, 2010). Hence, tobacco smoking is the major risk factor leading to the progress of COPD and that correlates with the prevalence and severity of chronic bronchitis and emphysema (Gold-Guidelines, 2009). These diseases are currently more common in males over 55 years although the incidence in females is increasing, paralleling the increase in cigarette smoking by women. Smoking cessation is therefore, the first line management for those with COPD. Other risk factors, which include air pollution or infection, can produce a chronic inflammation of the bronchi (Jensen et al., 2000). Furthermore, occupational exposures (e.g. coal dust) may also contribute to the development of COPD (Fujita and Nakanishi, 2007). In the absence of an identified inhaled irritant there is a genetic link that is associated with someone presenting with emphysema at a young age (< 40 years old). These unfortunate patients have a marked deficiency of alpha α-1 antitrypsin (dAlmaine Semple et al., 1980; Tobin et al., 1983), and occurs in about 1-2% of COPD causes (Bellamy and Booker, 2004).

2.2.2.1 Pathophysiology of COPD

The pathological entity of COPD involves bronchitis and emphysema (either alone or together). Inflammation associated with irritant factors which can produce a chronic inflammation of the airways which causes physiological changes (Hunninghake and Crystal, 1983; Jensen et al., 2000). These changes are associated with an increase in mucus and predominance of inflammatory cells in various parts of the lungs and airway walls. Figure 2.7 describes how neutrophils, macrophages and CD8+ T lymphocytes
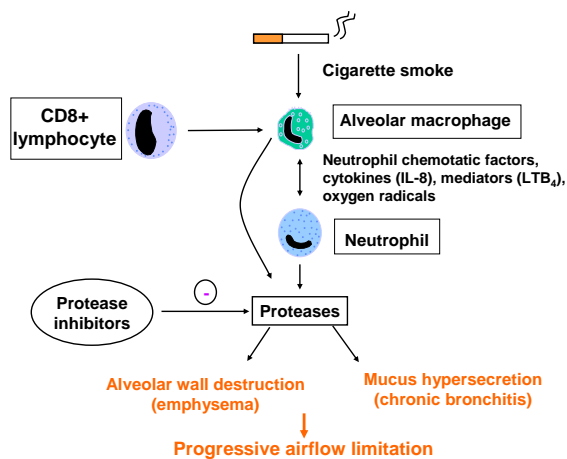
Figure 2.7. Disease processes in chronic obstructive pulmonary disease (Reproduced from Branes (2000).

(Barnes, 2000b) as well as other mediators, (including leukotriene B4, interleukin 8, and tumours necrosis factor) contribute to the inflammatory process. Further amplification of the inflammatory status in the airway can be triggered by factors such as viral or bacterial infection. These inflammatory cells particularly the neutrophils are responsible for the release of elastase-proteolytic enzymes (anti-elastase) that destroy elastin in the lung. This results in damage to the airways and lung tissue (elastically breakdown) with a loss of alveolar wall integrity. The loss of lung elastin, especially in emphysema, contributes to airway collapse, particularly during exercise. Alpha-1-antitrypsin is a natural defence mechanism to these changes and it is those with low levels of this agent that are more susceptible to these effects caused by inhaled irritant, and these are more prone to COPD.

As time progresses and the subject continues to smoke physiological abnormalities gradual continue. This leads to mucus hyper secretion, airways wall thickening with bronchial fibrosis, airflow limitation and hyperinflation. Hyperinflation is a natural process by the body to try to keep the airways open. This is achieved by a flattening of the diaphragm, which results in less effective contraction and reduced alveolar efficiency, which in turn leads an increase in the residual volume (RV). Over time

this leads to severe airflow obstruction, resulting in insufficient expiration to allow the lung to deflate fully prior to the next inspiration and leading to air trapping. This can be translated or indicated by a decline in the FEV_1 and a decreased FEV_1/FVC ratio to < 70% (Nathell et al., 2007). There is also a raised total lung capacity (TLC), residual volume (RV) and functional residual capacity (RFC).

Furthermore, destruction in the alveolar walls leads to a decrease in the effective respiratory membrane surface area that causes decreased gas exchange. There is an increase in blood carbon dioxide concentrations, which causes an increase of respiratory rate of COPD patients, hence a pink appearance of these patients is observed. Moreover, there is increasing evidence that COPD involves systemic features, particularly in severe stages. Cachexia (loss of fat mass), weakness and loss of skeletal muscle mass, osteoporosis and chronic anaemia may develop in COPD patients (GOLD-Guidelines, 2006; Cazzolaet al., 2007).

A main response of some individuals to the irritant effects, mainly from cigarette smoking, is to increase mucus production which leads to classical chronic bronchitis. Mucus cells proliferate and the excessive production leads to a cough, breathlessness and impaired oxygen saturation. An acute exacerbations often occur, where there is a rapid and sustained worsening of symptoms beyond normal day-to- day variations (GINA, 2011).

2.2.2.2 Diagnosis and classification of COPD

The diagnosis and classification of COPD depends upon individual findings based on age, severity, medical history and physical examination, and is confirmed by spirometry, the degree of breathlessness and exercise tolerance. Spirometry is a standardized and reproducible test that objectively confirms the presence of airflow obstruction. Characteristically, spirometry shows a decreased forced expiratory

55

volume in one second (FEV_1) and a decreased FEV_1/FVC ratio (Pauwels et al., 2001). Figure 2.8 describes the link between the reduction in the FEV_1 with age and smoking and explains why smoking cessation is the first line management for those with COPD (Fletcher and Peto, 1977).
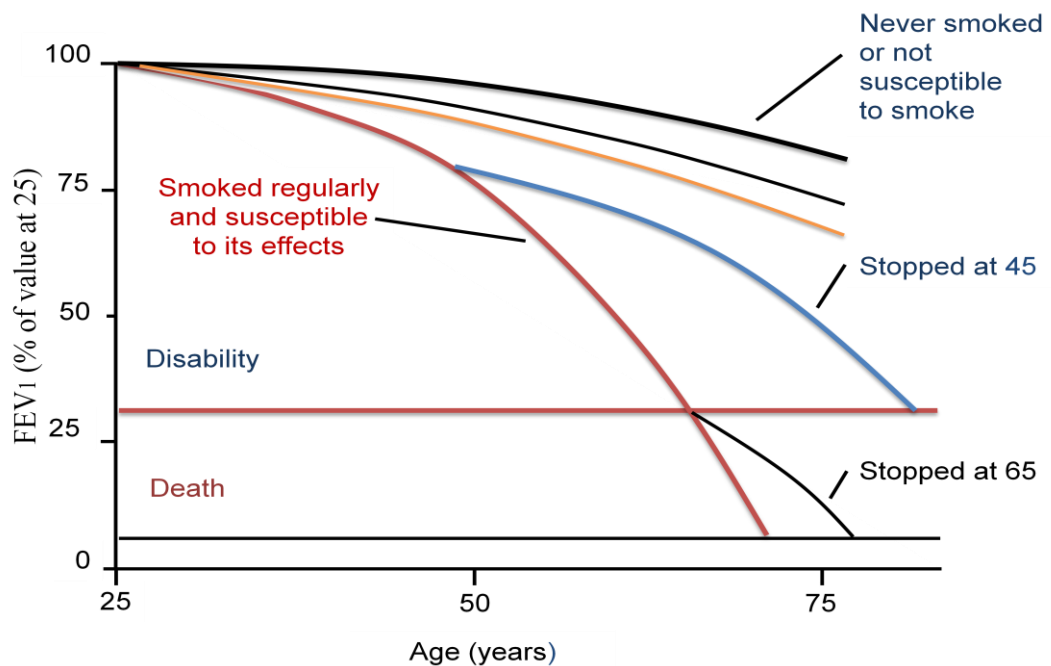
Figure 2.8. The relationship between FEV_1, age and smoking history (Fletcher and Peto, 1977).

NICE (2011) states that "diagnosis of COPD should be considered in patients over the age of 35 [over 40 according to the GOLD Guideline, 2009] who are exposed to one risk factors (predominately smoking) and who have COPD symptoms and signs including; breathlessness, chronic cough, regular sputum production, frequent winter 'bronchitis' or wheeze (Pauwels et al., 2001). According to NICE, COPD Guidelines (2011) the criteria to consider a COPD person is a FEV_1/FVC ratio < 0.70 and an $FEV_1 < 80$ % of predicted values. Clinical symptoms and exercise tolerance together with smoking history and spirometry are used to confirm COPD. Spirometry pre and post a bronchodilator usually shows irreversible airflow limitation (NICE, 2010).

Assessment of the COPD severity level is crucially important to initiate the proper pharmacotherapy treatment and subsequently evaluate the disorder prognosis. The severity stage determination, thus, should include the degree of airflow obstruction, exacerbations frequency and other prognostic factors

Table 2.4. Classification of severity of airflow obstruction GOLD (2008), and the NICE (2010) classification of COPD

Post-bronchodilator FEV_1/FVC	FEV_1 % predicted	NICE (2004)	ATS/ERS4 2004	GOLD (2008)	NICE (2010)
Post-bronchodilator FEV_1/FVC	FEV_1 % predicted	Severity of airflow obstruction			
			Post-bronchodilator	Post -bronchodilator	Post-bronchodilator
< 0.7	≥ 80%		Mild	Stage 1 –Mild	Stage 1 –Mild*
< 0.7	50–79%	Mild	Moderate	Stage 2 – Moderate	Stage 2 – Moderate
< 0.7	30–49%	Moderate	Severe	Stage 3 – Severe	Stage 3 – Severe
< 0.7	< 30%	Severe	Very severe	Very severe** Stage 4 –	Stage 4 – Very severe**

*Symptoms should be present to diagnose COPD in people with mild airflow obstruction
**Or FEV_1 %< 50with respiratory failure.

The Medical Research Council (MRC) dyspnoea scale (Fletcher et al., 1959) is a valid method for assessing severity which correlates with formal exercise tests, quality of life and activities of daily living, but it does not include a lung function test. This dyspnoea scale Table 2.5, has been recommended to be used to assess the grade of breathlessness according to the level of exertion required.

Table 2.5. Medical Research Council (MRC) dyspnoea scale, NICE (2010), adapted from Fletcher et al (1959).

Grade	Degree of breathlessness related to activities
1	Not troubled by breathlessness except on strenuous exercise
2	Short of breath when hurrying or walking up a slight hill
3	Walks slower than contemporaries on level ground because of breathlessness, or has to stop for breath when walking at own pace
4	Stops for breath after walking about 100 m or after a few minutes on level ground
5	Too breathless to leave the house, or breathless when dressing or undressing

Recently, several studies have recommended using a multidimensional grading scheme to classify the severity and impact of COPD because it is more useful than the predicted percentage of FEV_1 measurement alone (Celli et al., 2005; Cazzola et al., 2007). This index, called "BODE" (for body mass index (BMI), obstruction, dyspnoea, and exercise capacity) has been shown to a better predictor of survival in COPD than FEV_1 alone (Celli et al., 2004).

The Bode index is the body-mass index (B), the degree of airflow obstruction (O) and functional dyspnea (D), and exercise capacity (E) according to the criteria described in Table 2.6. Values between 0 and 10 are obtained and the higher the score then the higher is the risk of death in patients with COPD.

Table 2.6. The Bode Index.

Variable	*Points on BODE Index			
	0	1	2	3
FEV1 (% predicted)	≥65	50-64	36-49	≤35
6-Minute Walk Test (meters)	≥350	250-349	150-249	≤149
MMRC Dyspnea Scale	0-1	2	3	4
Body Mass Index	>21	≤21		

*Body Mass Index (BMI) weight (kg)/height (m2). If the BMI is < 20, this reflects a
Poor prognosis

2.2.2.3 Management of Stable COPD

The main goals for the management of COPD are to achieve better standards for diagnosis, treatment, improvement of health status and quality of life, and a reduction of mortality (GINA, 2011). These should be achieved by relieving symptoms and by preventing disease progression (deterioration) and exacerbations. COPD management programs include pharmacological and non-pharmacological options, patient education and the modification of risk factors (NICE Guideline, 2004, Gold Guidelines, 2009). Smoking cessation is the cornerstone of management and confers many benefits, including a slowing of the accelerated rate of FEV_1 decline as shown in Figure 2.8, and an improvement in COPD symptoms (Celli et al., 2004), thereby reducing mortality (Calverley et al., 2008). Several studies have addressed and confirmed that the risk factors particularly cigarette smoking are associated with the progression of COPD (Watson et al., 2006; Cazzola et al., 2007). Fletcher and Peto (1977) in their study, described in Figure 2.8, first highlighted that smoking is the most significant cause of airflow obstruction with an accelerated loss of lung function that some smokers develop.

Beyond education and smoking cessation, the goals of pharmacologic treatments are to enhance survival, quality of life, and the functional status as well as lessen mortality.

2.2.2.3.(a) Pharmacotherapy of COPD

Pharmacological management for COPD includes bronchodilators, corticosteroids, antibiotics, and mucolytics (Cazzola et al., 2007). A summary of the National Institute for Clinical Excellence (NICE) recommendation (2010) for the management of stable COPD is presented in Table 2.7 with the Pharmacotherapy described in more detail in Table 2.8.

➢ Bronchodilators (Relievers)

Inhaled Bronchodilators; including short and long acting (β_2-adrenergic agonists and anti-cholinergic agents) are considered the mainstay of COPD treatment. These are effective in alleviating symptoms of bronchoconstriction that relax smooth muscle around the airways, increase the caliber of the airways and improve air flow and improve exercise capacity, with increases in the FEV_1, although in some patients these changes are small (ATS, 2009).

Table 2.7 shows that inhaled bronchodilators are progressively introduced and increased to the combination of an inhaled long acting β_2 agonist and an inhaled long acting anti-cholinergic. The combination of these two drugs in one inhaler is not yet available. A short and long acting β_2 – adrenergic agonist can be used together but if a long acting anti-cholinergic is used then a short acting anti-cholinergic should not be prescribed.

Table 2.7. The NICE guideline recommended management of stable COPD reproduced from (NICE, 2004).

Smoking	Breathlessness and exercise limitation		Frequent exacerbations	Respiratory failure	Cor pulmonale	Abnormal BMI	Chronic productive cough	Anxiety and depression
• Offer help to stop smoking at every opportunity • Combine pharmaco-therapy with appropriate support as part of a programme	Deleted Deleted in update Optimise inhaled therapy using the algorithm (2a) below Deleted in update If still symptomatic consider adding theophylline Offer pulmonary rehabilitation to all patients who consider themselves functionally disabled (usual MRC grade 3 and above) including those who have had a recent hospitalisation for an exacerbation Consider referral for surgery: bullectomy, LVRS, transplantation	Deleted	• Offer annual influenza vaccination • Offer pneumococcal vaccination • Give self-management advice • Optimise bronchodilator therapy using the algorithm (2a) below Deleted in update	• Assess for appropriate oxygen: - LTOT - ambulatory - short burst • Consider referral for assessment for long-term domiciliary NIV	• Assess need for oxygen • Use diuretics	• Refer for dietetic advice • Refer to 'Nutrition support in adults' (NICE clinical guideline 32) • Give nutritional supple-ments if the BMI is low	• Consider trial of mucolytic therapy • Continue if symptomatic improvement	• Be aware of anxiety and depression and screen for them in those most physically disabled • Deleted • Refer to 'Depression in Adults with a Chronic Physical Health Problem' (NICE clinical guideline 91)

Palliative care
Opiates should be used when appropriate for the palliation of breathlessness in patients with end-stage COPD unresponsive to other medical therapy
Use benzodiazepines, tricyclic antidepressants, major tranquillisers and oxygen when appropriate
Involve multidisciplinary palliative care teams

Table 2.8. Pharmacotherapy for breathlessness and exercise limitation.

Stop therapy if ineffective	• Use short-acting bronchodilator prn (beta$_2$-agonist or anticholinergic)
	• If still symptomatic try combined therapy with a short-acting beta$_2$-agonist and a short-acting anticholinergic
	• If still symptomatic use a long-acting bronchodilator (beta$_2$-agonist or anticholinergic)
	• In moderate or severe COPD: If still symptomatic consider a trial of a combination of a long-acting beta$_2$-agonist and inhaled corticosteroid. Discontinue if no benefit after 4 weeks
	• If still symptomatic consider adding theophylline

> Corticosteroids

Inhaled corticosteroid (ICSs), have a limited role in the management of COPD patients, and their effectiveness is still controversial (Calverley et al., 2003; Man and Sin, 2005). However ICS is considered as the cornerstone of asthma therapy. The reason is that different mediators cause inflammation (eosinophil, mast cell) in asthma and (neutrophils, macrophage) in COPD (Barnes, 2000b). The mediators that cause inflammation in COPD have only a limited responsiveness to corticosteroids, while those mediators responsible for inflammation in asthma are dramatically affected by inhaled corticosteroids (Barnes, 2000b). Several studies using ICS agents in patients with mild COPD have shown no effect on the rate of FEV$_1$ decline (Pauwels et al., 1999; Smith et al., 2004; Sutherland and Cherniack, 2004). However, they have been shown to decrease acute exacerbations in those with either moderate or severe COPD (Calverley and Koulouris, 2005). It is recommended that ICS can be prescribed to patients with FEV$_1$ $\leq$ 50% predicted and who have 2 or more exacerbations per year (NICE, 2010; Gold-Guidelines, 2009). Adding an inhaled

corticosteroid to an established long-acting β_2- agonist regime does reduce acute exacerbations and slow the rate of decline in health status (Macie et al., 2006).

A study showed that a combination a of a ICS (fluticasone) with salmeterol (a LABA) resulted in improved lung function, prolonged frequency time of an exacerbation and improved the quality of life compared with mono therapy or placebo treatment (Calverley et al., 2003). However the decreased mortality rate just failed to reach significance level and there was an increase in the number of pneumonias. The study was not dose finding and used the highest recommended dose. Another study conducted by Soriano et al (2002) showed that regular use of "fluticasone propionate" either alone or in combination with salmeterol is associated with an improved survival of COPD, with an initial improvement in the first three to six months (Bellamy and Booker, 2004) but no effect on the subsequent rate of decline in the FEV_1 (Soriano et al., 2002).

A combination therapy of long- acting β_2-agonist and ICS (budesonide/ formoterol) combined in a single DPI, called Symbicort®, provided improved lung function, a prolonged time to the first exacerbation (Calverley et al., 2003) and improved quality of life compared with either mono-therapy or placebo therapy (Welte et al., 2009). Also, other studies have confirmed the benefit of budesonide in combination with formoterol when compared to the individual components or placebo (Szafranski et al., 2003) and reduced the risk of exacerbations by approximately 20%-25% (Welte et al., 2009). Moreover, this combination has been shown to decrease lung hyperinflation and to increase exercise tolerance (O'Donnell et al., 2006).

After all options, described in Table 2.8 above have been exhausted then patients are usually prescribed oral prednisolone despite the high risk to benefit ratio. However, the NICE-2004 and GOLD 2006 Guidelines for the management of COPD do not

recommend the use of oral corticosteroids as long term maintenance therapy in patients with stable of COPD. For acute exacerbations, systemic corticosteroids have been shown to improve airflow limitations, and symptoms (Teresa and Martin, 2010). Other therapeutic options include mucolytics as well as annual influenza vaccination.

2.2.2.3.(b) Non-Pharmacological Management of COPD

Non- pharmacological management of COPD is useful in parallel with therapeutic management to achieve the overall goals of the disease management plan. Non- pharmacological management includes pulmonary rehabilitation and long term oxygen therapy (LTOT). The rehabilitation programs include physical exercise training and disease education. It has been shown that the pulmonary rehabilitation results in an improvement in multiple outcome of considerable importance to the COPD patient (Folgering and van Herwaarden, 1993; Singh et al., 1998; Cazzola et al., 2007) and health- related quality of life (HRQoL) (Reardon et al., 2005).

2.2.2.4 Differences between Asthma and COPD.

Although there are some overlaps between asthma and COPD, they are separate disorders with different aetiologies, pathologies, natural history and responses to treatment (Barnes, 2008). Table 2.9 summarises the main differences between asthma and COPD.

Table 2.9. The main difference between asthma and COPD.

	COPD	Asthma
Smoker or ex-smoker	Nearly all	Possibly
Symptom under age 35	Rarely	Often
Chronic productive cough	Common	Uncommon- may occur during exacerbations
Breathlessness	Persistent / progressive	Variable
Night time waking with breathlessness and/or wheeze	Uncommon	Common
Significant diurnal or day-to-day variable of symptoms	Uncommon	Common

2.3 Drug delivery and Inhalation Route

Smoking the leaves of the Atropa belladonna plant to reduce cough in India, approximately 2000 BC, is frequently mentioned as the first reference to pulmonary drug delivery (Grossman, 1994; Bisgaard et al., 2002). The treatment by inhalation of various chest infections and tuberculosis was used in Europe (UK) in the 17th and 19th century (O'Callaghan and Wright, 2002).

The asthma cigarette was considered as the first portable inhaler (Everard, 2003). This was followed by the jet nebulizer in the 1930s and then by the glass and rubber bulb nebulisers for delivering adrenaline. Later on in 1950s, more convenient portable devices called "pMDIs" were introduced despite their disadvantages.

The pressurised metered dose inhaler (pMDI) was first introduced in 1956 for delivering doses of either adrenaline or isoprenaline for the treatment of asthma. Its popularity with isoprenaline was demonstrated by a 600% increase in prescriptions and sales between 1959 (Crompton, 2006). However, pMDI sales dramatically decreased following an increase in deaths attributed to the isoprenaline pMDI and a

warning issued by the Committee of Safety Medicines in 1966. In 1969 the salbutamol pMDI subsequently replaced the isoprenaline pMDI, to become the most frequently prescribed short-acting β-agonist inhaler. In 1972, the inhaled corticosteroid beclometasone dipropionate was also introduced via a pMDI. Dry powder inhalers were first introduced as single dose capsules that had to be broken inside a device prior to inhalation. The Spinhaler containing sodium cromoglycate was introduced in 1967 and was followed by the Rotahaler. The first multidose dry powder inhaler was the Turbuhaler in 1987 and was then followed by single doses inside an inhaler (Diskhaler and then Accuhaler). Many others types of DPI have followed.
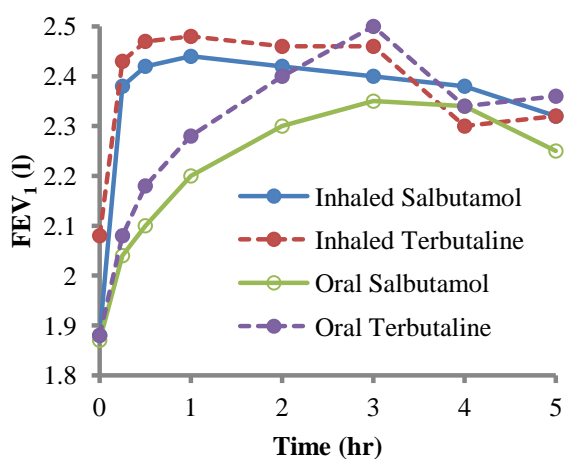
Figure 2.9. Onset of action using inhaled and oral routs of administration (Webb et al., 1982; Everard., 2003).

The pulmonary route allows inhaled medication to be delivered directly to the therapeutic sites in the airways of the lungs (Virchow et al., 2008). Due to this direct delivery a low dose is required compared to a therapeutically equivalent oral dose hence there is a large reduction in systemic adverse effects. There is a fast onset of action as shown in Figure 2.9 (Webb et al., 1982), and a lower rate of side-effects (Pauwels et al., 1997). A high therapeutic ratio is achieved compared with systemic delivery (Newman et al., 1981a; Virchow et al., 2008). Therefore, this route is considered as the optimum route for administering the majority of the drugs for the

treatment of obstructive lung disease (Toogood, 1989; Pauwels, 1997). In addition, to asthma and COPD, inhaled therapy can be used to treat other respiratory diseases such as: bronchopulmonary dysplasia and cystic fibrosis (De Boeck and Breysem, 1998) where large doses of antibiotics are inhaled (mostly by nebulisation). Furthermore, other drugs are under development for systemic therapy using aerosol delivery. These include insulin to treat diabetes, gene therapy vectors to treat cystic fibrosis (CF), vaccines for measles, chemotherapy agents for lung cancer, morphine to relieve pain and for acute pain management and ergotamine for migraine.

Different inhaler devices are available to deliver these drugs; pressurised metered dose inhalers (pMDIs), which are used either alone or attached to a spacer or valved holding chambers (VHCs), dry powder inhalers (DPIs) and nebulisers. These inhalation devices produce an aerosol cloud of medication that provides an emitted dose that is capable to deposit medicine into the lungs during an inhalation manoeuvre. The fraction of the emitted dose with this capability is termed the fine particle dose. The fine particle dose is the amount of particles in the emitted dose that have an aerodynamic diameter of less than 5 μm. Particles below this size range have the greatest likelihood to be deposited on the airways in the lungs during an inhalation (Rees et al., 1982; Newman, 1985; Chrystyn, 1999).

A summary of the aerodynamic characteristics of the dose emitted from an inhaler is presented in Table 2.10. (Laube et al., 2011). These terms are derived from in-vitro measurements.

Table 2.10. Definitions of commonly used in-vitro terms that describe an aerosol (Laube et al., 2011).

Term	Abbreviation	Definition
Labelled dose or nominal dose*		The mass of drug that is available within the aerosol generator per actuation. This is the dose that is metered.
Total emitted dose or delivered dose	TED	The mass of drug emitted per actuation that is actually available for inhalation at the mouth.
Fine-particle dose	FPD	The mass of particles, 5 mm in size within the total emitted dose.
Fine-particle fraction	FPF	The fine particle dose divided by the total emitted dose.
Aerodynamic equivalent diameter	dae	The diameter of a fictitious sphere of unit density (1 $g^{.cm-3}$) that has the same gravitational (settling) velocity in the same gas as the actual particle.
Mass median aerodynamic diameter	dae,µm or MMAD	The MMAD divides the aerosol size distribution in half. It is the diameter at which 50% of the particles of an aerosol by mass are larger and 50% are smaller.
Geometric standard deviation	σg or GSD	The GSD measures the dispersion of particle diameter and is defined as the ratio of the median diameter to the diameter at ¡1 SD (s) from the median diameter. In a cumulative distribution plot of the aerodynamic diameter and mass of particles, the GSD is calculated as the ratio of the median diameter to the diameter at 15.9% of the probability scale, or the ratio of the diameter at 84.1% on the probability scale to the median diameter. Aerosols with a GSD ≥1.22 are considered polydisperse. Most therapeutic aerosols are polydisperse and have GSDs in the range of 2–3.

* Lung deposition can be presented as a percentage of the nominal or emitted dose. Note that these two parameters are not the same.

Drug delivery via the pulmonary airways is more complex than oral therapy. To achieve successful therapy requires a delivery system that during an inhalation generates drug particles of an appropriate size, that have the capability to penetrate beyond the oropharynx and larynx and deposit onto the target area in the lungs (Labiris and Dolovich, 2003) to have a pharmacological effect (Byron and Patton, 1994).

To achieve effective targeting within the airways there are a number of factors that can govern the penetration and deposition of inhaled aerosols. Aerodynamic diameter is generally thought to be the most important particle related factor that affects aerosol deposition. Figure 2.10 shows that there is a relationship between aerodynamic diameters and lung deposition (Köbrich et al., 1994). There are three main mechanisms of particle deposition that have been suggested to be responsible for the deposition of inhaled aerosol particles depending upon on their size. The three main mechanisms are impaction, sedimentation and Brownian diffusion as shown in Figure 2.11.
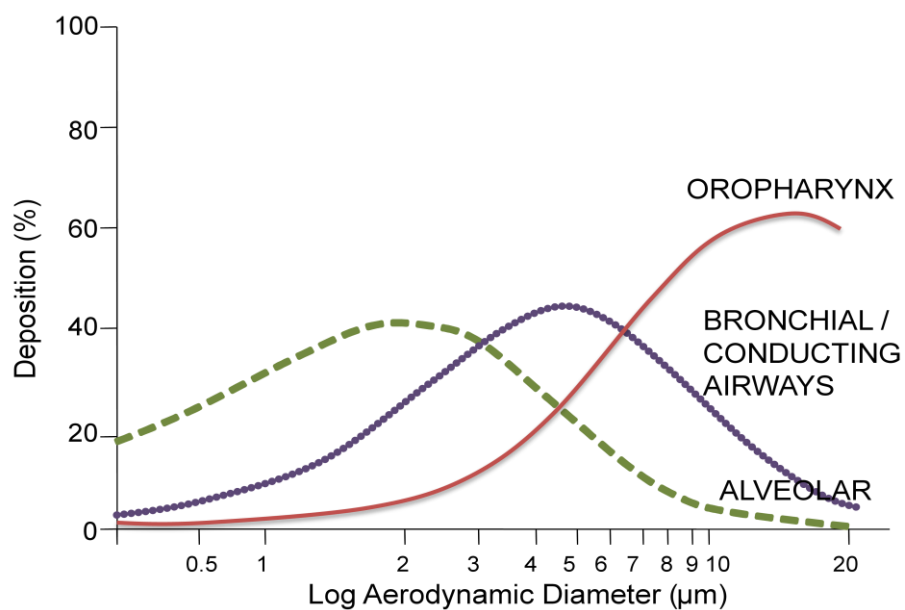
Figure 2.10. The relationship between aerodynamic diameter and lung deposition (Köbrich et al., 1994; Laube et al., 2011).
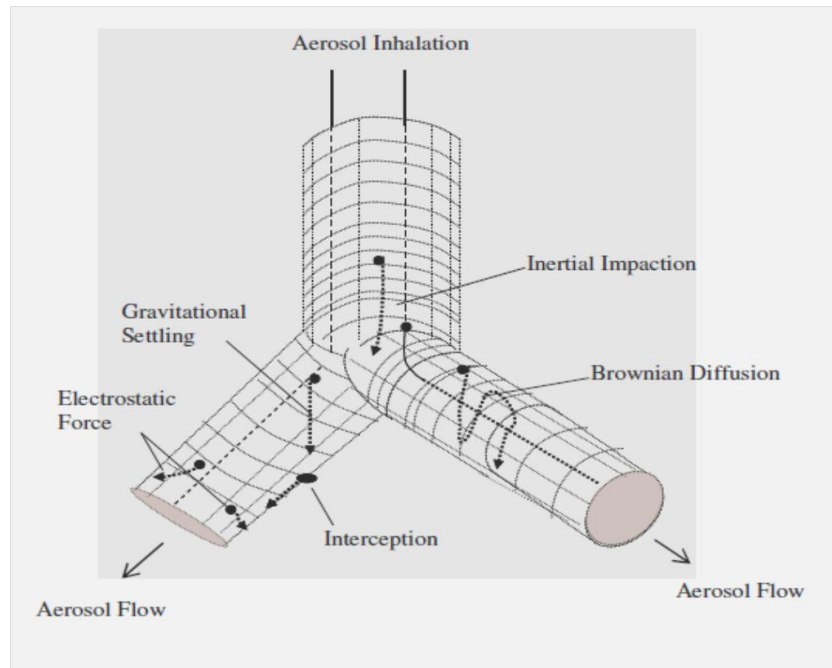
Figure 2.11. Respiratory drug particles deposition mechanisms in human lung (Yu and Chien., 1997).

This figure also shows that other effects such as interception impaction and electrostatic forces are responsible for some deposition in smaller airways (Heyder et al., 1986). *Inertial impaction* (inertial particle transport) is a physical phenomenon, which mainly influences the deposition of larger particles. When the dose is emitted from an inhaler the airflow (at the mouth) is fast especially from a pMDI. The particles in the emitted dose join the airflow down into the airways. In the mouth and down to the larynx and further down the trachea the airflow is fast and so large particle (those larger than 5 μm) will deposit in the oro-pharyngeal region. These particles will be swallowed and the drug absorbed into the systemic circulation after gastro-intestinal absorption. Particles < 5 μm will enter the lungs via the right and left bronchus and down into the large airways. Here the airflow is still relatively fast and thus particles just below 5 μm will deposit by impaction at the bifurcation of these larger airways (Labiris and Dolovich, 2003).

The second important mechanism is ***Sedimentation***, i.e. "gravitational attraction" which is responsible for deposition of smaller particle sized < 5µm and towards 1µm. As the inhaled airstream flows down the narrowing airways the flow becomes slower and slower. In the smaller airways of the conducting zone of the lungs the particles are suspended in a very slow moving airflow. These particles will deposit due to gravity. This process of sedimentation is proportional to the aerodynamic particle size and to the period during which the drug particles stay in the lungs (Newman et al., 1981a; Everard, 2003). Consequently the chance of sedimentation increases with residence time in these more peripheral airways (Newman et al., 1982). For this reason, a breath holding manoeuvre after an inhalation is important (Everard et al., 1997; Hillery et al., 2001).

The third mechanism is ***Brownian diffusion*** which is the primary transport mechanism for very small particles especially those from 1µm to 0.1-1µm in diameter. The particles are suspended in a very slow moving airstream and move by colliding into each other and if they collide with the airway wall then the particles deposit otherwise they are exhaled (Labiris and Dolovich, 2003). This mechanism is inversely proportional to the particle size and directly proportional with length of stay in the lungs (Hillery et al., 2001). Again a breath hold is important.

A high and slow airflow has a profound effect on the overall deposition of inhaled drug particles in the lung (Everard, 2003). An increase in the inspiratory flow will enhance deposition by inertial impaction in the upper airways as well as the oropharynx (Usmani et al., 2005). Also, an increased inhalation volume will lead to an increase in the penetration of particles deeper into lung and thus enhance deposition into the alveolar region (Pavia et al., 1977). Also, the period of breath holding increases particle deposition by gravitational sedimentation and diffusion

(because it increases the time that particles stay in the lung (Dhand and Fink, 1999). Training the patient the correct inhalation technique improves drug delivery to the lungs (Newman et al., 1991b), particularly in terms of the rate at which the patients inhale, and the period of breath holding (Newman et al., 1980; Newman et al., 1991b). The most significant factor for pulmonary deposition is the patient's inhalation technique. This is covered extensively later.

In addition, important patient related factors play a role in pulmonary drug delivery. These include the morphology of the oropharynx and larynx and the patient's inspiratory volume and flow rate. The airway calibre also influences the amount of drug deposited into the airways (Lipworth and Clark, 1997).

2.3.1 Inhalation Devices and Drug delivery

A number of inhaler devices have been introduced to provide medications to the lungs. The most frequently used inhalers are the pressurized metered dose inhalers (pMDI or MDIs) and dry powder inhalers (DPIs), while nebulizers are sometimes used in specific circumstances.

2.3.1.1 Pressurized Metered Dose Inhaler (pMDI or MDI)

The pMDI was introduced in the 1950s, and the first portable multi-dose inhaler designed to deliver a fine aerosol drug to the lungs (Vaswani and Creticos, 1998; Fink, 2000). It is frequently prescribed to deliver inhaled bronchodilators (β_2 agonists and anti-cholinergic agents) and anti-inflammatory agents (corticosteroids) for the management of lung disease. The pMDI is the most widely prescribed inhaler device worldwide (Pauwels et al., 1997; Lavorini and Corbetta, 2008) and, it is still the most popular inhalation method in the UK (Vaswani and Creticos, 1998; Crompton, 2004). pMDIs have a number of advantages in that they are compact, cheap, portable, relatively inexpensive, provide consistent dose emission, and are multidose

with up to 200 metered dose (Newman, 1991). They are available to deliver different inhaled formulations (Lavorini and Corbetta, 2008). A pMDI, shown in Figure 2.12 consists of a pressurised aluminium canister containing the formulation that fits into a holder which is the mouthpiece. The nozzle of the canister fits into a holder which has an aperture through which the dose is discharged from the canister when it is pressed. Inside the canister a metering valve with a spring allows a dose to be dispersed and emitted. The formulation in the canister is traditionally either a suspension of micronized active drug suspended or dissolved in a propellant. The formulation also contains surfactants and lubricants (Newman et al., 1981a), as appropriate, to maintain the action of the spring valve.
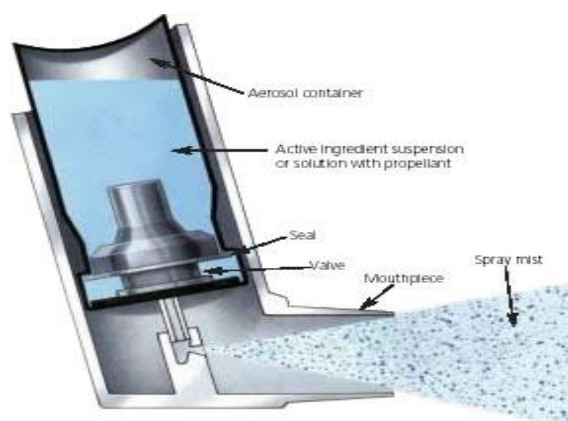
Figure 2.12. A schematic of the pMDI (source:

www.solvaychemicals.com/docroot/fluor/static_files/images/solkane_227_134a_pharma_application)

Pressing the top of the canister in the actuator's (mouthpiece) seating opens the metering valve resulting in its contents being expelled. The liquefied propellants vaporise and provide the required potential energy to expel a hetero-disperse aerosol of droplets that consist of tiny drug particles. When the depression of the canister is released the canister nozzle closes and the metering cup encases the next dose from the formulation inside the canister therefore, it is important to shake the pMDI

immediately before dose actuation. The dose release pressure is 3-5 times atmospheric pressure, thus the initial velocity of dose leaving the mouthpiece is high, approximately 100 k/hr or 70 miles/hr. After dose actuation, the aerosol particles rapidly decelerate and the propellant evaporates. During inhalation the propellant gas may cause cough, throat irritation and paradoxical bronchoconstriction whilst the cool temperature hitting the back of the throat can involuntarily stop the patient's inhalation. This latter phenomena is called the Cold Freon Effect (Crompton, 1982a; Newman and Clarke, 1983). There is a high degree of oro-pharyngeal deposition which is enhanced if there is inadequate co-ordination of the start of an inhalation and dose actuation and when the inhalation is too fast (Crompton, 1982a; Newman and Clarke, 1983). Poor co-ordination and inhaling too fast are common problems (Al-Showair et al., 2007a). These common problems associated with pMDI use are the reason why most patients cannot use pMDIs correctly, even after repeat tuitions (Crompton, 2004: Crompton et al., 2006: Virchow et al 2008). To overcome these problems associated with pMDIs, breath actuated pMDIs (BA-pMDIs), spacers (Bisgaard et al., 2002), and dry powder inhalers (DPIs) have been introduced.

Until recently, the propellants used in the pMDI formulations were chlorofluorocarbons (CFCs). These were very useful dispersion mediums for the drug substance and other excipients (Young et al., 2003). Traditionally all formulations were a suspension of micronized drug particles suspended in the CFC propellant. Due to the damage to the ozone layer by CFCs (Molina and Rowland, 1974) and in accordance with the Montreal Protocol (1994) on substances that deplete the ozone layer, the CFCs have been now been replaced with the more environmental friendly hydrofluoroalkanes (HFAs). This change is now almost complete and at present time there are only a few pMDIs that still contain CFCs

(Laube et al., 2011). The hydrofluoroalkanes (HFAs) have different physical and chemical properties which meant that all pMDIs had to be reformulated. The primary aim was to formulate pMDIs with the same dose emission characteristics as their CFC counterparts (Cripps et al., 2000).

The HFAs have a higher boiling point than CFCs. Hence, the HFA formulations emit an aerosol with a slower velocity at initial release and it is warmer (Gabrio et al., 1999). Thus the potential of the Cold Freon Effect and oro-pharyngeal deposition is reduced with a greater potential for better lung deposition (Leach et al., 1998).

The reformulation of pMDIs with HFAs did present a challenge to the pharmaceutical industry because different excipients were required. Most products were formulated with dose emission characteristics similar to the CFC-pMDI counterpart but this was not possible for some drugs. Hence some corticosteroids, notable beclometasone dipropionate, were difficult to reformulate. This problem was solved by formulating a solution rather than a suspension of drug particles. This meant that the aerosolised dose emitted contained much smaller particles, referred to as extrafine or ultrafine particles. This produced a significant improvement in lung deposition, increased systemic delivery and clinical efficacy compared to its CFC counterpart (Leach et al., 1998; Leach et al., 2002). Figure 2.13 shows the lung deposition (53%) from a HFA-BDP compared (4%) to a CFC BDP (Leach et al., 2005).

The greater lung deposition is due to the fact that these HFA pMDIs emit extrafine beclometasone dipropionate particles with a MMAD of 1.1µm (Fergusson et al., 1991). It also leads to more efficient peripheral lung deposition and lower oropharyngeal deposition compared to the CFC formulation (Leach et al., 1998; Leach et al., 2002).
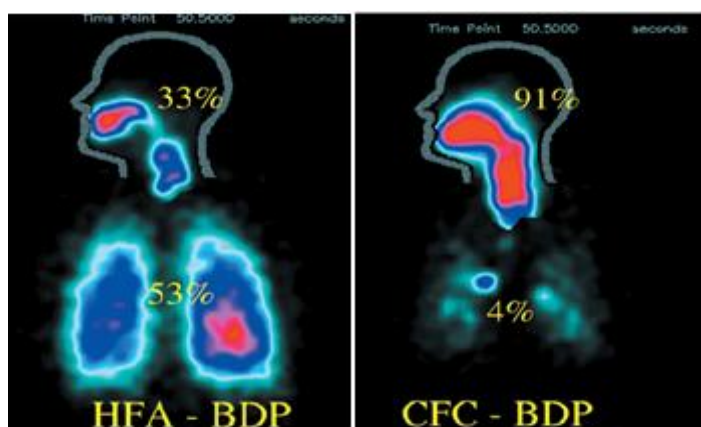
Figure 2.13. Scintigraphic images of enhanced lung deposition from HFA-BDP versus the same patient inhaling CFC-BDP (Leach et al., 2005).

Consequently, this formulation has been shown to provide an equivalent clinical response at half the dose of the innovator CFC-BDP (Becotide®, Galxo-SmithKline) formulation (Busse et al., 1999). The brand name of this product is Qvar® (Teva Pharmaceuticals). An alternative approach for BDP was to re-formulate pMDIs with HFA propellants using Modulite® Technology to control the size of the particles emitted from the pMDI (Ganderton et al., 2002; Lewis et al., 2005). The aerodynamic characteristic of the emitted dose are the same as the CFC-BDP pMDI. The dose for this product, Clenil® (Chiesi Pharmaceuticals), is the same as that of the innovator product. Due to the difference between the recommended doses for Qvar® and Clenil® the MHRA have recommended that these products should be prescribed by brand name. Becotide has been discontinued.

2.3.1.1.(a) Spacers

In the 1980s spacers were introduced to overcome the co-ordination problems associated with the use of the conventional pMDI. Spacers act as a simple extension tube attached to the pMDI mouthpiece that is designed with a chamber to enable the dose emitted from a pMDI to slow down. The patient inhales from a static cloud and this helps with better lung deposition (Barry and O'Callaghan, 1996; Richards et al.,

2001; Roller et al., 2007; Lavorini and Fontana, 2009). The large particles emitted from a pMDI are left in the spacer during an inhalation. Oropharyngeal deposition is reduced (Toogood et al., 1984) and there is also a reduction in the systemic delivery because less is swallowed (Barry and O'Callaghan, 1996; Richards et al., 2001; Roller et al., 2007; Lavorini and Fontana, 2009).

Spacer may improve the effect of inhaled medications, particularly for patients who they are not able to use their inhaler (pMDI) properly (Godden and Crompton, 1981; Newman and Newhouse, 1996). Holding chambers have shown to improve pulmonary deposition from approximately 10% (with pMDI alone) to $\geq$ 20% (Newman et al., 1995b). A range of studies have investigated the value of spacers with regards to coordination, but the literature contains mixed results and many use bronchodilator doses at the plateau of the dose response relationship.

Godden and Crompton (1981) first demonstrated an improved bronchodilatation response in asthmatic patients by improved FEV_1 after using the spacer compared to the conventional pMDI (Godden and Crompton, 1981). In accordance to these outcomes, a similar study confirmed that the addition of a tube extension significantly increased PEFR values compared with the original pMDI (Langaker and Hidinger, 1982). Others have shown that a pMDI used with a spacer provided increased responses to short acting β-adrenergic bronchodilators, even for patients with adequate technique compared to the pMDI used alone (Fontana et al., 1999; Lavorini et al., 2004; Lavorini et al., 2006; Lavorini et al., 2008a). In contrast, a number of studies have demonstrated that spacers did not add any clinical advancement compared to a standard pMDI, since there was no significant difference in the bronchodilator effect (Gomm et al., 1980; Epstein et al., 1983). However this could be due to using doses at the top of dose response course (Newman, 1985).

Spacers differ by volume, length, shape, construction material and are valved or non valved systems. Versions referred to as holding chambers contain a one way valve in the mouthpiece which direct air that is exhaled out away from the chamber while during an inhalation the air is pulled through the chamber. This type of spacer is known as a valved holding chamber (VHC) and can be used with an inhalation that uses a normal tidal breathing pattern. Spacers attached to pMDIs are recommended for patients who have difficulties with pMDIs particularly co-ordination (BTS/SIGN, 2009; GINA, 2009). A spacer attached to pMDI is the recommended inhalation method for children < 6 years old.

Figure 2.14. Shows that spacers have different sizes and designs. The Volumatic™ spacer (GlaxoSmithKline, UK) is the most widely used worldwide (Chuffart et al., 2001). It is a diamond shaped large, valved spacer with a volume of 750 ml. In-vitro studies have shown an increased fine particle dose delivery (Barry and O'Callaghan, 1994), and in-vivo studies have shown an increase in lung deposition compared to the pMDI alone (Newman, 2004). Another spacer with a large volume is the Nebuhaler® spacer (AstraZeneca, Sweden) but this has now been discontinued. The AeroChamber Plus® spacer (Truddell International, Canada) is a 149 ml tube design that is available as infant, child and adult versions depending on the size of the mask. These are colour coded; the version with an adult a mask is blue and this is also available with a mouthpiece instead of the mask, children with a mask is yellow, and for infants with a mask it is orange. (Kraemer, 1995). Another spacer the Babyhaler® (GlaxoSmithKline, UK) has a volume of 350ml (Newman, 2004). The Nebuchamber® (AstraZenaca, Sweden) was made of metal and had anti-static properties but has now been withdraw.

Figure 2.14. Different Types of Spacers A) Neubhaler (Metal spacer B) The Volumatic™ spacer C) Babyhaler® D) Nebuhaler® spacer (E)The Aero-Chamber Plus® spacers (Trudell Medical International (TMI), Canada

It has been found that during an acute attack, the use of multiple single doses of a short-acting β_2-agonist through a pMDI plus spacer is an effective alternative to a nebuliser (Duarte et al., 2000; Cates et al., 2003). GINA (2008) also states that the use of a spacer attached to a pMDI is preferred during the treatment of an acute asthma exacerbation instead of using a nebulizer. A study demonstrated that 5 separate doses from a pMDI and a spacer provided the same relative lung deposition as 5mg nebulised from a jet nebulizer during acute exacerbations in patients with asthma and COPD (Mazhar and Chrystyn, 2008).

Despite, the efficiency of spacers and their advantages, they suffer from the obvious disadvantage of making the spacer more bulky and less portable than a pMDI (Onyirimba et al., 2003; Nair et al., 2008). This can affect patient compliance and

acceptance (Brown et al., 1990; Newman, 2004). Recent studies have highlighted the patient's lack of acceptance regarding the use of spacers over other devices (Lenney et al., 2000).

Other problems associated with spacers are that there are made of polycarbonate plastic material and so are prone to develop a static electrical charge on the inner walls which may result in inconsistent medication delivery (Lavorini and Fontana, 2009). Thus, the proportion of the inhaled dose may vary greatly with different spacers. Changing from one spacer to another may be unimportant with some drugs but be critical for others (Lavorini and Fontana, 2009). Static can be reduced or solved by washing a spacer with household detergent without rinsing it with water and then allowing it to air dry (Kenyon et al., 1998). Also, coating the inner walls with antistatic lining can reduce static (O'Callaghan et al., 1993). The AeroChamber Plus will soon be introduced with an anti-static lining. A non- static spacer that is made of metal also limits the effect of the static charge e.g. Nebuchamber[®], but this has been withdrawn. The Vortex[®], is a non-static spacer due to its extremely thin metal layer on the inner surface of a plastic spacer. Generic and comprehensive instructions on the how to use a pMDI attached to a spacer have been published by Laube et al (2011). Table 2.11 shows generic and comprehensive instructions on the how to use a pMDI attached with a spacer (Laube et al., 2011).

Table 2.11. Detailed instructions on how to use pressurised metered-dose inhalers (pMDIs) with spacers: for patients ≥ 6 yrs old.

(Caregiver should determine if child can perform this technique correctly)
1) Shake four or five times if suspension formulation.
2) Take the cap off.
3) Prime the inhaler (refer to the PIL for specific instructions).
4) Insert the mouthpiece of the pMDI into the open end of the spacer and ensure a tight fit. If a reverse flow spacer is used, insert the valve stem of the pMDI into the port on the mouthpiece of the spacer.
5) Place the mouthpiece of the spacer in the patient's mouth with the teeth over the mouthpiece and the lips sealed around it.
6) Instruct the child to exhale slowly, as far as comfortable (to empty their lungs).
7) Actuate one dose into the chamber of the spacer and start to inhale slowly through the mouthpiece. Some spacers will make a whistling noise if inspiration is too fast.
8) Maintain a slow and deep inhalation through the mouth, until the lungs are full of air. This should take a child 2–3 s and an adult 5 s.
9) At the end of the inhalation, take the inhaler out of the mouth and close the lips.
10) Continue to hold the breath for as long as possible for up to 10 s before breathing out.
11) Breathe normally.
12) If another dose is required, repeat steps 1–11.
13) If ICSs are used, rinse mouth afterwards.

2.3.1.1.(b) Breath Actuated Pressurised Aerosol (BA-pMDI)

Breath-actuated metered-dose inhalers (BA-pMDI) were introduced to achieve good synchronisation between dose actuation and start of an inhalation, These devices contain a conventional pressurised canister with a flow-triggered system driven by a spring to release a dose automatically during the start of an inhalation (Newman et al., 1991b), so that firing and inhaling are automatically coordinated. Figure 2.15 shows that lung deposition from BA-pMDI is the same as good coordination. The

Autohaler® was the first to be introduced to the market in the early 1990's (Newman et al., 1991b) followed by the EasiBreathe®. The actuation occurs at a flow of approximately 20 L/min for the EasiBreathe and ≈30 l/min for the Autohaler (Hardy et al., 1996; Laube et al., 2011). In one study, only < 5 % of patients were unable to achieve the threshold inspiratory flow rate required for actuation of the Autohaler and there were fewer errors (Fergusson et al., 1991), compared with using a standard pMDI (Molimard et al., 2003). These inhalers are considering as an alternative to the standard pMDI for patients who are not able to use a conventional pMDI correctly (Bisgaard et al., 2002). Figure 2.15 shows how lung deposition increased in patients when they used a BA-pMDI.
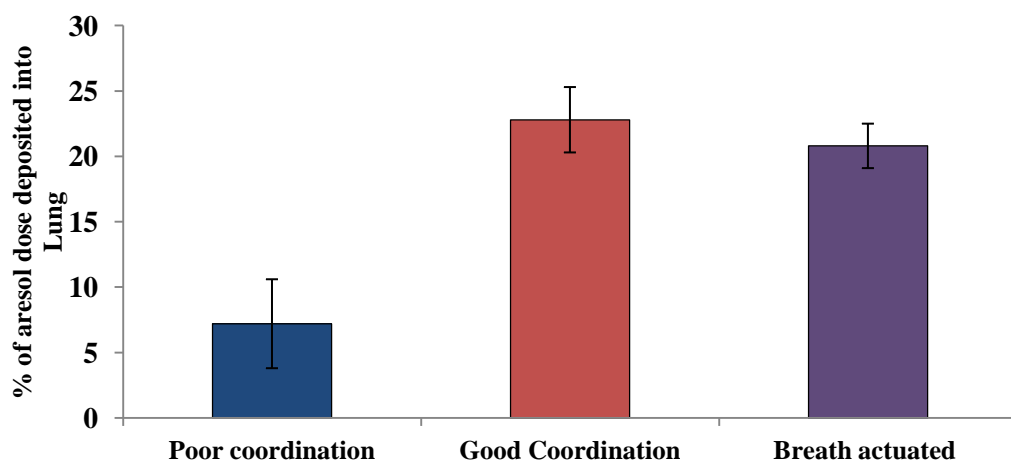
Figure 2.15. Mean (SD) lung deposition in good and poor coordinator and when the poor coordinators used a breath actuated device (Newman et al., 1991b).

The effectiveness of BAI-pMDIs was reported in a large (n=5556) patient study of new asthmatics using GP visits and the number of SABA and ICS prescriptions as outcome measures. The study showed that the asthmatics using a BA–pMDI had fewer prescriptions and used less healthcare resources (Price et al., 2003). The EasiBreathe BA-pMDI has many features over conventional pMDIs that include ease of use with less frequent errors (Lenney et al., 2000; Newman, 2004). Moreover,

healthcare professionals found it easier to teach and patients easier to learn and to use than a conventional pMDI (Price et al., 1999). It has been found that the errors when using BA-pMDIs are less frequent than when using a standard pMDI (Lenney et al., 2000; Crompton, 2004). The Autohaler BA-pMDI can be used easily by children over 7 years old (Pedersen and Mortensen, 1990).

A major disadvantage of BA-MDIs is that they are only available with salbutamol and BDP (Qvar®). Furthermore the licence for the beclometasone dipropionate does not include children < 12 years of age. Another disadvantage is their item cost but they may prove to be cost effective in terms of resource saving in the long run (Langley, 1999).

2.3.1.1.(c) The pMDI Inhalation Technique

Soon after the pMDI was introduced the problems patients have using a pMDI were first reported (Saunders, 1965). After the introduction of salbutamol (1969) and beclometasone dipropionate (1972) pMDIs use increased. The issues about pMDI inhalation technique surfaced with reports from Paterson & Crompton (1976) and Crompton (1982). These showed that inhaling through the nose instead of the mouth, involuntary stopping the inhalation phase (the Cold-Freon Effect) and co-ordination between the start of an inhalation and the release of a dose as well as not breath holding after the inhalation manoeuvre were common mistakes made by patients. Many reports have followed but only a few have highlighted that not using a slow inhalation is the most common error made by patients (Nimmo et al., 1993; Hesselink et al., 2001; Al-Showair et al., 2007a). Incorrect or unsatisfactory use of the pMDI technique may lead to a sub-optimal therapeutic effect, especially for inhaled corticosteroids. This has been given as a reason why > 50% of adult patients do not get the maximum effectiveness from their inhalers (Crompton, 1990).

(i) Co-ordination between the start of an inhalation and actuation of the dose

Poor co-ordination between the start of an inhalation and the actuation of a pMDI canister is one of the most common mistakes that patients made when using pMDIs (Newman et al., 1981a; Crompton, 1982b; Ganderton, 1997). Figure 2.15 shows that in asthmatics with poor co-ordination lung deposition was only 7% compared to 22.8% in those with good co-ordination (Newman et al., 1991b). Hindle et al (1993a), using urinary salbutamol pharmacokinetic methodology, showed that no co-ordination resulted in poor lung deposition as shown in Figure 2.16.
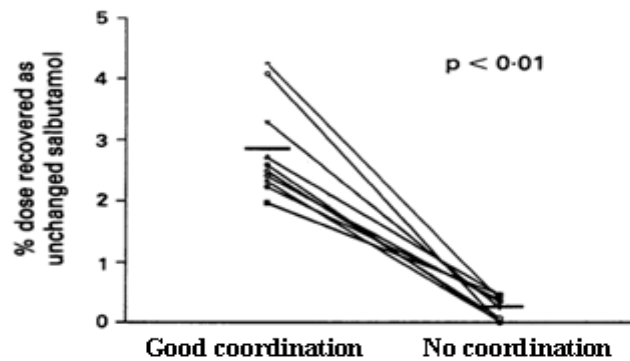
Figure 2.16. Mean and individual values of the relative lung bioavailability of urinary salbutamol after inhalation by two different manoeuvres (Hindle et al., 1993).

The optimum actuation time (good co-ordination) has been defined by Goodman et al (1994) as 0 to 0.2 seconds between the start of an inhalation and pressing the canister to release a dose. This is based on the gamma scintigraphy studies of Newman et al (1980; 1981a; 1981b). More objective confirmation of this time for co-ordination was provided by Farr et al (1995). This study measured lung deposition using gamma scintigraphy following 5 different computer controlled inhalation manoeuvres.

- ➢ Slow/early: inhalation flow of 30 L/min and actuation after 300 ml hence the time of co-ordination is 0.6 second

- ➢ Slow / late: inhalation flow of 30 L/min and actuation after 3000 ml hence the time of co-ordination is 6 second

- ➢ Medium / early: inhalation flow of 90 L/min and actuation after 300 ml hence the time of co-ordination is 0.2 second

- ➢ Fast / early: inhalation flow of 270 L/min and actuation after 300 ml hence the time of co-ordination is 0.1 second

- ➢ Fast /late: : inhalation flow of 270 L/min and actuation after 3000 ml hence the time of co-ordination is 1 second

Figure 2.17 shows that the medium/early provided the highest total lung deposition and more was deposited in the peripheral regions.
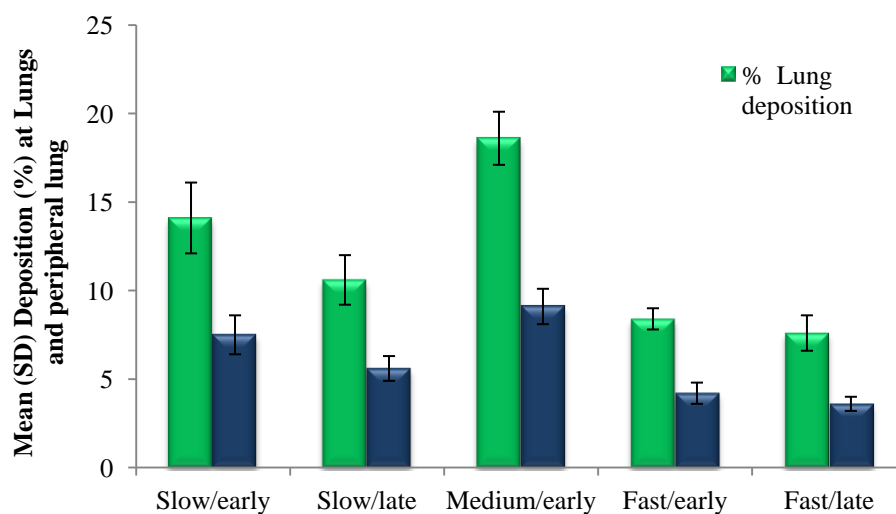
Figure 2.17. The effect of co-ordination and flow rates on the mean (SD) lung deposition from a Smart Mist pMDI (Farr et al., 1995).

Broeders et al (2003) measured electronic profiles of adult asthmatic and COPD patients when they used a pMDI and used the 0-0.2 second criteria, recommended by Goodman et al (1994) for good co-ordination. She and her co-workers found that co-ordination was inadequate in 40% of patients.

The recent transition to HFA propellants has resulted in two different formulations of BDP (see section 2.3.1.1). One formulation (Qvar®) emits extrafine particles with a MMAD around 1μm. A similar formulation of ciclesonide is also available in a pMDI (Leach et al., 2006). A gamma scintigraphy study has shown that for pMDI formulations that emit extrafine particles then co-ordination is not critical as shown in Figure 2.18 (Leach et al., 2005). The study involved 7 mild asthmatics (mean FEV_1 91% predicted) (Leach et al., 2005).
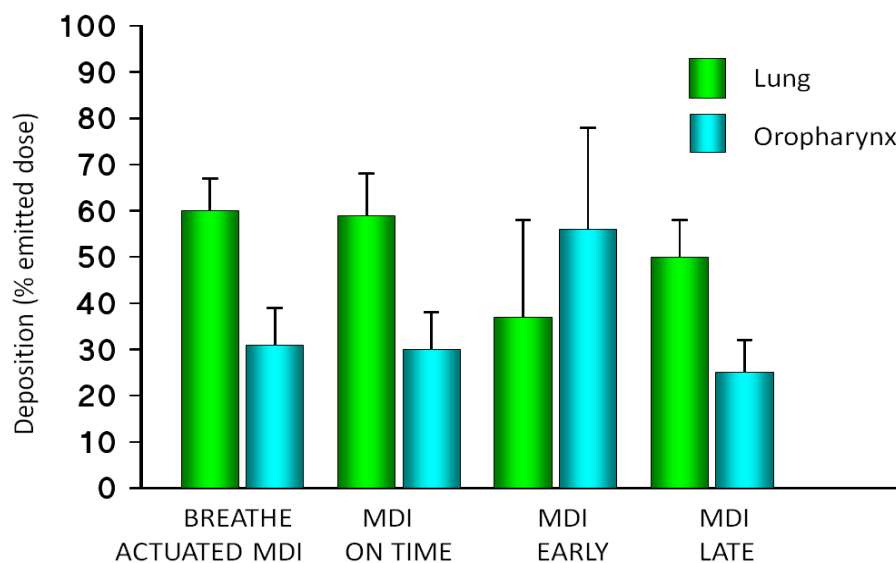
Figure 2.18. Mean (SD) lung deposition of ultrafine beclometasone particles emitted from a HFA pMDI following different inhalation manoeuvres.

The early was timed at 0.5 seconds before the start of an inhalation while the late was 1.5 seconds after the start. Subjects inhaled for 3 seconds with an inhalation volume of about 3 L which suggest that there flows would be approximately 60 L/min. Furthermore Newman et al (1980; 1981) reported that co-ordination was not

important as long as the patient had started inhaling with a slow flow rate. The pMDI formulations used in these late studies would have been those that emit particles sizes similar to those of the common and traditional pMDI with MMADS around 3µm. Although this was supported by Tomlinson et al (2005) using urinary salbutamol pharmacokinetic methodology the results are not consistent with those of Farr et al (1995) with respect to co-ordination timing and Newman et al (1981a, 1981b) did show that when inhalation flow was faster a late inhalation did result in decreased lung deposition.

In general most pMDI do not emit ultrafine particles (and of these there is only Qvar that is commonly prescribed) and most patients inhale too fast (Al-Showair et al, 2007a). When there is no co-ordination or it is early than lung deposition will be low. Although a late actuation with a slow flow does result in some lung deposition and would not be a critical error the amount deposited in the lungs with good co-ordination is better. In general, the criterion for good co-ordination used by Goodman et al (1994) and Broeders et al (2003), which was confirmed by gamma scintigraphy (Farr et al., 1995), would be 0 to 0.2 seconds.

(ii) Slow Flow Rate

Studies have shown that a slow flow rate provides better lung deposition than a fast flow. In the first study that reported about flow, seven patients inhaled using a flow of 30 L/min and 5 others used a flow of 90 L/min. Both groups used a breath-hold of 10 seconds after each inhalation. Co-ordination for both was good and defined as dose actuation soon after the patient had started their inhalation. Mean (SD) lung deposition was 14.3(2.0) and 9.2(1.6) % respectively (Newman et al., 1982). Previously this lung deposition data had been reported by a simultaneous bronchodilator response in these patients; the percentage change in the FEV_1 (15

minutes post dosing) was 29.5(14.3) and 16.6(11.6)% following the slow and fast inhalations (Newman et al., 1980).

From the data in the above papers of Newman et al (1980; 1982), Goodman et al (1994) defined an acceptable inspiratory flow rate between 25-90 L/min whilst a more extensive review by Pauwels et al (1997) stated that flows should be <90L/min. This is confirmed by the data presented above by Farr et al (1994) in Figure 2.17.

Further evidence of better lung deposition with a slow inhalation was reported in a study comparing gamma scintigraphy and urine pharmacokinetic methodology to identity lung deposition of terbutaline inhaled from a pMDI (Newman, 1995). The study involved 8 healthy volunteers using inhalations of 30 and 180 L/min. Figure 2.19 shows the difference in total lung deposition using the urine method. This involved blocking the orally absorbed fraction with oral charcoal and collecting urine over a prolonged period post inhalation.
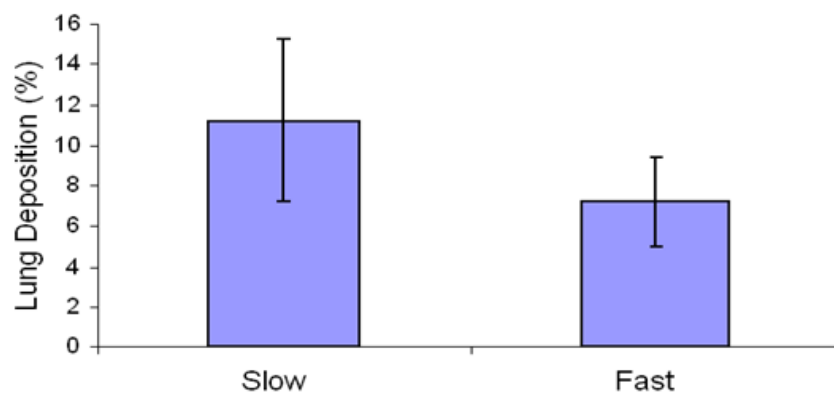
Figure 2.19. Mean (SD) relative lung deposition (Newman et al., 1995b).

In contrast gamma scintigraphy suggested that there was no difference. This was due to a problem with gamma scintigraphy when using a fast inhalation that is highlight in Figure 2.20. This figure shows that as expected there is more deposition in the

central zone of the lungs with a fast inhalation. A part of this would be cleared by mucociliary clearance. In contrast urinary pharmacokinetic methodologies measure drug cleared from the lungs following systemic delivery. Since gamma scintigraphy measures amounts cleared from the lungs by systemic absorption and by mucociliary clearance then care should be exercised when interpreting gamma scintigraphy data when fast flows are used.
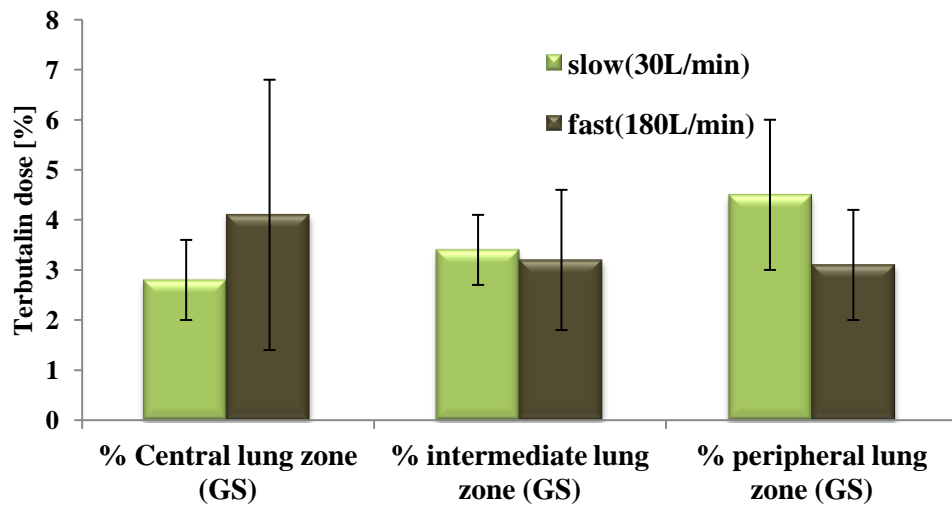
Figure 2.20. Mean (SD) deposition into different zones of them lungs (from Newman et al, 1995).

The above figure demonstrates that when the inhalation flow is fast then there is a tendency for more central lung deposition at the expense of peripheral deposition and that there is more peripheral deposition when the flow is slow. Faster inhalation flows give rise to greater deposition in the oropharyngeal area (Dolovich et al., 1981; Newman et al., 1981b)

Using a urine salbutamol method Hindle et al (1992) demonstrated that the slower the inhalation flow then the better was the relative lung deposition as shown in Figure 2.21. Their slow flow was around 10 L/min whereas the faster flow was 50 L/min. Using this method Tomlinson et al (2005) confirmed better lung deposition

from slow flow in asthmatic patients and this was complimented by better protection by salbutamol following broncho-provocation challenge with inhaled methacholine.
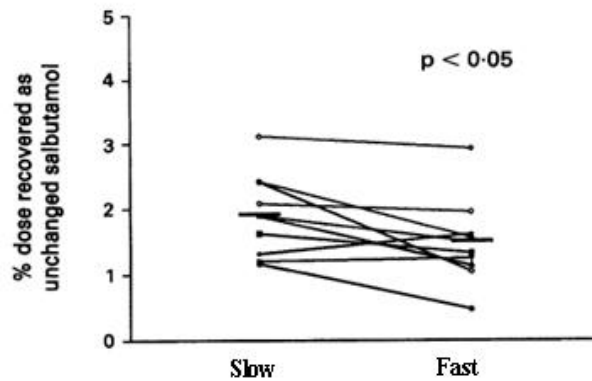
Figure 2.21. Individual and mean relative lung deposition following slow and fast inhalations (Hindle et al, 1992).

The study by Usmani et al (2005) quantified lung deposition using gamma scintigraphy following inhalation of different particle sizes and the effect of flow (30 and 60 L/min). Figure 2.23 shows that there was increased peripheral and decreased central deposition with slower flows and that the influence of flow is dependent on the particle size (hence MMAD) of the aerosol. They showed that flow has little effect if extrafine particles are used. In practice this would only apply to Qvar and ciclesonide pMDIs whereas the majority of pMDIs have MMADS in the 3-6 μm range. Clinical evidence for the recommendation of a slow flow < 90L/min was provided in the study by AlShowair et al (2007). When 36 mild asthmatics (FEV_1 71.4% predicted) were trained to use a slow inhalation flow with their pMDI (< 90L/min) their Asthma Quality of Life changed by 0.74 (above the 0.5 clinical significance value).
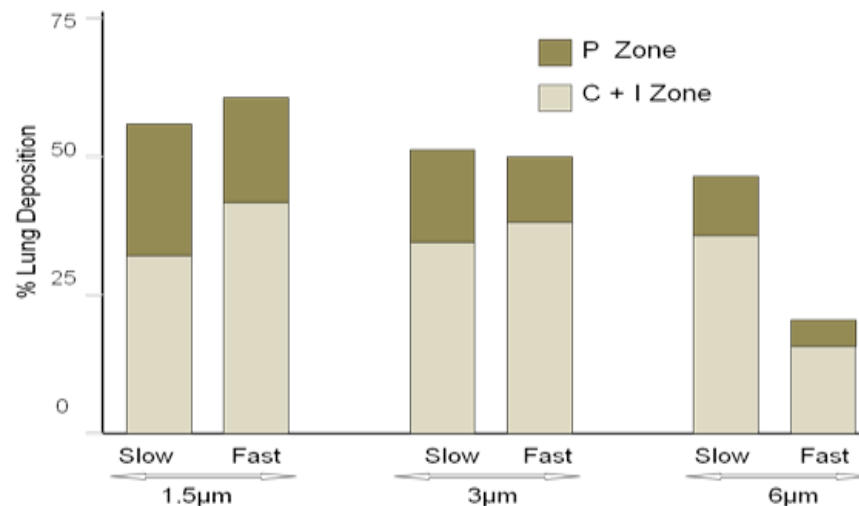
Figure 2.22. Effect of fast and slow inhalation rates on aerosol deposition in central (C) and intermediate (*I*) and the peripheral (*P*) regions of the lung. Reproduced from (Usmani et al., 2005).

There was no change in their FEV_1. The authors concluded that the increase in the Asthma Quality of Life is due to their better asthma control and since there was no change in their FEV_1 then the results reflect better delivery of their inhaled corticosteroids into the peripheral regions of the lungs.

In summary an inhalation flow of < 90L/min is the most acceptable when using a pMDI and can be classified as a slow flow.

(iii) Inhaled Volume.

An inhalation that continues for as long as possible has been recommended (Laube et al, 2011). Since it has also been recommended that patients exhale gently as far as comfortable then an inhalation from residual volume (RV) to total lung capacity would be ideal. It has been found that the alveolar deposition increases ≈ 40% for each 1L increase in the inhaled volume when a slow deep inhalation technique is used (Pavia et al., 1977). Hindle et al (1993b) reported that relative lung deposition was greater when subjects exhaled before their inhalation as shown in Figure 2.23.
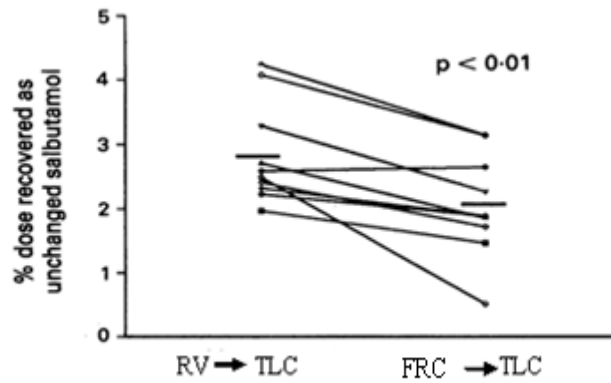
Figure 2.23. Mean and individual values of the relative lung deposition when inhaling from residual volume (RV) compared with inhaling from functional residual capacity (FRC) (Hindle et al., 1993)

Farr et al (1994) reported that the inhaled volumes of nine healthy volunteers when they inhaled from a Smart Mist pMDI were a mean (SD) of 3.72(0.24) litres and Broeders et al (2003) found 2.7 (1.1) litres in 10 mild asthmatics (FEV$_1$ 96% predicted), and 2.9(0.7), 2.6 (0.2) and 2.3(0.2) litres in 16 mild, 16 moderate and 16 severe COPD patients. All these were highly trained techniques so they would have used an exhalation before their inhalation. Farr et al (1995) reported an inhalation volume/forced expiratory volume ratios of 70.5(3.6)% for the inhalation manoeuvres with the highest inhalation volumes. This ratio for the best lung deposition (medium /early – see above) was 61.0 (5.4) %. Goodman et al (1994) defined a deep inhalation as a ratio of >60% (based on the reports of Newman et al, 1980; 1981; 1982 as well as Lawford et al, 1982; 1983).

(iv) Breath hold

Breath-holding is one of the essential steps during the inhalation manoeuvre (Laube et al., 2011). The principle of breath holding for as long as is comfortable after an inhalation is widely accepted as being essential for improved pulmonary deposition (Newman et al., 1981a; Hindle et al., 1993). This allows inhaled particles to settle in

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the airways by gravitational sedimentation (Hillery et al., 2001). The likelihood of sedimentation increases with the residence time in the airway (Everard et al., 1997; Suarez and Hickey, 2000). Consequently, breath-holding is used to optimize pulmonary drug delivery (Dhand and Fink, 1999).

Newman et al (1982) showed that lung deposition in asthmatics was greater for a 10 second breath hold as shown in Figure 2.24. They also reported that there was a respective increase for deposition in the conducting airways and in the respiratory portion of the lungs.
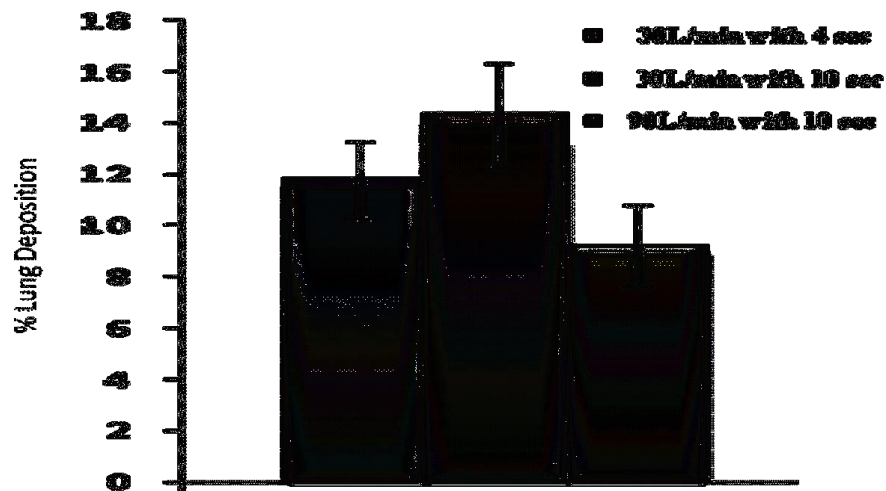
Figure 2.24. Percentages of dose deposited in the whole lung (Newman et al., 1982).

Similar results were reported for the relative lung bioavailability of salbutamol post inhalation (Hindle et al., 1993) as shown in Figure 2.25. In this figure a slow inhalation was used and thus like in Figure 2.25 lung deposition does occur when there is no breath hold because of the residence time from the slow inhalation.
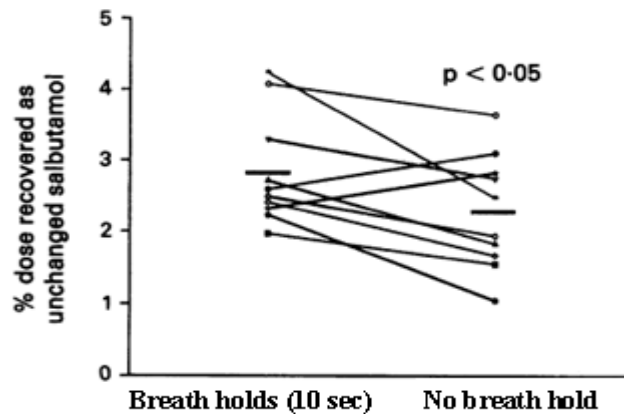
Figure 2.25. Mean and individual values of the relative lung bioavailability of salbutamol with respect to breath hold after inhalation (Hindle et al., 1993).

2.3.1.1.(d) The pMDI inhalation technique and clinical effectiveness

The quantities of drug from a pMDI in the lung are small (Newman et al., 1981b; Borgström and Newman, 1993), in that only about 10-20% of the emitted dose reaches the lungs even when the correct inhalation technique is used (Pauwels et al., 1997). A high proportion of the emitted drug particles are deposited in the mouth and oropharynx. Nevertheless, incorrect or unsatisfactory use of the pMDI may lead to less than the optimal therapeutic response (Newman et al., 1981a; Duerden and Price, 2002; Everard, 2003; Virchow et al., 2008). This issue of pMDI technique is more vital with the ICS than inhaled bronchodilators because the feedback of inhaled bronchodilator (as reliever drug) is an immediate response and these patients can compensate from a poor technique by inhaling another dose (Chrystyn & Price, 2009). This practice is a good indicator that the patient's inhalation technique needs to be checked.

The correct inhalation technique when using pMDIs involves firing the pMDI while breathing in deeply and slowly (Haughney et al., 2008), continuing to inhale after firing, and this should be followed by a breath-holding for around 5-10s (Ernst,

1998; Crompton and Barnes, 2006), to allow particle sedimentation (Newman et al., 1981b). Table 2.12 describes the ideal inhalation technique with a pMD that was recently recommended by the ERS / ISAM Task Force (Laube et al, 2011).

Table 2.12. The ERS /ISAM task force recommendation for the inhalation technique when using pMDI (Laube et al, 2011).

| |
|---|
| 1) Shake four or five times if suspension formulation. |
| 2) Take the cap off. |
| 3) Prime the inhaler (refer to the PIL for specific instructions). |
| 4) Exhale slowly, as far as comfortable (to empty the lungs). |
| 5) Hold the inhaler in an upright position. |
| 6) Immediately place the inhaler in the mouth between the teeth, with the tongue flat under the mouthpiece. |
| 7) Ensure that the lips have formed a good seal with the mouthpiece. |
| 8) Start to inhale slowly, through the mouth and at the same time press the canister to actuate a dose. |
| 9) Maintain a slow and deep inhalation, through the mouth, until the lungs are full of air. This should take an adult 4–5 seconds, a child 2-3 seconds. |
| 10) At the end of the inhalation, take the inhaler out of the mouth and close the lips. |
| 11) Continue to hold the breath for as long as possible, or up to 10 s before breathing out. |
| 12) Breathe normally. |
| 13) If another dose is required, repeat steps 4–12. |

A large study investigating the inhalation technique of 1173 asthmatic outpatients using their pMDI, found that fifty-one percent had co-ordination problem, 24 % of these patients stopped inhaling after actuation (cold freon effect) and 12% inhaled through their nose (Crompton, 1982b). Other studies have shown that between 8-59% have poor or inadequate inhalation techniques when using their pMDI (Cochrane et al., 2000; Broeders et al., 2009). Only 7.6% of asthmatics could use their pMDI with a slow and deep inhalation with good co-ordination and the most common error was inhaling too fast. A series of studies performed by Crompton and colleagues between 1982 and 2000 assessed the inhalation technique after the

patients read the PIL. Between 21%-54% were unable to use their pMDI efficiently even after reading the PIL (Crompton, 1982b; Crompton and Duncan, 1989; Lenney et al., 2000).

When an Aerosol Inhalation Monitor was used to evaluate pMDI technique in clinic settings a high incidence of errors with respect to co-ordination and flow were found and training did not improve the patient's pMDI technique (Harwell et al, 2010). An observation study using a checklist assessment of pMDI technique in asthma subjects and COPD, showed that at least 30 % of the patients made at least one or more errors, and coordination technique was the essential mistake by all patients (Hesselink et al., 2001). In a real life study by Molimard et al (2003) the frequency of errors through the pMDI increased with age particularly patients over > 65 years. In addition to the traditional errors 31% of patients did not press the canister only once during their inhalation. A recent investigational study has found a strong association (p=0.008) between the misuse of inhalers and older age in a large sample of experiences outpatients. This later study also confirmed that inhaler misuse correlated (p<0.001) with an increase of hospital visits and good technique was associated with previous training (Melani et al., 2011). A summary of some of the inhaler technique reports is presented in Table 2.13.

Table 2.13. The percentage of patients making errors with each inhalation step as recommended by Laube et al (2011). [Key to references: A - Epstein et al, 1979; B - Pedersen et al, 1986; C - Pedersen et al. 1986; D - Scott -Smith, 1986; E - Horsley and Bailie, 1988; F - Manzella et a., 1989; G - Goodman et al, 1994; H - van Beerendonk et al, 1998; I - Molimard et al, 2003; J - Melani et al, 2011].

Percentage (%) of errors user of inhalation techniques steps of pMDI based on the steps in table 1									
Ref (n)	A (68)	B (132)	C (85)	D (2)7	E (84)	F (234)	G (59)	H (56)	I (552)	J (843)
Step 1	29	49	34	-	32	18	-	57	33.5	37
Step 2	4	-	-	-	5	-	-	5	-	0.15
Step 3	-	-	-	-	-	-	-	-	-	
Step4	-	45	51	0	58	23	-	66	30.4	50
Step 5	-	-	-	-	-	19	-	-	-	9
Step 6	-	-	-	-	15	30	-	-	-	-
Step 7	13	-	-	-		25	-	-	-	.7
Step 8	34	55	17		40		47	68	25.5	33
Step 9	43	67	28	45		26	39-42	70	37.2	52
Step 10	-	-	-	-	-	-	-	-	-	
Step11	43	42	39	59	66	31	24	53	31	53
Step 12	-	-	-	-	48	-	-	-	-	-
Step 13	23	-	-	-	46	54	-	-	-	-

2.3.1.1.(e) pMDI technique and asthma control

In the first study by Saunders (1965) the bronchodilator response with respect to inhaler technique was first reported and this was followed by others (Newman et al, 1980; Lawford et al, 1982; Rivlin et al, 1983; Lawford et al, 1983) and extended to methacholine challenge (Tomlinson et al, 2005).

A large observational study of 3811 patients showed that about 76% of patients made at least an error when using their pMDI (Giraud and Roche, 2002) and that their asthma control deteriorated as the number of inhalation technique errors increased as shown in Figure2.26.
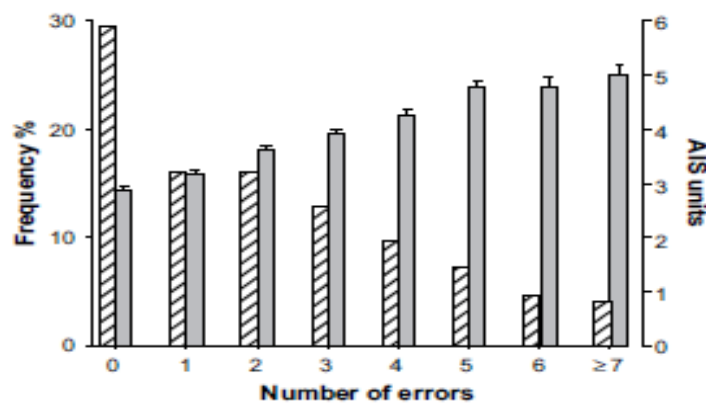
Figure 2.26. Misuse of MDIs is directly linked to decreased asthma stability. (Giraud & Roche, 2002).

In childhood asthma Kemps et al (2003) reported that the inhaled corticosteroid dose was decreased during detailed clinic management of children with asthma and the only other change was that their inhaler technique had improved. Another study involving asthmatic children reported that there was a significant improvement in their inhalation technique and their overall asthma severity scores when a good technique was used (Minai et al, 2004). In adult asthmatics that were trained to use a slow inhalation flow with good co-ordination a clinically significant improvement in

their asthma quality of life, of 0.74, was reported (Al-Showair et al., 2007a). In a real life study associations between inhaler misuse and an increased risk of hospitalisation ($p=0.001$), emergency room visits ($p<0.001$), courses of oral steroids ($p<0.001$) and antimicrobials ($p<0.001$) as well as poor disease control ($p<0.00001$) have been reported (Melani et al, 2011).

Therefore, many recommendations have been published stressing the fact that patients should be trained how to use their inhalers efficiently and that there dose or inhaler should not be altered unless their inhaler technique as well as their level of compliance has been assessed (GINA, 2011; BTS/SIGN 2011).

2.3.1.1.(f) Improving Inhalation Technique for pMDI and Training Tools

The correct inhalation technique by patients is vital for efficient drug delivery, and so, it is important to improve inhalation technique to achieve the optimum therapeutically outcome with minimal side effects. Improving inhaler technique by patients is crucial, resulting in an increase in the effectiveness of response (Orehek et al., 1976). Paterson and Crompton as early as 1976 have emphasised that patients should be trained how to use a pMDI correctly in order to get maximum benefit. Training patients can significantly improve the pMDI technique. Gayrard and Orehek (1980) illustrated that only 28% of untrained patients demonstrated adequate technique with a pMDI compared to 52% that had been trained. Also, Horsley and Bailie (1988) found that the correct pMDI technique increased from 31% before counselling, to 72% immediately after counselling (Horsley and Bailie, 1988). A number of studies have suggested that pMDI techniques training significantly improve a patient's technique through the pMDI compared to leaving the patient to study the PIL (Patient Information leaflet) only (Crompton and Duncan, 1989; Nimmo et al., 1993). Demonstrations with verbal instruction have shown a

significant improvement of pMDI technique with asthmatic children (Kamps et al., 2000) leading to reduced inhaled corticosteroid doses (Kamps et al., 2004). However, in a study of 100 adults tested for their ability to use six different inhalers only 21% were found to use their inhaler efficiently following instructions associated with the inhaler (Lenney et al., 2000). It has been found that even after pMDI technique counselling and subsequent demonstration by patients, only 50% used their pMDI correctly soon afterword (Shim and Williams, 1980). Another study has shown that using a multimedia programme for training inhaler technique was as good as using the PIL (Savage and Goodyer, 2003). A pMDI should only be prescribed to patients who have demonstrated that they can use it correctly. This problem is compounded by the fact that with time many patients lose the ability to use their pMDI correctly (Shim and Williams, 1980) and thus many patients revert back to an incorrect inhalation technique within a short period (Duerden and Price, 2002; Crompton, 2006; Lavorini et al., 2010). The patient's inhalation technique should be checked regularly and they should receive repeated counselling and monitoring during follow up (Kamps et al., 2000; Crompton and Barnes, 2006; Broeders et al., 2009) so that there is improved disease control (Haughney et al., 2008).

A number of inhalation training aids have been introduced to help patients use their inhalers correctly, these include; the Aerosol Inhalation Monitor (AIM, Vitalograph, Ltd, Buckingham, UK), the 2Tone Trainer™ (Canday Medical Ltd, UK) and the In-Check Dial (Clement Clarke Ltd, UK).

2.3.1.1.(i).1 Aerosol Inhalation Monitor

The Aerosol Inhalation Monitor (Vitalgraph Ltd, UK) is an electronic device that is attached to a placebo pMDI. It measures the patient's inspiratory flow rate and monitors co-ordination. The required inhalation flow is 10-50 L/min and good co-

ordination is related to this flow when the canister is depressed. The operator provides a subjective assessment of breath hold by pressing a button when the patient comes to the end of this. The AIM is programmed to accept a minimum 5 second hold between the end of the inhalation and the end of the breath hold. Feedback is by a green or red light system for coordination, flow and breath-hold.

The device has been used in many studies to assess patients' inhalation technique with a pMDI (Wilson et al., 1997; Wilson and Lipworth, 1999). A significant increase in the percentage of correct pMDI technique was found after patient's were trained with the aerosol monitor (Skaer et al., 1996). In acute asthma the device has been used to verify correct inhalation technique of patients and as a trainer aid with variable success (Lavorini et al., 2010). A practice based study by Hardwell et al (2010) reported that a majority of asthmatic patients were unable to use pMDIs correctly (inadequate co-ordination and inhale too fast) and the training did not improve their techniques (Hardwell et al., 2010). In contrast a community pharmacy study reported that only 2 out of 33 patients used their inhaler correctly according to the AIM and after training sessions this increased by a further 15 patients (Sarvis et al., 2004).

2.3.1.1.(ii).2 2Tone Trainer™

The 2Tone Trainer™ (Canday Medical Ltd) is a training tool to help slow the inhalation flow rate when using a pMDI. This training device is a simple plastic tool of similar shape and size to that of a pMDI but without a canister as shown in Figure 2.27. Instead of a canister there are two ''reeds'' inside the device. These reeds are designed to make a one tone sound when the inhalation flow rate exceeds 30 l/min. Below 30 l/min, there is no noise and the inhalation flow is classified as too slow.
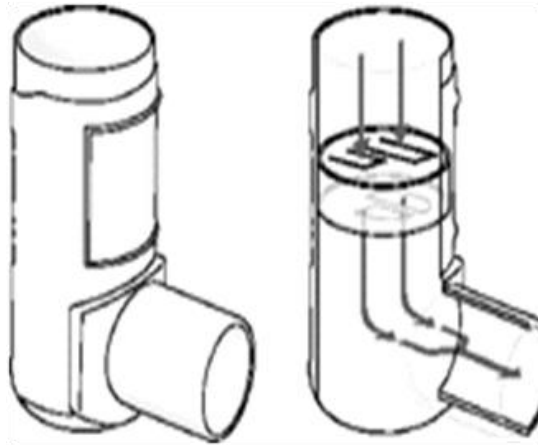
Above 60 l/min, the second reed is triggered producing a two- tone noise (high pitch) and this is classified as too fast. Between 30-60 l/min (the ideal inhalation flow rate through the pMDI) there is only the one tone sound that defines correct inhalation flow.

Figure 2.27. The 2Tone Trainer (adapted from Al-showair et al 2007a)

In a clinical study by Al-Showair et al (2007a) the potential of the 2Tone Trainer for improving the pMDI technique of asthmatic patients was demonstrated. In this study there were 3 groups: those with good pMDI technique without training (these demonstrated good co-ordination and inhalation flow < 90L/min) – GT Group, one group with inhalation flows of > 90L/min that received verbal pMDI technique training before they left the clinic – VT group and a final group (2T) that inhaled with flows > 90L/min and received pMDI training plus the 2Tone trainer to practice with before they left the clinic.

Figure 2.28 shows that inhalation flow in the 2T group decreased significantly more than those in the VT group whilst those in the GT group remained unchanged. The reduction in flows in the 2T group were accompanied by a decrease in the Asthma Quality of Life score by > 0.5, as shown in Figure 2.29 indicating a significantly clinical improvement in asthma control.
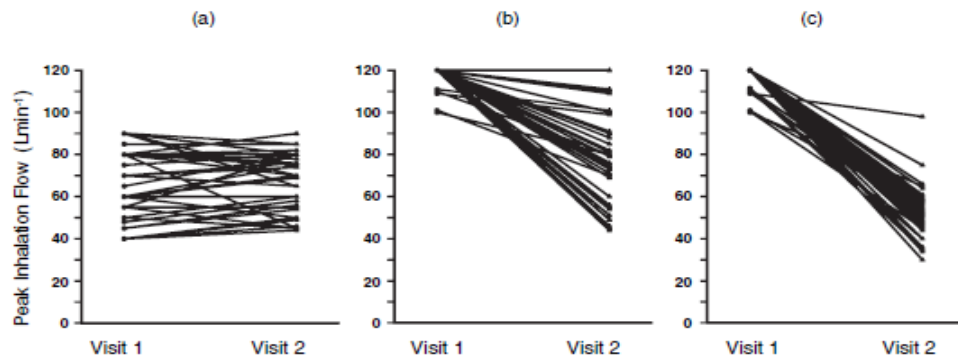
Figure 2.28. The PIF of each individual using an MDI in the (*left*, *a*) GT group, (*middle*, *b*) VT group, and (*right*, *c*) 2T group (Al-Showair et al., 2007a).
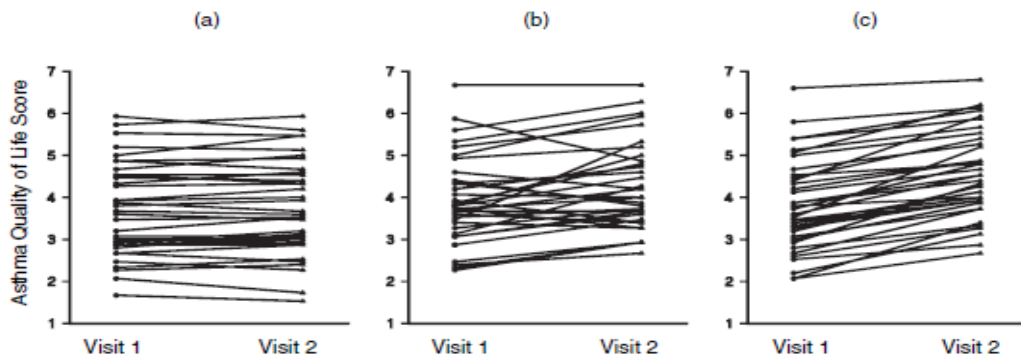
Figure 2.29. The AQLQ score of each individual using an MDI in the (*left*, *a*) GT group, (*middle*, *b*) VT group, and (*right*, *c*) 2T group (Al-Showair et al., 2007a).

2.3.1.2 Dry Powder Inhalers (DPIs)

Dry powder inhalers (DPIs) were originally introduced in order to avoid the known environmental problems of the CFC propellants and the poor inhalation technique associated with pMDIs (Vidgren et al., 1988; Prime et al., 1999; Tarsin et al., 2006; Virchow et al., 2008). All DPIs are breath-actuated, so patients do not have to coordinate between inhalation and actuation, therefore many patients find DPIs much easier to use than pMDIs (Bisgaard, 1997; Cegla, 2004; Virchow et al., 2008) and a convenient alternative for some patients.(Svedmyr et al., 1982).

The first portable DPI introduced to the market was the Spinhaler® (Fisons) in 1970 for the delivery of disodium cromoglycate (Bell et al., 1971; Sanders, 2007).

The first salbutamol DPI was the Rotahaler (GlaxoSmithKline, UK) which was introduced in 1977 (Hetzel and Clark, 1977). Both these devices were a single-dose system with a hard gelatine capsule containing a formulation of the dose. This was followed by the Diskhaler (GlaxoSmithKline, UK), in 1980 that contained formulations of salbutamol, beclometasone dipropionate and later salmeterol xinofoate formulations sealed inside a blister. A disk containing 4 or 8 blisters was inserted into the inhaler by the patient and replaced when all the blisters were empty. Other DPIs were also introduced to the market using different dosing principles. The Turbuhaler (AstraZeneca, UK) which was launched containing budesonide, in 1988, was the first multi reservoir-type device (Wetterlin, 1988). The Diskhaler was followed by the Accuhaler (GlaxoSmithKline, UK), known as the Diskus outside the UK, in 1994 as a multi-unit dose system (Pover et al., 1988) that contains the sealed blisters, containing the formulation, on a strip inside the device. Other multiple dosing reservoir DPIs followed (Clickhaler, Easyhaler Pulvinal, Novolizer and Twisthaler) all with different dose emission characteristics (Chrystyn, 2006). On the basis of these historical developments, DPIs are often classified depending on the device design, whether a single-dose, multi-dose or multi unit dose (Srichana et al., 1998).

DPIs are breath activated, so coordination of inhalation and actuation is not required and this makes them easier to use compared to a pMDI. Switching patients that have difficulty with coordinating pMDIs to DPIs has resulted in an improvement in outcomes (Borgstrom et al., 1994). However, breath actuation can be also be a disadvantage for DPIs because an initial highly inspiratory flow rate is required to

de-aggregate the formulation of a dry powder inside the DPI into respirable particles. Hence a forceful inhalation is required (Borgstrom et al., 1994). During an inhalation each DPI requires a certain minimum inspiratory flow to produce respirable particles and this could be an important potential limitation of DPIs as mentioned in the Table 2.14 (below). Studies have shown that patients with asthma especially (pre-school) children (Pedersen et al., 1990) and those with COPD (Al-Showair et al., 2007b) have problems achieving these minimum flows through some DPIs and that inhalation flow is reduced during acute exacerbations (Bentur et al., 2004). The recommended technique for DPIs is a forceful, deep inhalation (Fink, 2000; Anderson, 2001; Laube et al., 2011) from the start that is maintained for as long as possible (Laube et al., 2011). The main advantages and disadvantages of DPI are presented in Table 2.14.

Table 2.14. Advantages and disadvantages of dry powder inhalers (adapted from Chrystyn & Price 2009a).

Advantages of DPIs	Disadvantages of DPIs
Breath-actuated and so no need for patient coordination required	Some are single dose
	Some need to be shaken before use
	Dose preparation errors can be critical mistakes
No propellant	Attention required to orientation of inhaler during and after (before inhalation) dose preparation
Most have dose counters	Flow dependent dose emission
Short treatment time	Needs a fast acceleration rate at the start of the inhalation
Small and portable	Poor quality (or no) dose emitted if inhalation flow is too slow
	Uncertainty of dose emission during acute exacerbations
	Can result in high oro-pharyngeal deposition
	More expensive than MDIs
	Need to be stored in a cool and dry place

2.3.1.2.(a) De- aggregation of the formulation in a DPI

In DPIs, the drug is formulated as finely micronized particles in a reservoir, blister or gelatine capsules. To ensure the likelihood of drug deposition in the airways during an inhalation then particles $< 5\mu m$ need to be emitted from an inhaler. In general these particles do not have good flow properties because of their size, their surface is not smooth and the surface has a static charge. All these lead to poor powder flow properties whereas good powder flow is required for the formulation in a DPI. Good powder flow is essential during manufacture to ensure consistent and reproducible filling of inhalers or dose measuring for capsules and blisters. DPIs that are designed with a reservoir to contain the formulation and dose metering occurs prior to patient use also require good flow properties to ensure that dosing is accurate and consistent. The formulation for a DPI is therefore modified to improve its flow properties. Often the micronized active drug is mixed with large inert carrier particles, normally lactose, which prevents aggregation and improves the flow of the formulation. Some reservoir DPIs, notably the Turbuhaler, do not contain a coarse carrier and their drug particles are formulated as spheres which have good flow properties. When the dose is low (e.g. formoterol) then lactose is used as bulking agent when the spheres are formulated for the Turbuhaler.

Currently, all DPIs are breath activated devices and rely on the inspiratory effort of the patient to release the powder dose from the metered cup, the dosing disk, the blister or the capsule. The same inspiratory effort also provides a turbulent energy (measured as a pressure change) source inside the inhalation channel of the DPI between the exposed dose (after dose preparation) and the exit of the mouthpiece. This energy is created inside the inhaler by the interaction between the internal

resistance of the DPI and the inhalation flow (Clark and Hollingworth, 1993) according to the relationship.

$$\sqrt{P} = Q \times R$$

Where P is the turbulent energy, Q is the inhalation flow and R is the resistance. The turbulent energy is represented by a pressure change inside each DPI during the inhalation manoeuvre. Pressure is measured by various units (all are related) with kilopascals (kPa) used for DPIs although cmH_2O are sometimes used (1kPa=10.1972 cmH_2O). Hence DPIs are classified as passive inhalers. This energy breaks up (de-aggregates) and transforms the metered powder formulation (drug-carrier) into an emitted dose that contains a FPD and MMAD that have the potential for lung deposition (Chrystyn, 2003; Chrystyn, 2009). Figure 2.30 described the process of de-aggregation in the inhalation channel of a DPI.
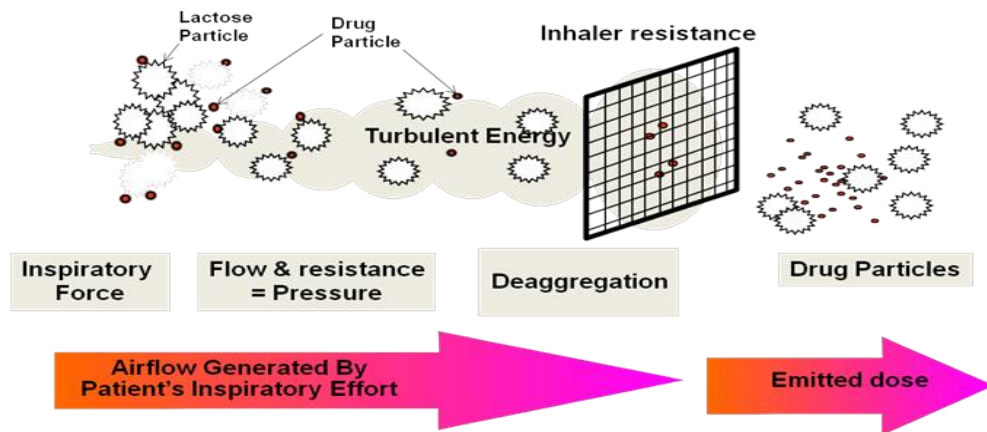
Figure 2.30. Schematic design of the de-aggregation of the metered DPI dose during an inhalation (Chrystyn, 2003).

The large carrier particles, such as lactose, emitted after the de-aggregation will impact in the mouth and the oro-pharynx and be swallowed. A sufficient inhalation flow rate (IFR) should be generated during an inhalation to create an internal turbulent energy that is capable of de-aggregating the formulation and generating a

respirable dose from each DPI device (Pitcairn et al., 1994; Srichana et al., 1998; Barnes, 2000a; Broeders et al., 2003a; Broeders et al., 2003b; Virchow et al., 2008) The faster the inhalation flow through a DPI then the greater energy will provide more efficient break-up of the formulation (Chrystyn, 2003)

2.3.1.2.(b) DPI internal resistance

The internal resistance of a DPI is a consequence of its design, and contains elements of flow restriction to increase the kinetic energy of the air flow through the device during an inhalation. Local pressure drops or high air velocities are necessary for adequate de-aggregation as well as dose entrainment in the inhaled airstream from the metering cup inside the DPI. The resistance of a DPI can be classified with respect to the inhalation flow required to produce a pressure drop of 4kPa with an inhalation of 4 litters and can be measured using the above equation by altering the flow (from 10 to 100 L/min) and measuring the corresponding pressure drop. Each type of DPI has its own unique resistance which ranges from those with high to low (Clark and Hollingworth, 1993; Laube et al., 2011) as shown in Figure 2.31.
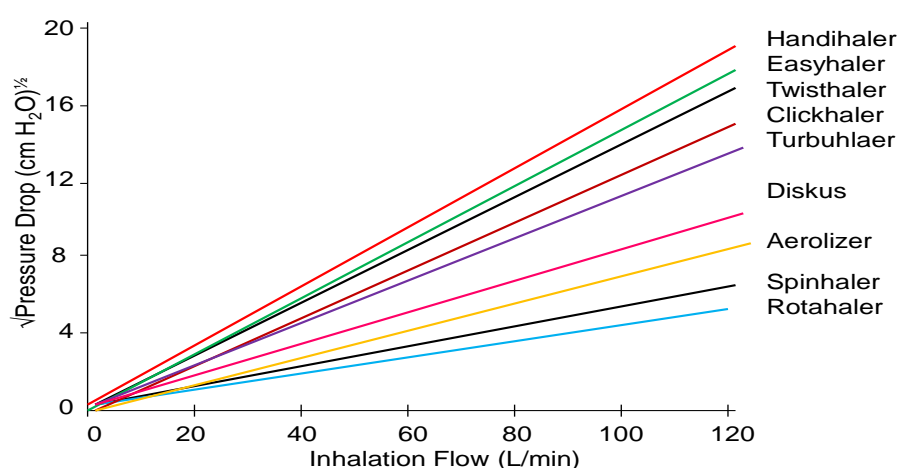
Figure 2.31. The resistance of different dry powder inhalers (Chrystyn, 2009)

The figure confirms why Laube et al (2011) classified the resistance of DPIs from low (Aerolizer) to medium (Accuhaler) into medium/high (Turbuhaler) then to high (Easyhaler). Figure 2.32 also reveals that for a set turbulent energy the flow required through a DPI with low resistance will be faster than that required through a DPI with high resistance. This is a concept that is misunderstood by many because they focus on flow in isolation whereas it is turbulent energy that is important. The higher the resistance and the greater the patient's airflow obstruction then the lower will be their inhalation flow as shown in Table a 2.15 and Figure 2.32 (Chrystyn, 2009). Thus low flow does not necessarily translate to inadequate turbulent energy and de-aggregation during patient use.

Table 2.15. Mean (SD) inhalation flows achieved by patients (classified according to the severity of their disease – mild, moderate and severe) using different inhalers. N is the number of patients, age is reported in years and inhalation flows in L min^{-1}.

	ASTHMATIC CHILD			ADULT ASTHMATIC			COPD		
Severity	MILD	MOD	SEV	MILD	MOD	SEV	MILD	MOD	SEV
N	101	20	8	7	10	13	34	36	25
Age	10.5 (4.2)	9.5 (3.6)	10.3 (3.2)	48.3 (14.7)	53.3 (19.7)	66.0 (10.0)	78.5 (10.2)	75.6 (9.4)	72.6 (9.9)
MDI	112(16)	98(24)	109(18)	>120	111(15)	106(16)	102(21)	100(23)	95 (28)
Aerolizer	102(22)	82 (26)	91 (16)	108(16)	84 (22)	81 (23)	69 (21)	72 (24)	64 (22)
Diskus	87 (23)	71 (23)	80 (17)	92 (19)	71 (22)	70 (21)	60 (17)	63 (21)	56 (16)
Turbuhaler	72 (17)	58 (18)	66 (12)	76 (21)	56 (19)	54 (18)	47 (13)	48 (16)	43 (14)
Clickhaler	73 (16)	57 (16)	65 (11)	72 (21)	54 (18)	53 (18)	47(13)	48 (17)	42 (14)
Twisthaler	58 (12)	47 (14)	53 (10)	60 (18)	45 (16)	44 (15)	39 (11)	40 (14)	35 (11)
Easyhaler	54 (11)	43 (14)	49 (7)	55 (13)	40 (12)	40 (12)	33 (10)	35 (13)	31 (10)
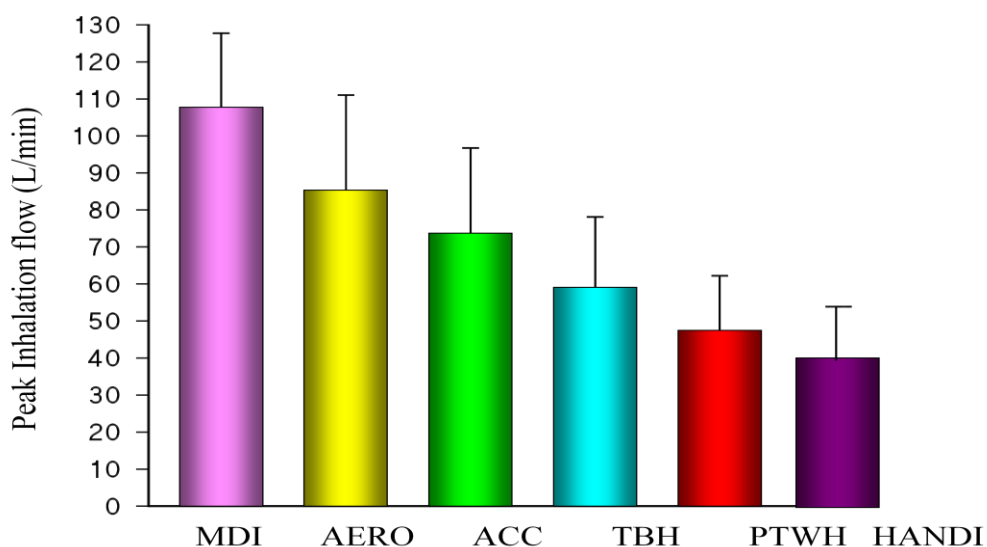
Figure 2.32. Mean (SD) peak inhalation flows of asthmatic patients through different DPIs (AERO – Aerolizer, ACC – Accuhaler, TBH – Turbuhaler, PTWH – Twisthaler, HANDI – Handihaler).

Several, studies have shown that DPIs with a higher resistance provide more lung deposition than those with a lower resistance (Clark and Hollingworth, 1993; Chrystyn, 2009). This is due to the effects of inhaling against a resistance (Borgstrom, 2001). It could be also be due to the momentum of particles inhaled in that during a slow inhalation less will be deposited in the oro-pharyngeal zone and more will penetrate into the peripheral areas of the lungs.

2.3.1.2.(c) Flow dependent dose emission

The above equation of Clark and Hollingworth (1993) describes that for the same DPI then the faster the inhalation flow then the greater will be the generated turbulent energy. This will lead to more efficient de-aggregation of the dose. Ross and Schultz (1996) reported that dose emission from a salbutamol pMDI was not affected by flow but there was a difference between the dose emission from a salbutamol Diskhaler when using a slow and a fast flow as shown in Figure 2.33.

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They reported similar results for a salbutamol Rotahaler and a terbutaline Turbuhaler.
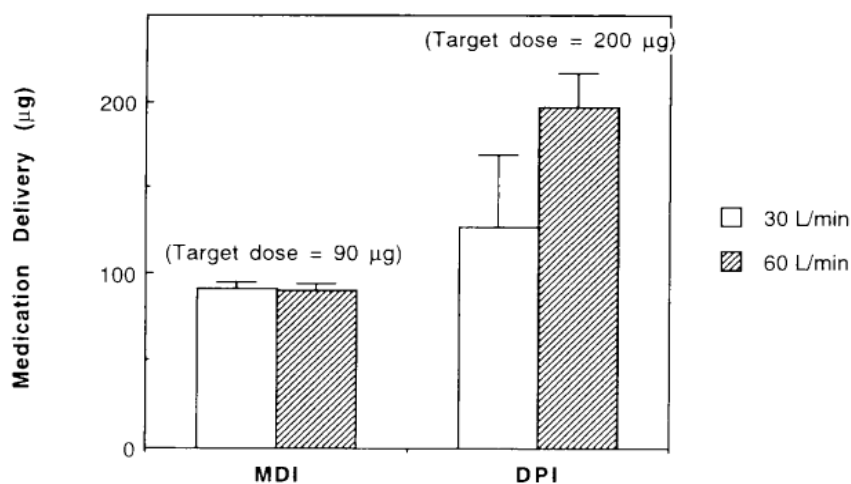
Figure 2.33. Mean (SD) dose emission from a salbutamol pMDI and Diskhaler at different inhalation flows (Ross & Schultz, 1996).

Hill and Slater (1998) highlighted that de-aggregation was inhalation flow dependent by reporting a higher fine particle dose with flow from an Accuhaler and a Turbuhaler. De Koning (2001) investigated the effect of both PIF and IFR on more than one DPI device and concluded that the Turbuhaler is highly sensitive to IFR, producing a maximal fine particle fraction of 50% of label (budesonide) at 60L/min, while 23-33% for the fluticasone Diskus. Also he observed that the Accuhaler and Cyclohaler are only slightly IFR dependent (de Koning, 2001). A further study conformed the greater flow dependent dose emission from the Turbuhaler compared to the Accuhaler and the Easyhaler (Palander et al., 2000) and from a single capsule DPI, the Aerolizer (Weuthen et al., 2002).

An ex-vivo study by Tarsin et al (2006) also confirmed these results by reporting that the respirable dose emitted from the Seretide® Diskus was more consistent and independent of IFR, while that from the Symbicort® Turbuhaler DPI (AstraZeneca,UK) was more dependent on the patient's inhalation flow (Tarsin et al.,

2006). In this study the authors collected electronic profiles of severe asthmatics when they inhaled through a Seretide Accuhaler and a Symbicort Turbuhaler and then replayed these in the electronic lung. They showed the de-aggregation changes with flow by reporting the FPDs and MMADS as shown in Figure 2.34 and 2.35.
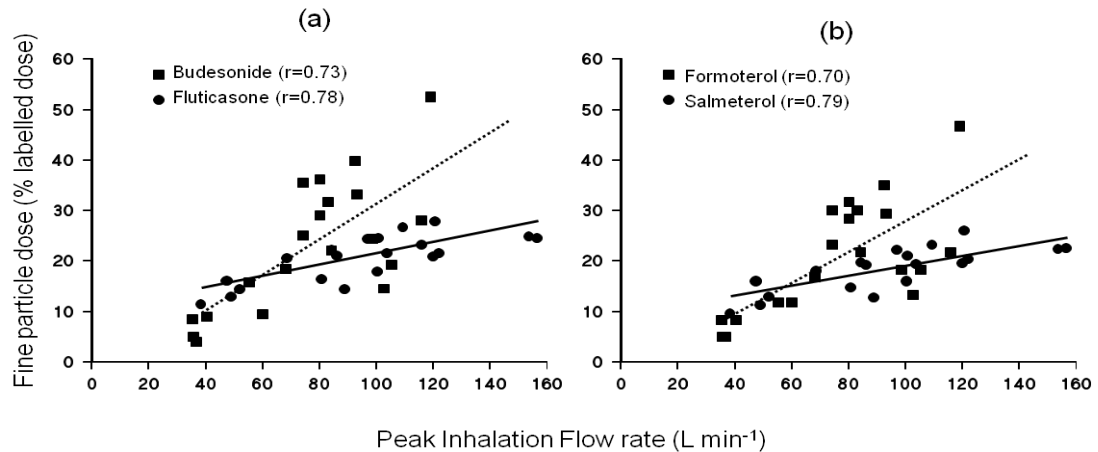
Figure 2.34. The fine particle dose emitted from (a) Symbicort Turbuhaler and (b) Seretide Accuhaler when each electronic profile was replayed in the electronic lung (Tarsin et al, 2006).
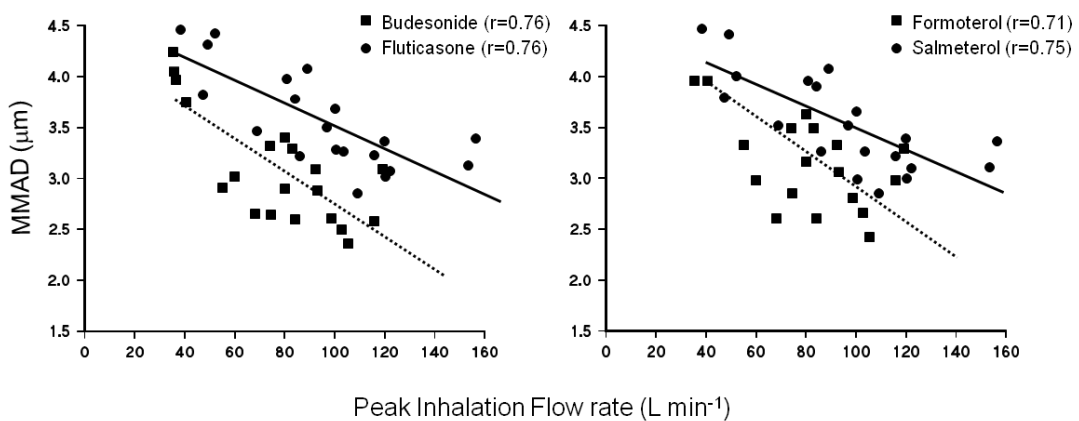
Figure 2.35. The mass median aerodynamic diameter of the dose emitted from (a) Symbicort Turbuhaler and (b) Seretide Accuhaler when each electronic profile was replayed in the electronic lung (Tarsin et al, 2006).

The flow dependent dose emission phenomena have led to a debate on the optimal inhalation flow for each device and many studies have been carried out on how patients can/cannot achieve this flow. It has been shown that the in-vitro dose

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emission characteristics translate to flow dependent lung deposition as shown in Figure 2.36 (Newman et al, 1991; Borgstrom et al, 1994).
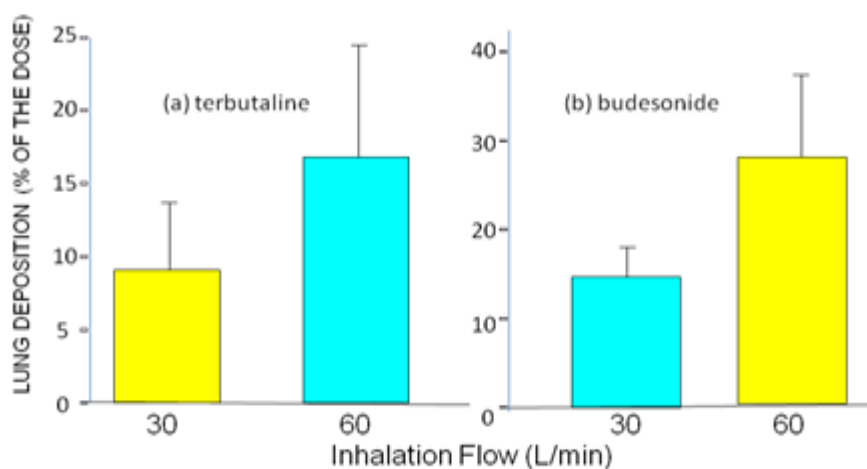
Figure 2.36. Mean (SD) flow dependent lung deposition from a Turbuhaler (a) terbutaline (Newman et al, 1991) and (b) Budesonide (Borgstrom et al, 1994).

The studies in figure 2.36 revealed no charge in the peripheral: central lung zone ratios. The small MMADs with high flow will counteract the increased tendency for more central the lung deposition

Differences in the in-vitro and in-vivo lung deposition results were show to translate to different clinical response (Nielsen et al., 1997). However some response was obtained at low flows. Therefore the argument about flow dependent dose emission is not clinically relevant. More importantly there is a flow below which de-aggregation of the dose is inefficient as shown by the in-vitro study reported by Nadarassan et al (2010) that is shown in Figure 2.37. This study used a formoterol Turbuhaler.
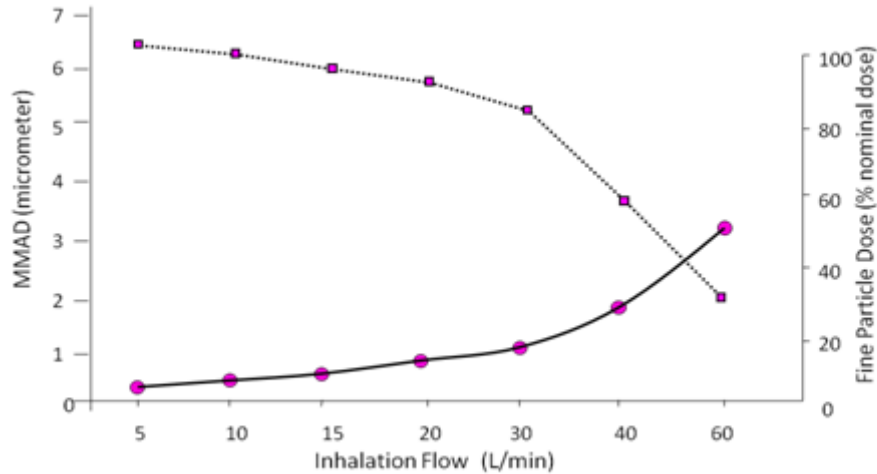
Figure 2.37. The effect of flow on the MMAD (dashed line) and the FDP (continuous line) of formoterol from a Turbuhaler (Nadarassan et al., 2010)

The above figure shows that for the Turbuhaler there is a flow below which the de-aggregation of the dose is inefficient. This is highlighted by marked change in the MMAD and the FPD below 30L/min. A patient study, involving asthmatic children, measuring FEV_1 response to inhaled terbutaline confirmed the in-vitro results in that there is a critical flow below which de-aggregation occurs. The results of this clinic study are described in Figure 2.38 (Pedersen et al, 1990).
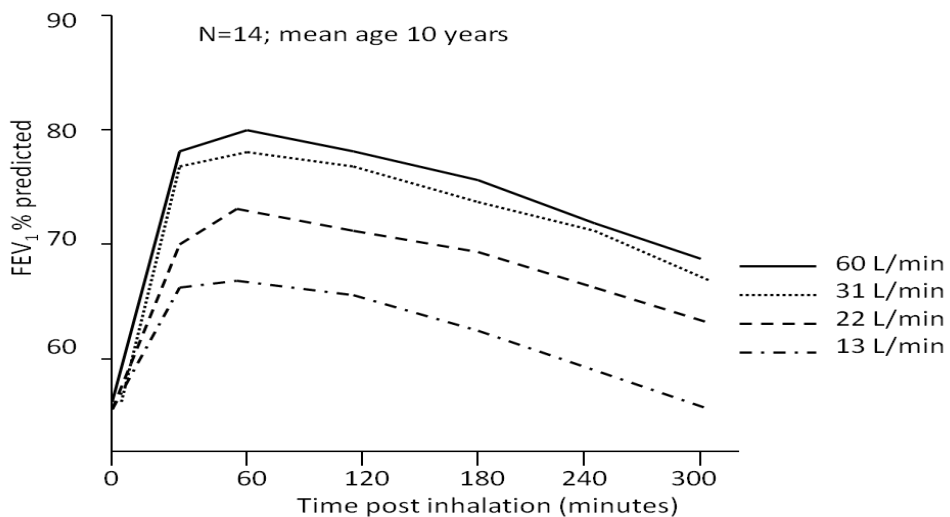
Figure 2.38. Mean response post inhalation of terbutaline from a Turbuhaler at different inhalation flows.

The above figure also demonstrates that caution should be exercised when interpreting bronchodilator results in studies using inhalers. Figure 2.38 clearly shows the lack of a difference between the 30 and 60 L/min results suggesting measurements at the top of the dose response curve. The main issue with respect to flow from a DPI is the rate below which therapeutic response is reduced (Laube et al, 2010). The Easyhaler (Koskela et al., 2000) and Clickhaler (Newhouse et al., 1999) have both been shown to be effective at inhalation flows below 30 L/min. Both these DPIs have a higher resistance than the Turbuhaler and so the turbulent energy equivalent to that in a Turbuhaler will be achieved at lower flows. This observation consolidates why inhalation flows should not be considered in isolation and that it is irrelevant to compare a low flow through a high resistance DPI directly to a faster flow through a DPI with low resistance (Azouz and Chrystyn, 2012). Neilsen et al (1998) reported that the Accuhaler was clinically effective at flows of 30L/min while for the Handihaler (Chodosh et al., 2001) this is probably below 30 L/min whereas >90 L/min needs to be achieved through the low resistance Aerolizer (Nielsen et al., 1997).

2.3.1.2.(d) Patient inhalation flows through DPIs

Studies have shown that patients with asthma especially children (Pedersen et al, 1990) and those with COPD (Al-Showair et al., 2007b) have problems achieving these minimum flows through some DPIs and that the inhalation flow is reduced during acute exacerbations (Bentur et al., 2004). The Easyhaler has been shown to be effective at low flows even when the peak inhalation flow rate was 16 L/min because it has high resistance (Malmstrom et al, 1999). Figures 2.39 and 2.40 show the inhalation flow rates of children when they use a Turbuhaler (Pedersen et al, 1990) and an Easyhaler (Malmstrom et al., 1999).
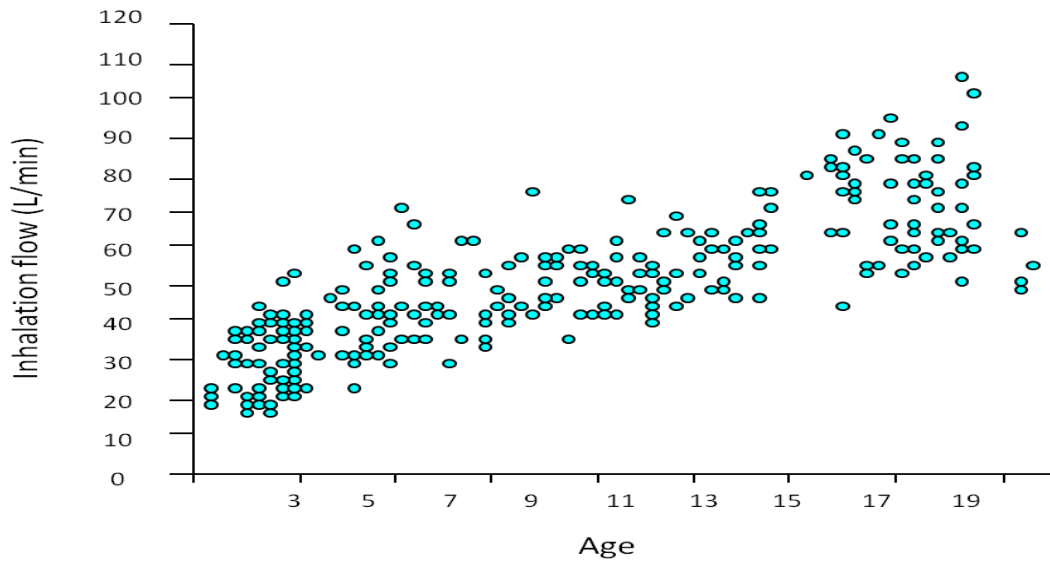
Figure 2.39. Inhalation flows of children when they inhale through a Turbuhaler (Pedersen et al, 1990).
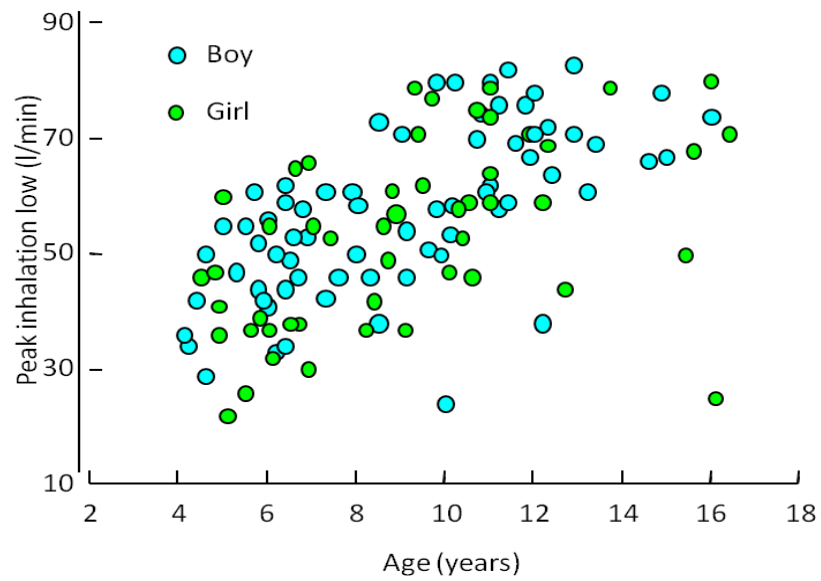
Figure 2.40. Inhalation flows of children when they inhale through an Easyhaler (Malmstrom et al., 1999).

A summary of the inhalation flows of patients through different DPIs is presented in Table 2.16.

Table 2.16. Patient inhalation flows when they use inhalers.

Patients	Comment	reference
Turbuhaler		
74 COPD	Mean FEV_1 41.9 (12.8) % predicted. Pre counselling <30, 30-40, 40-60 and >60 L/min numbers were 14, 31, 23 and 6. Post counselling these changed to 7, 16, 41 and 10.	Nsour et al, 2001.
24 Asthmatic	Mean FEV_1 57.0 (18.9) % predicted. Pre-counselling mean (SD) PIF 48.0 (16.8) and post counselling 54.7 (17.6) L/min. Inhaled volume pre and post counselling was 1.75(0.68) and 1.94(0.62) L. Time to peak 0.54(0.46) and 0.43(0.23) seconds. 5 patients <30 pre counselling and 3 post counselling	Hawksworth et al, 2000
163 COPD	Mean FEV_1 47.8 (9.9) % predicted. Mean (SD) PIF was 45.9 (14.1) l/min. Pre counselling numbers <20, 20-29, 30-59, >60 were 4, 19, 114 and 26. 84 patients verbally trained and the 15 that inhaled <30 changed to 10	Al-Showair et al, 2007
20 Severe asthmatics	Mean (SD) PEFR 52.7(6.0) % predicted. Mean (SD) PIF 76.8(26.2) L/min and inhaled volume of 2.4(0.8) Litres. Patients highly trained.	Tarsin et al, 2006
110 COPD	Mean (SD) FEV_1 of 0.70(0.21) litres and PIFR of 53(12). Maximal inhalation. zero <28 L/min. 83 generated 40-59 L/min and 32 >60L/min	Dewar et al, 1999
18 COPD	Median (range) FEV_1 54 (33-70) % predicted. Mean (range) PIF 59 (45-73) L/min and inhaled volume of 2.2 (1.39-3.42) Litres. Highly trained	(Derom et al., 2007)
48 COPD and 16 asthmatic	16 mild, moderate and severe. Mean (SD) PIF 76.0(4.6), 64.9(4.9) and 68.6 (4.1) L/min before training and 85.4(2.2), 84.4(2.7) and 73.3(4.1) post training. No one <30L/min. Slope significantly increased post training. Inhaled volumes were 2.6(0.2), 2.6(0.3) and 2.3(0.2) litres pre and 2.8(0.2), 2.9(0.3) and 2.6(0.3) post training. 10 asthmatics mean FEV_1 96(7.8) % predicted. Mean (SD) PIFR 76.9(4.6) pre and 82.1(3.4) post. Inhaled volumes of 2.9(0.3) and 3.1(0.3) litres	Broeders et al, 2003
Asthmatic children	38 aged 3-6 years.- Mean PIF was 59L/min 39 aged 7-10 years mean PIF was 70L/min	(Stahl et al., 1996)
Asthmatic children	34 aged 4 to 13 years – see figure j 15 with an acute attack (4 and 5 years old PIF range of 14-36 L/min 9 <28L/min	Pedersen et al, 1990
Asthmatic children	72 , 36 in group A – training (n=12 aged 3 , 4 and 5 years each), group B no training (n=12 aged 3 , 4 and 5 years each). Baseline PIF values – 25 inhaled <30L/min especially in 3 and 4 year old. Mean PIF after training in the 4 and 5 year olds in Group A was 46.4L/min compared to group B which was 33.2 L/min (n=24 in each age group). The latter increased to 40.4 L/min after they had been trained. In the 3 year olds group	Agertoft and Pedersen, 1998

	A 28L/min and group B 33.2 L/min.	
30 Adult asthmatics	FEV_1 88% predicted. PIF average of 68 L/min and range of 55-95 L/min	(Meijer et al., 1996)
101 Asthmatic adults	Four had a PIF <30L/min. Mean PIF was 59L/min range of 25-93 l/min	(Engel et al., 1989)
Acute asthma	99 with acute exacerbations. FEV_1 1.1(0.7) litres. Mean age 42 years. PIF with Turbuhaler was 152(77) L/min reduced to 60(20) with Turbuhaler. 2 patients less than 30 L/min (both recorded 26 L/min)	Brown et al, 1995
Accuhaler		
163 COPD	Mean FEV_1 47.8 (9.9)% predicted. Mean (SD) PIF was 57.5 (17.9) l/min Pre counselling numbers <30, 30-59, 60-90, >90 were 0, 8, 79, 69, 7. 84 patients were verbally trained and none inhaled <30 L/min	Al-Showair et al, 2007
20 Severe asthmatics	Mean (SD) PEFR 52.7(6.0)% predicted. Mean (SD) PIF 94.7 (32.9) L/min and inhaled volume of 2.8(1.1) Litres. Patients highly trained	Tarsin et al, 2006
48 COPD and 16 Asthmatic	16 mild, moderate and severe. Mean (SD) PIF 107.8.(7.2), 91.8(6.8) and 95.9(6.3)) L/min before training and 124(2.8), 121.3(3.0) and 103(6.4) post training. No one <30L/min. Slope significantly increased post training. Inhaled volumes were 3.0(0.2), 2.9(0.2) and 2.6(0.2) litres pre and 3.2(0.2), 3.1(0.2) and 2.8(0.2) post training. 10 asthmatics mean FEV_1 96(7.8)% predicted. mean (SD) PIFR 111.6(6.8) pre and 115.3(4.9) post. Inhaled volumes of 3.1(0.3) and 3.3(0.3) litres	Broeders et al, 2003
Asthmatic children	N=129 aged 3-10 only 2 <30L/min – a 5 year old and a 10 year old..	Nielsen et al, 1998
Easyhaler		
21 Asthmatics	Mean PIFR 28.7(5.1) L/min. age range 7-65 years. Lowest PIF was 22 and similar bronchodilation to MDI+spacer.	(Koskela et al., 2000)
120 + 15 Asthmatics	PEF 86(21)% predicted. 4 -16 years old. Mean (SD) PIF was 56(15) L/min range 22-82. In the 15 PIF ranged from 16-80 L/min – similar bronchodilation to 200mcg salbutamol MDI+spacer.	(Malmstrom et al., 1999)
93 COPD	Mean (range) FEV_1 51 (18-96)% predicted. The mean PIF was 54 L/min (range 26–95 L/min)	(Malmberg et al., 2010)

Handihaler		
26 COPD	Mean FEV_1 % predicted 37.6 range of 16-65. Median PIF of 30.0 with a range of 20.4 to 45.6 L/min	(Chodosh et al., 2001)
163 COPD	Mean FEV_1 47.8 (9.9)% predicted. Mean (SD) PIF was 28.6(10.0) l/min Pre counselling numbers <20, 20-29, 30-59 were 3251 and 70. 84 patients were verbally trained 20 out of 26 increased their flow >30L/min.	Al-Showair et al, 2007
pMDI		
163 COPD	Mean FEV_1 47.8 (9.9)% predicted. Median (SD) PIF was 110 (75-120) l/min. Pre training in 55 out of 84 inhaled >90 and only 7 post training.	Al-Showair et al, 2007
48 COPD and 16 Asthmatic	16 mild, moderate and severe. Mean (SD) PIF 127.9(5.5), 134.0(8.1) and 142.1(14.7) L/min before training and 118.8(3.9), 117.0(5.3) and 115.4(6.2) post training. 22% inhaled <90L/min pre and 21% after training. No one <30L/min. Slope significantly increased post training. Inhaled volumes were 2.9(0.7(, 2.6(0.2) and 2.3(0.2) litres pre and 2.9(0.7)2.6(0.2) and 2.3(0.2) post training. inhalation times of 1.7(0.1),1.6(0.2) and 1.3(0.2) seconds pre and 1.7(0.1), 1.7(0.2) and 1.5(0.1) post training. 10 asthmatics mean FEV_1 96(7.8) % predicted. mean (SD) PIFR 149.6(19.2) pre and 123.3(9.0) post. Inhaling <90L/min decreased from 17 to 13%. Inhaled volumes of 2.7(1.2) and 2.7(1.3) litres pre and post with inhalation times of 1.3(0.1) and 1.4 (0.1) seconds	Broeders et al, 2003

2.3.1.2.(e) Acceleration of flow

Since the de-agglomeration takes place inside the device before the metered dose leaves the DPI then acceleration rate at the start of the inhalation through a DPI is vital (de Boer et al., 1996; Everard et al., 1997) Hence, a fast initial rate at the start of an inhalation is crucial. This can determine the quality of the emitted dose and the FPF (Everard et al., 1997), and it has been shown that this correlates to the peak inhalation flow achieved by patients (Broeders et al., 2001).

Figure 2.41 shows two possible inhalations through a DPI that achieve the same PIF. One starts immediately and has a fast acceleration while the other starts slowly and gradually builds up to the same PIF (Chrystyn and Price, 2009b). Superimposed on this is when the dose leaves the inhaler.
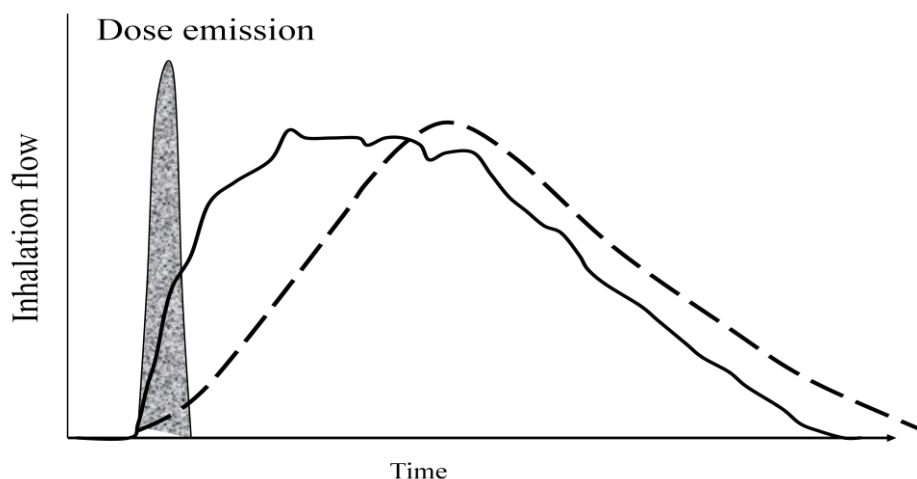
Figure 2.41. The inhalation flow against time profiles of two different inhalation manoeuvres through a DPI. The two profiles have the same peak inhalation flow. The one with the steep acceleration is a forceful inhalation from the start of an inhalation (solid line) whereas the profile with a gentler acceleration is an inhalation manoeuvre that starts slowly and gradually builds up into a flow that is as fast as possible (dashed line). Superimposed onto the profiles is the time period during which the dose is de-aggregated and emitted from the DPI. (Chrystyn & Price, 2009).

Patients should, therefore be instructed to inhale through the DPI forcefully and that this should be from the beginning of their inhalation (Laube et al., 2011).

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The inhalation profile of a patient may have an effect on the drug delivery and distribution of drug particle size (Miller et al., 2000). It is important therefore to identify the acceleration rate, inhalation flow rate (IFR) and inhalation volume (IV) when patients use DPIs because these variables may affect both the FPD and the site of lung deposition (Bell et al., 1971) and may consequently influence the desired clinical outcome (Ross and Schultz, 1996; Virchow et al., 2008). It has been shown that dose delivery and the lung deposition are determined by the patient's variable inspiratory air flow (Newman et al., 1994; Cegla, 2004).

A more forceful inhalation will result in a greater fine particle fraction (Borgstrom et al., 1994) with a smaller MMAD (Chrystyn, 2003). Each inhalation manoeuvre with a DPI should be as fast as the patient can achieve and this maximum forceful inhalation should commence from the beginning of the inhalation and continue for as long as possible (Laube et al., 2011).

2.3.1.2.(f) Dose preparation

Some DPIs are a single unit dose inhaler and therefore, the patient has to prepare a dose (capsule), prior to each inhalation as described in the PIL of the device. Incorrect performance by patients may result in them inhaling no dose irrespective of the inhalation manoeuvre they use. It has been shown that dose preparation errors frequently occur with capsule DPIs (Schulte et al., 2008). In general patients have more problems using single dose than multi-dose DPIs (Moore and Stone, 2004; Wilson et al., 2007). Also the dose from these devices is reliant on the inhalation volume to empty the dose out from the capsule thus it is important that the patient inhales twice (Laube et al., 2011). In multiple reservoir inhalers, such as the Turbuhaler, Easyhaler and the Clickhaler, the device must be kept in the upright position when the dose is metered to ensure accurate filling of the dosing cup.

A study assessed the inhaler technique of the Turbuhaler, Rotahaler, and Diskhaler and found that 40% of patients were unable to perform all steps correctly (van der Palen et al., 1995). Other studies have shown the rate of misuse of Turbuhaler ranged from 26% to 94% (van der Palen et al., 1999; Hesselink et al., 2001; Molimard et al., 2003) and confirmed that the most common mistakes when using the Turbuhaler included a failure to turn the base (not rotating the basal grip in the upright position) before inhalation. Figure 2.42 describes that there is a similar incidence of error irrespective of device although these are more common with the pMDI (Molimard et al, 2003). This study also reported that the patients' GPs were falsely confident that their patients were using the correct inhalation procedure when they used their inhalers. It is important, therefore, that prescribers are aware of the inhalation procedures for each device (Melani, 2007).
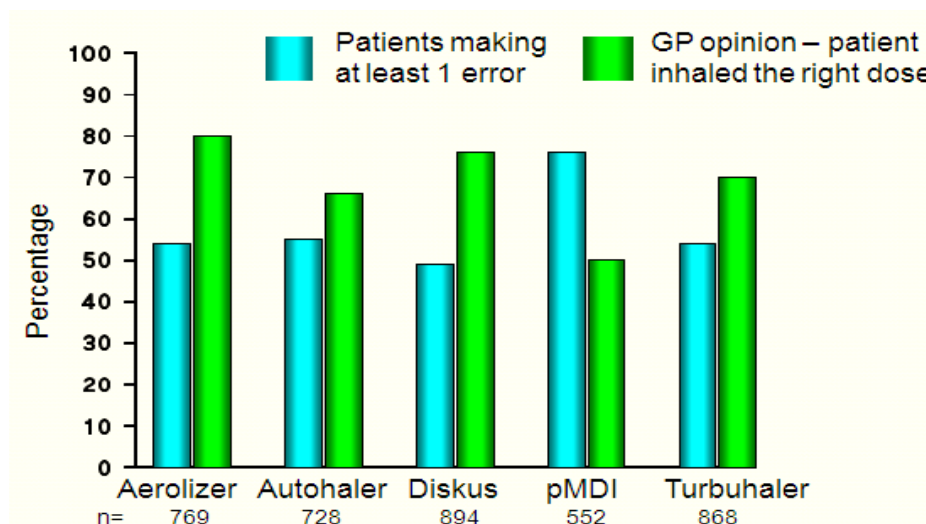
Figure 2.42. Percentage of patients making one error and the perception of their GPs adapted from (Molimard et al 2003).

Table 2.17 shows some of the common errors that patients make using DPIs (Molimard et al., 2003; Melani et al., 2011). Exhaling into the mouthpiece or/ not exhaling before an inhalation, not making a forceful inhalation and no breath hold

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were the most common errors made by patients. Also patients had problems with holding the Turbuhaler upright and twisting its base when loading a dose.

Table 2.17. Errors made by patients using DPIs in real life situations (Molimard et al, 2003; Melani et al 2011).

Inhalation procedure	Melani et al, 2011 (n=1664)			Molimard et a, 2003 (n=3811)		
	Handihaler	Accuhaler	Turbuhaler	Aerolizer	Accuhaler	Turbuhaler
Did not insert capsule	9	n/a	n/a	0.7	n/a	n/a
Did not pierce capsule	3	n/a	n/a	3.8	n/a	n/a
Did not hold upright -	n/a	n/a	23	n/a	n/a	18.1
Did not load a dose	-	7.3	14		7+2.5	
Did not rotate grip backwards and forwards	n/a	n/a	Not reported	n/a	n/a	14.9
Exhaled into the device mouthpiece	19	22	14	6.9	6.6	5.3
No exhalation	Not reported	Not reported	Not reported	32.8	26.4	25.4
Did not inhale by mouth	2	1	0	1.4	1.9	0.9
Not a forceful and deep inhalation	24	28	22	Not reported	Not reported	Not reported
Breathe out into the device	19	21	11	Not reported	Not reported	Not reported
No breath hold	25	32	28	28.4	26.4	31
No check if any dose left in capsule after an inhalation	30	n/a	n/a	n/a	n/a	n/a

Table 2.17 above shows that many patients exhaled into the DPI before an inhalation. Exhaling into a DPI following dose preparation will introduce moisture into the device and blow out the metered dose. This will increase humidity within the device which decreases dispersion of the particles, and will result in an impairment of drug delivery (Meakin et al., 1993). High humidity will affect the formulation and large agglomerates will form. These are not easy to de-agglomerate sufficiently into fine particles during an inhalation (Price et al., 2002; Young et al., 2003; Pedersen et al.,

2010) and so dose emission is reduced (Meakin et al., 1995). Moisture in the formulation will also deteriorate powder flow leading to inconsistent dose metering. DPIs should be stored in a cool dry place.

In the real life study by Melani et al (2011) they found that independent of the inhaler older age ($p=0.008$), lower schooling ($p=0.001$) and the lack of inhaler technique training ($p<0.001$) was linked to inhaler misuse. This was also associated with an increased risk of hospitalisations ($p=0.001$), and poor asthma control ($p<0.001$) as well as more courses of oral steroids ($p<0.001$) and antimicrobials ($p<0.001$). It has been suggested that many healthcare professionals, including physicians, pharmacists, nurses, and respiratory therapists, lack sufficient knowledge on the correct use of pMDIs and DPIs (Self et al., 2007; Kim et al., 2009). Consequently, healthcare professionals should be instructed and trained in the use of each individual device (Broeders et al., 2009) Patient education as well as training in inhaler use is crucial for the effective treatment and long-term control of asthma and COPD (Melani, 2007; Kim et al., 2009). Table 2.18 describes the accepted generic inhalation technique instructions when using a DPI (Laube et al., 2011). Of these the dose preparation instructions are specific for each type of inhaler. Hence, the recommendation for the dose preparation is to refer to the Patient Information leaflet.

Table 2.18. The most ideal inhaler technique for DPIs (Laube et al., 2011).

No	Most desirable inhaler technique
1	Take the cap off (some do not have a cap).
2	Follow the dose preparation instructions in the PIL.
3	Do not point the mouthpiece downwards once a dose has been prepared for inhalation because the dose could fall out.
4	Exhale slowly, as far as comfortable (to empty the lungs). Do not exhale into the DPI.
5	Start to inhale forcefully through the mouth from the very beginning. Do not gradually build up the speed of inhalation.
6	Continue inhaling until the lungs are full.
7	At the end of the inhalation take the inhaler out of the mouth and close the lips. Continue to hold the breath for as long as possible, or up to 10 s.
8	Breathe normally.
9	If another dose is required, repeat steps 1–8.

Health care professionals should ensure that the patient is able to use their inhaler effectively (Crompton et al., 2006). Also, physicians must ensure that a convenient device is prescribed for each individual patient with appropriate instructions and that it is an inhaler that they can and will use (Laube et al, 2011). Moreover, regular checking of the patient's inhalation technique is essential, because inhaler technique tends to deteriorate over a period of time (Lavorini et al., 2010). Hence a review of each patient's inhalation technique should be a regular component of follow-up care. Educational and motivation programs are also useful as a supplement to ensure correct inhaler technique. (Lavorini et al., 2010).

To help train patients to use a fast inhalation then the IN-Check Dial (Clement Clarke International, UK) is a useful aid. It does show the patient's IFR through different DPIs and its helps the healthcare professional to prescribe the most appropriate inhaler for individual patients (Chrystyn, 2003).

2.3.1.2.(g) The IN-Check Dial™

The IN-Check Dial® (Clement Clarke Ltd., UK) is a simple and portable instrument that is similar to a Peak Expiratory Flow Meter except that patients have to inhale forcefully through the device instead of using a forced exhalation. Figure 2.43 shows that the IN-Check-Dial has two parts; an inspiratory flow meter calibrated with a range of inspiratory flow rates (15 to 120 L/min), and a rotating dial mouthpiece that selects a different resistance corresponding to the Autohaler (3M Health care), Accuhaler (GlaxoSmithKline, UK), the Easi-Breath (Teva Pharmaceuticals, UK), Clickhaler (UCB Pharma, UK) and Turbuhaler (AstraZeneca, UK). The instrument has been designed to measures IFR by setting the meter's dial to mimic the internal resistance of a number of DPIs (Van der Palen, 2003; Crompton, 2004).

Figure 2.43. The In-Check Dial® (Clement Clarke Ltd., UK) and The rotating dial to select inhaler resistance (Lavorini et al., 2010).

Although it is claimed that this tool can identify the most appropriate inhaler device for patients based on their ability to learn and achieve an optimal flow rate (Broeders et al., 2003b; Chrystyn, 2003; Van der Palen, 2003; Amirav et al., 2005) it is not a device selection tool because there is no clinical evidence to support this (Azouz and Chrystyn, 2012). Although, the IN-Check-Dial does not measure the initial acceleration of the inhalation, studies have shown that this correlates with PIF when

patients use DPIs provided that they start with a maximal acceleration of their inhalation flow (Broeders et al., 2003a; Lavorini et al., 2010). There is a red disk indicator that moves along the tube to the fastest flow achieved and thus observation of this can identify an immediate forceful inhalation manoeuvre.
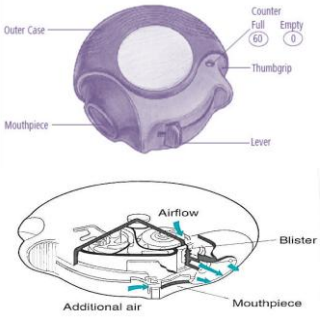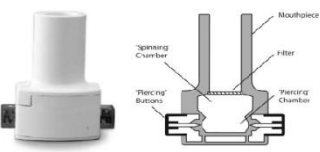
The IN-Check Dial was found to correlate to electronic measurements of IFR (Broeders et al., 2003a; Tarsin et al., 2006). Several studies, therefore, have highlighted the potential use of the IN-Check-Dial in clinical practice to identify the optimal IFR through a DPI (Nsour et al., 2001; Van der Palen, 2003; Amirav et al., 2005). Generally, patients should be encouraged and instructed to inhale 'hard and deeply' via their DPIs (Nsour et al., 2001; Van der Palen, 2003). This is considered as a significant step towards obtaining optimum benefit from a patient's prescribed medication.
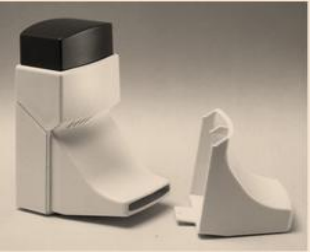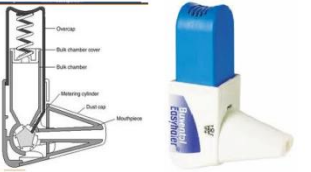
2.3.1.2.(h) Types of Dry powder Inhalers (DPIs)

Each DPI has its own unique dose preparation and resistance. In general they should not be tilted downwards once a dose has been prepared for inhalation (Laube teal, 2011) because the dose will fill out. When the DPI is presented as a single dose capsule then each dose should be inhaled using two separate inhalations. Information about some common DPIs available in the UK is provided in Table 2.19.

Table 2.19. Types of Dry powder Inhalers (DPIs).

Inhaler	Type	Resistance	Drugs (UK)	Dose preparation	Comments
Accuhaler					
	Single blisters, multidose	Medium	Salbutamol Salmeterol Fluticasone Salmeterol / fluticasone combination	The mouthpiece is exposed by rotating the outer case and then sliding a lever to open the delivering channel in the mouthpiece and expose the dose in blister container.	Dose emission is not entirely dependent on an individual patient's inspiratory manoeuvre (Virchow et al.,2008). Studies have suggested that the effect of flow dependent dose emission is relatively small (Palander et al., 2000: Tarsin et al., 2006) .
Aerolizer					
	Single dose capsules	Low	Formoterol	A capsule is placed in the centre of the inhaler well and it is then is pierced by pressing and releasing the button on either side of the device	Wieshammer et al (2008) and Khassawneh et al (2008) have evaluated the handling of inhaler devices and overall the Aerolizer had low error rates. In-vitro (Weuthen et al., 2002) and in-vivo (Nielsen et al., 1997) studies have shown flow dependent dose emission

Clickhaler					
	Reservoir, multidose	High	Salbutamol Beclometasone	The dose is loaded from the hopper by clicking or pressing the button on the top of the device whilst holding the inhaler upright. The Clickhaler has a dose counter and lock-out mechanism after 200 doses	Effective flow rate is within the range of 15 – 60 L/min such that the minimum flow can be achieved by children > 6 years and adults (Nantel and Newhouse, 1999; Newhouse et al., 1999). No difference bronchodilator response to salbutamol at various inspiratory flow rate (15, 30, and 60 L/min) by patients with stable asthma (Newhouse et al., 1999). Similar results were obtained in patients with COPD (Morice et al., 2000). Furthermore, another study has indicated that the majority of children $\geq$ 3 years were able to inhale reliable through the Clickhaler (Iqbal et al., 2003).
Easyhaler					
	Reservoir, multidose	High	Salbutamol Formoterol Beclometasone Budesonide	The powder flows from the drug reservoir into the metering cup, by pressing the top which fills the volumetric holes in the rotating drum.	Palander et al (2000) shown that the emitted dose and the fine particle fraction were less flow dependent from the Easyhaler and the Accuhaler than the Turbuhaler Palander et al.,(2000), and the total dose emission from the Easyhaler was fairly consistent irrespective of the inhalation flow (Chrystyn, 2006). Effective at low flows (Malmstrom et al, 1999).

Handihaler					
	Single dose capsules	High	Tiotropium bromide	The inhaler is loaded with a capsule which is placed into the capsule chamber at the centre of the device and then pierced by depressing the side button, which makes the dose ready for inhalation.	Due to its high resistance it has been suggested that patients with COPD may not able to generate a high inspiratory sufficient flow to de-aggregate the formulation and obtain bronchodilation (Chodosh et al., 2001). Using an inhalation flow lower than 28.3L /min through the Handihaler shows a decline of about 20% in the fine particle dose (Chodosh et al., 2001). Inhalation volume has been shown to be important for the dose emission of tiotropium from the Handihaler (A. Al-Fadhl, 2005). COPD patients have problems exceeding 20L/min during inhalation (Al-Showair et al, 2007).
Novolizer					
	Reservoir, multidose, Disposable cartridges	Medium	Salbutamol Budesonide	Pressing the button loads a dose. Dose is released at 35L/min. Audio and visual feedback that a dose has been inhaled	The dose has to be inhaled at a flow rate $\geq$ 35 L/min to release the dose (Kohler, 2004; Virchow et al., 2008) otherwise the patient will receive no dose and cannot prepare another dose for inhalation. Young children with stable asthma can generate relatively higher PIFs through the Novolizer (Vogelberg et al., 2004). In addition, using this device, was found to improve compliance and asthma control (Moller et al., 2003). In-vivo flow dependent lung deposition (Newman et al. 2001).
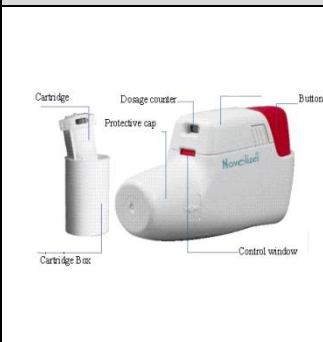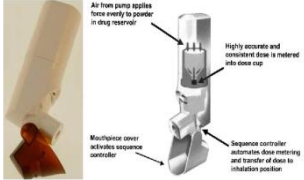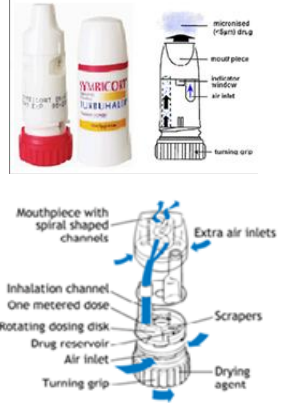
Spiromax					
	Reservoir, multidose.	Medium/ high	Not yet available	The device has an internal pump that dispenses an accurate dose using a controlled air pressure that is activated by the mouthpiece cap. The opening of the mouthpiece cover by patient also advances the dose counter (Zeng et al., 2002).	The Spiromax also contains cyclone separator channels that are designed to create turbulent flow during an inhalation and provide efficient de-aggregation of the lactose- drug particles. The in-vitro dose emission from Spiromax has been shown to be less dependent on airflow than the Turbuhaler, and has a greater dose consistency (Hirst et al., 2002). A dose handling study has found that the Spiromax was easier to use and to learn how to use compared to the Turbuhaler. (Keating and Faulds, 2002).
Turbuhaler					
	Reservoir, Multidose	Medium / high	Terbutaline Formoterol Budesonide Formoterol / budesonide combination	The formulation contains spheres of drug particles so that it has good flow properties. Lactose as a bulking agent in formoterol. Holding the Turbuhaler in an upright position and twisting the base forwards, until a click is heard, and then backwards	The particle size of the drug that is emitted depends on the patient's inspiratory flow (Everard et al., 1997). Significant flow dependent dose emission (Palander et al, 2000). In-vivo flow dependent lung deposition (Newman et al, 1991; Borgstrom et al, 1994). In-vivo bronchodilator response reduced below 30L/min (Pedersen at al, 1990). Young children with asthma (Pedersen et al, 1990 and COPD (Al-Showair et al, 2007) have problems inhaling >30L/min especially when obstruction is severe (Chrystyn, 2009)

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2.4 Patient Compliance with prescribed inhaler medication

Poor inhalation technique leads to inefficient lung deposition resulting in a reduced therapeutic effect. Of these doses preparation errors are very important because these are more likely to provide no dose whereas a poor inhalation technique would provide some response. Another critical issue is patient compliance because this result in no dose delivered to the lungs. An unused inhaler would be the most expensive inhaler. Poor compliance by a patient contributes to disease instability and may lead to a worsening with an increase in morbidity and mortality rates as well as increasing healthcare costs (Chrystyn, 2005; Rau, 2005). A review, in asthmatic patients by Cochrane (1992), indicated poor compliance among asthmatic patients ranging between 20 - 80%, whilst Hoskins et al (2000) reported 16 to 50%. During regular reviews, almost a third of asthmatic patients were not taking their prophylactic medication as prescribed (McCowan et al., 2005). The increase of time without ICS is associated with poor asthma control, and increased hospitalisation rates (Melani et al., 2011) and appears to contribute up to 61% of deaths from asthma (Rau, 2005). To improve compliance several approaches have been suggested with a recommendation of a focus to using clear instructions by healthcare personnel as well as responding to the patients and their treatment particularly their ICS (Horne, 2006). It has been shown that patient education improves compliance with ICS (Onyirimba et al., 2003). Choosing therapy and inhalers preferred by patient helps compliance especially if they find them easy to use. Patient preference is a key issue but all studies except one have been sponsored by a pharmaceutical company and hence the results are biased. The preference of patients, in the one unsponsored study, is described in Figure 2.44. This figure shows that of the seven devices which

the patients graded the BA- pMDI was the most favourable while the pMDI attached to a spacer was the least preferred inhaler (Lenney et al., 2000).
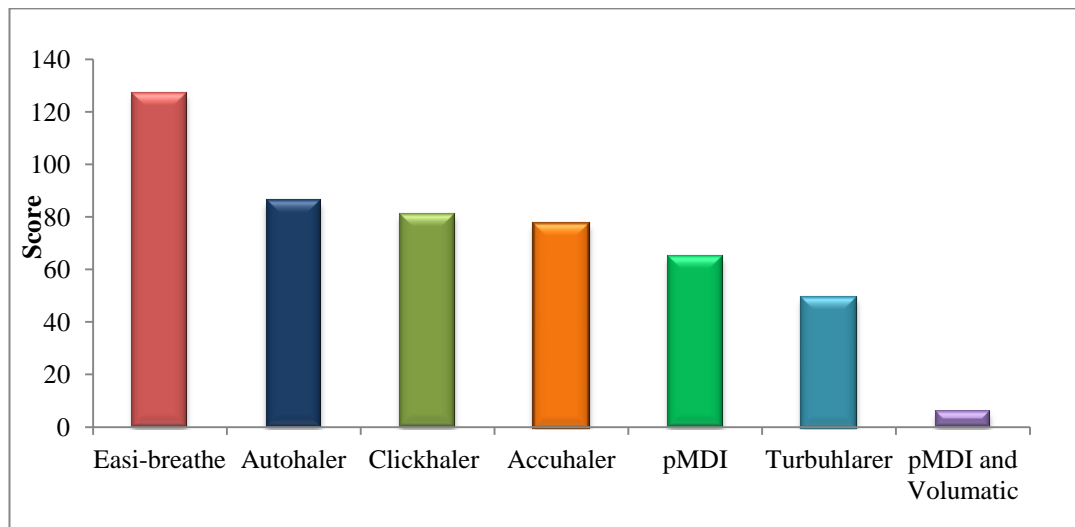
Figure 2.44. The preference of patients for seven devices by (Lenney et al., 2000)

2.5 Summary

The inhalation technique required to use a pMDI is generally described as a manoeuvre that is 'slow and deep' whilst a more clearer instruction is to inhale slowly until the lungs are full of air and to try to ensure that this complete inhalation takes 5 seconds. For a dry powder inhaler the instruction is 'deep and fast as you can' whilst a clearer explanation is as fast as possible, from the start, and maintain the inhalation as long as possible. In the past studies have focused on the general instructions and applied subjective assessment to identify if patient have problems using their inhalers. These studies suggest that a large proportion of patient do have problems using their inhalers but there is no objective assessment. The studies of this Thesis have been designed to provide objective assessments of inhaler technique and at the same time to quantify how patients use inhalers with respect to their inhalation flows (including the peak inhalation flow), inhalation volumes and inhalation times (including the time to the peak inhalation flow). Simple solutions to the main issue

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with respect to pMDI co-ordination and slow flow and with respect to DPIs using a fast inhalation from start will be identified and studied using objective methods.

Studies involving children and adults with asthma, those with chronic obstructive pulmonary disease and healthy volunteers have been designed when they inhale through a pMDI and a DPI. For the pMDI studies the time between the start of an inhalation and the pressing of the canister has been included to identify co-ordination and for DPI the acceleration of the inhalation flow through different devices has also been included.

2.5 1 Aims and Objectives

2.5.1 (a) Aims

➢ To capture the electronic inhalation profiles of children with asthma, adults with asthma and COPD patients together with healthy individuals as well as their disease control and spirometry.

➢ Identify the inhalation parameters from each profile.

➢ Show how simple methods can be used during the inhalation technique training session to improve patient inhaler administration when using a pMDi and DPI.

2.5.1. (b) Objectives

➢ Measure inhalation parameters (peak inhalation flow, inhalation duration, and inhaled volume) in children with asthma, adults with asthma and COPD when they inhale through pMDIs and spacers.

➢ Identify the impact of using a co-ordination cap and simple counselling to increase the duration of an inhalation on the pMDI technique of asthmatics.

- Measure inhalation parameters (peak inhalation flow, time to peak inhalation, the acceleration rate of each inhalation, inhalation duration and inhaled volume) in children with asthma, adults with asthma and COPD when they inhale through different DPIs.

- To identify the impact of focussing on a fast inhalation from the start during counselling by measuring inhalation profiles (peak inhalation flow, time to peak inhalation, the acceleration rate of each inhalation, inhalation duration and inhaled volume) when children with asthma, adults with asthma and COPD inhale using two different DPIs.

- Measure the change in the inhalation parameters when patients with asthma and COPD inhale through different DPIs after their recovery following hospital admission due to an acute exacerbation.

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Chapter 3:

Preliminary investigations on the inhalation characteristic of children with Asthma (CHILD), adult asthmatics (ADULT) and patients with chronic obstructive pulmonary disease (COPD) when they use a pressurised metered dose inhaler (pMDI) with and without spacers and a Soft Mist Inhaler.

3.1 Introduction

In 1976 Crompton started a series of reports (Paterson and Crompton, 1976; Crompton, 1982b), describing pMDI inhalation technique problems. Today (Crompton, 2006; Melani et al., 2011) these problems are no different to those in 1976. It is estimated that about 75% of patients make errors when using their pMDIs (Molimard et al., 2003), as they need to co-ordinate the device actuation with inhalation to receive the intended therapeutic dose. Moreover, 60-92% of patients inhale too fast and do not use a slow inhalation when they used their pMDI (Larsen et al., 1994; Al-Showair et al., 2007a). Failure to use a slow inhalation was more common than good co-ordination between dose actuation and co-ordination (Nimmo et al., 1993; Hesselink et al., 2001). It is estimated that approximately 50% of patients do not obtain sufficient therapy from their inhalers due to poor inhalation technique (Crompton and Duncan, 1989).

An extensive review has concluded that flows through a pMDI should be < 90L/min (Pauwels et al., 1997) whilst a gamma scintigraphy study has shown that a flow of 90L/min with a co-ordination time of 0.2 seconds resulted in the greatest total and peripheral lung deposition (Farr et al., 1995). Previously these criteria had been described as the ideal combination (Goodman et al., 1994) and were used by Broeders et al (2003). This latter study measured electronic profiles and reported that not using a slow flow was a more common mistake than good co-ordination. This latter study revealed that the inhalation volume of asthmatics was around 2.7L which is less than those reported by Farr et al (1995) in healthy volunteers. Broeders et al (2003) reported that inhalation volumes in COPD ranged from means for 2.3 to 2.7L with those who had more severe obstruction having the smaller inhalation volumes.

Spacers were introduced to help solve pMDI technique problems and to reduce oropharyngeal deposition. However, it has been reported that up to 40% of the children used their pMDI inadequately even with a spacer (Kamps et al., 2000). Training and regular inhaler technique follow up is therefore required (van Beerendonk et al., 1998; Kamps et al., 2000; Crompton, 2006). Although spacers should be used with a slow inhalation reports do not focus on this.

Most studies assessing inhalation technique are subjective. Goodman et al (1994) and later Broeders et al (2003) used electronic measurements to characterise the inhalation profile of patients when they used a pMDI (but not a spacer). Broeders et al (2003a) demonstrated the effect of training but inhalation flows remained too fast.

This study was designed to adapt available methodology to provide a preliminary assessment of measuring inhalation parameters of patients when they use a variety of inhalers. In this study patients have been asked to use their real life inhalation technique and so received no training about inhalation technique. Patients with asthma (both children and adults) and COPD when they used a pMDI alone and when it was attached to different spacers have been studied. Also inhalation parameters for a Respimat® (Boehringer Ingelheim, GmbH) have been obtained.

3.2 Research Aim and Objectives

3.2.(a) Aim

The main aim was to identify the inhalation parameters of children with asthma, (CHILD), adults with asthma (ADULT) and COPD patients when they inhaled through a pMDI and when the pMDI was attached to a Volumatic spacer and also when attached to an AeroChamber spacer, also to identify the inhalation parameters when patients with COPD used a Respimat.

3.2.(b) Objectives

Primary Objectives

To measure the inhalation profile when the patients inhale through a pMDI alone and when attached to a Volumatic and when attached to an AeroChamber as follows.

➤ Asthmatic children: peak inhalation flow (PIF in l/min), inhalation volume (IV in L) and inhalation time (Ti in sec) through a pMDI alone, a pMDI with a Volumatic spacer and attached to an AeroChamber as well as an EasiBreathe.

➤ Asthmatic adults: peak inhalation flow (PIF), inhalation volume (IV) and inhalation time (Ti sec) a pMDI alone, a pMDI with a Volumatic spacer and attached to an AeroChamber.

➤ COPD patient: peak inhalation flow (PIF), inhalation volume (IV) and inhalation time (Ti sec) through a pMDI alone, a pMDI with a Volumatic spacer and attached to an AeroChamber and when they inhaled through an EasiBreathe and Respimat.

Secondary Objectives

➤ To obtain patient's demographic features and measure their peak expiratory flow (PEF), forced expiratory volume in one second (FEV_1) and Forced Vital capacity (FVC).

➤ Identify the level of their disease.

3.3 Method

3.3.1 Study Population

3.3.2 Patient recruitment and sample size

NRES ethical approval was obtained as well as local R&D (Research and Development) approval from each centre [APPENDIX A-1]. Asthmatic adults / children and COPD patients attending an outpatient appointment and receiving regular care at the respiratory clinics of NHS hospitals (see below for the list of hospitals involved) who used a pMDI and a pMDI attached to a spacer were invited to take part in this research study. The study procedures were explained to all patients using the ethical committee approved Patient Information Leaflet [APPENDIX A1, A2, A3 and A4] which they kept. All subjects willing to take part gave their signed informed consent and for children their parent / care also gave consent (APPENDIX A5). Patients were free to withdraw or terminate, at any time from the study, without giving a reason. The data collected and records were kept strictly confidential and anonymous.

The NHS Hospitals which were involved as research sites:

- ➢ Leeds General Infirmary (LGI), Leeds, UK.
- ➢ St. James's University Hospital, Leeds, UK.
- ➢ Bradford Royal Infirmary, Bradford, UK.
- ➢ St. Luke's Hospital Bradford, UK.
- ➢ Airedale Hospital, UK

(a) Inclusion criteria

Patients who met all the following criteria were potential candidates for recruitment:

> ➢ Male or female, with stable asthma or COPD.

> ➢ Prescribed inhaled medication through a pMDI and had used a pMDI attached to a spacer.

> ➢ Age groups: asthmatic child (4-18 years)[CHILD], adult asthmatic asthma (18-55 years) [ADULT] and COPD (> 55 years)[COPD].

> ➢ Signed informed consent form.

(b) Exclusion Criteria

Patients who met the following criteria were excluded from participation:

> ➢ Prescribed inhaled medication for less than 4 weeks prior to enrolment.

> ➢ Other pulmonary diseases (e.g. Cystic Fibrosis, TB, pneumonia).

> ➢ An acute exacerbation of asthma or COPD or a short course of high dose oral prednisone during the last 2 weeks.

> ➢ Participation in another clinical research study in the 3 months prior to enrolment.

3.3.3 Study Design

A Micro-Loop Spirometer (Cardinal Health, UK) was adapted with an airtight holder on the air entry in-let of the spirometer's mouthpiece. Specially designed inhaler adapters were obtained to fit tightly onto the holders. Adapters unique for the mouthpiece of each inhalation method were obtained. These allowed an inhalation through the spirometer. The inhalation section of the option to measure a flow volume loop with the spirometer was chosen. The data from each profile was downloaded into a Microsoft Access spreadsheet to compute the inhalation parameters.

Each patient's demographic data was obtained and their spirometry (PIF, FEV_1 and FVC) was measured. Disease severity classification for asthma was made according to GINA (2008) and for COPD according GOLD (2006)

The patients were asked to inhale through the Micro-Loop when it was fitted with:

I. An empty pMDI [pMDI]

II. An empty pMDI attached to a Volumatic spacer (GlaxoSmithKline, UK) [VOLUMATIC].

III. An empty pMDI attached to an AeroChamber spacer (Truddell International, Canada) [AEROCHAMBER].

IV. An Empty EasiBreathe [EASIBREATHE].

V. COPD only −an empty Respimat® (Boehringer Ingelheim). [RESPIMAT]

The order was randomised and each patient made two separate inhalations. Prior to inhalation through the Respimate patients were given the patient information leaflets to study.

Each patient was instructed to use the same technique as they would use at home − their real life inhaler technique. All inhalations were made during one visit. From each inhalation profile the following inhalation parameters were obtained:

- Peak inhalation flow, in litres per minute (PIF).

- Inhalation volume, in litres (IV).

- Duration of the inhalation, in seconds (Ti).

The profile with the slowest PIF was chosen for data analysis. Patients were also asked to complete a questionnaire as follows:

➢ Adult asthmatic: the Asthma Control Questionnaire (ACQ – Juniper et al 1999b) see [APPENDIX A-6] and Juniper's Asthma Quality of Life - mini version (AQLQ) – see [APPENDIX A-7] (Juniper et al., 1999a)

➢ Children: Paediatric Asthma Caregivers Quality of Life – PACQLQ (Juniper et al.,1996b). [APPENDIX A-8] and Asthmatic children: Paediatric Quality of Life – PAQL (Juniper et al., 1996a)[A -9]

➢ COPD: St George's Respiratory questionnaire (SGRQ)- See [APPENDIX A-10] (Jones et al, 1992).

3.3.4 Data Collection

Quantitative and qualitative data were collected from the 3 groups (children with asthma, asthmatic adults and COPD patients)

Main outcomes were:

➢ Peak inhalation flow (PIF).

➢ Inhalation volume (IV).

➢ Duration of inhalation (Ti).

The Secondary measures were**;**

➢ Demographic data

➢ Level of asthma / COPD control using quality of life questionnaires (see above)

➢ Spirometry (PEF, FEV_1, FEV_1% predicted and FVC)

3.3.5 Data Analysis

The statistical analysis of the study was carried out using the Statistical Package for Social Sciences (SPSS) software version 17. The study data was first classified into scale, categorical (nominal) or ordinal categories, as appropriate, and an SPSS

dataset was then set up for the analysis. The statistical analysis was performed and presented as follows

➢ Descriptive statistics: mean and standard deviation.

➢ For scale data; normal distribution of the data was examined using histograms and statistical tests for normality; the Kolmogorov-Smirnov and Shapiro-Wilk tests

➢ Comparisons (differences) of measurements through different inhalers within the same group were performed using the related (paired)-samples t-test (for parametric data) and the Wilcoxon test (for non-parametric data)

➢ Comparisons (differences) of measurements between different the groups were performed using the independent-samples t-test (for parametric data) and the Mann-Whitney U test (for non-parametric data).

3.4 Results

3.4.1 Study Population

A total of 109 patients were recruited and completed this study as shown in Table 3.1. Individual details are presented in APPENDIX B-1, B-2 and B-3, together with their % predicted values (refer to the enclosed DVD).

Table 3.1. Details of all subjects studied. All data is mean (SD) unless indicated.

Characteristics		CHILD	ADULTS	COPD
Number		20	57	32
Age in years		8.6 (2.8)	48.3(15.4)	64.8(12.1)
Sex (M/F)		15/5	11/46	17/15
Height (cm)		132.8(20)	165.5(9.01)	168.1(10.3)
Weight (Kg)		34.8(16.2)	76.5(17.7)	77.8(12.2)
FEV_1 (L)		1.5(0.72)	2.03(0.62)	1.3(0.6)
FEV_1 % predicted		77.4 (18.4)	71.1(17.0)	42.2(17.8)
PEF (L/min)		191.2(76.9)	304.1(114.4)	178.9(92.2)
PEF % predicted		63.1(15.7)	72.6(24.1)	46.1(18.3)
FVC (L)		1.6(0.7)	2.5(0.7)	2.0(0.8)
Disease severity*	Mild	9	15	4
	Moderate	8	23	20
	Severe	3	19	8
	Very severe	N/A	N/A	-

*asthma severity classified was based on GNA (2008) Guidelines

3.4.2 Inhalation Characteristics

A summary of the inhalation parameters of the asthmatic children is shown in the Table 3.2, adults with asthma in Table 3.3 and COPD patients in Table 3.4. The number of patients with slow, fast and very fast PIF values are shown in Table 3.5 and Figure 3.1. Individual vales are presented in Figures 3.2 to 3.10.

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Table 3.2. Inhalation characteristics of the asthmatic children when they inhaled through the pMDI, pMDI with Volumatic, pMDI with AeroChamber and EasiBreathe.

D*	pMDI			VOLUMATIC			AEROCHAMBER			EASIBREATHE		
	PIF(l/min)	IV(L)	Ti(sec)	PIF(l/min)	IV(L)	Ti(sec)	PIF(l/min	IV(L)	Ti(sec)	PIF(l/min	IV(L)	Ti(sec)
Mean	108.9	1.14	1.44	93.0	1.08	1.38	89.90	1.17	1.52	77.60	1.06	1.43
SD	40.4	0.59	0.27	49.7	0.61	0.25	40.7	0.59	0.30	41.2	0.66	0.22
min	62.0	0.5	1.0	37.0	0.3	1.0	38.0	0.3	1.0	36.0	0.3	1.0
max	224	3.0	1.9	206	2.9	1.9	206	2.6	2.2	211.0	2.9	1.8

**Devices

Table 3.3. Inhalation characteristics of the asthmatic adults when they inhaled through the pMDI, pMDI with Volumatic, pMDI with AeroChamber and EasiBreathe.

D*	pMDI			VOLUMATIC			AEROCHAMBER			EASIBREATHE		
	PIF(l/min)	IV(L)	Ti(sec)	PIF(l/min)	IV(L)	Ti(sec)	PIF(l/min)	IV(L)	Ti(sec)	PIF(l/min)	IV(L)	Ti(sec)
Mean	146.0	2.1	1.5	145.8	2.1	1.6	136.9	2.0	1.5	100.0	1.6	1.64
SD	58.8	0.9	0.3	67.5	0.8	0.4	68.9	0.9	0.3	39.0	0.82	0.31
min	40.0	0.6	1.1	44.0	0.4	1.1	30.0	0.5	0.3	52.0	0.73	1.10
max	284.0	4.5	2.2	286.0	3.9	2.6	301.0	4.2	2.2	205.0	3.7	2.80

Table 3.4. Inhalation characteristics of COPD patients when they inhaled through the pMDI, pMDI with Volumatic, pMDI with Aero-chamber and the EasiBreathe.

D*	pMDI			VOLUMATIC			AEROCHAMBER			EASIBREATHE		
	PIF(l/min)	IV(L)	Ti(sec)	PIF(l/min)	IV(L)	Ti(sec)	PIF(l/min)	IV(L)	Ti(sec)	PIF(l/min)	IV(L)	Ti(sec)
Mean	107.3	1.8	1.6	115.7	1.8	1.5	117.9	1.8	1.7	83.8	1.8	1.7
SD	50.6	1.0	0.2	50.4	0.9	0.4	49.1	0.8	0.4	29.1	1.1	0.5
min	33.0	0.4	1.1	34.0	0.6	1.1	37.0	0.5	1.1	38.0	0.9	1.1
max	242.0	5.3	1.9	277.0	4.7	2.8	287.0	4.4	2.6	155.0	4.9	3.5

Table 3.5. Summary of patients categorised with respect to their PIF.

PIFR (L/min)	PATIENTS NUMBER (PERCENTAGE)											
	ADULT n (%)				CHILD n (%)				COPD n (%)			
	pMDI	VoL	AERO	EASI	pMDI	VOL	AERO	EASI	pMDI	VOL	Aero-	EASIn=14
>200	11 (19.2%)	12 (21%)	14 (24%)	12 (21%)	1 (5%)	1 (5%)	1 (5%)	1 (5%)	3 (9.3%)	2 (6.25)	1 (3.1%)	0
90-200	36 (63%)	30 (52.63)	31 (54.3)	31 (54.3%)	12 (60%)	7 (35%)	10 (50%)	3 (15%)	19 (59.3%)	22 (68.75)	24 (75%)	7 (5%)
25-90	10 (17.5%)	15 (26.3)	12 (21.1)	14 (24.6%)	7 (35%)	12 (60%)	9 (45%)	16 (80%)	10 (31.2%)	6 (18.8%)	7 (21.9%)	7 (5%)

VOL- Volumatic, AERO-AeroChamber, EASI-EasiBreathe
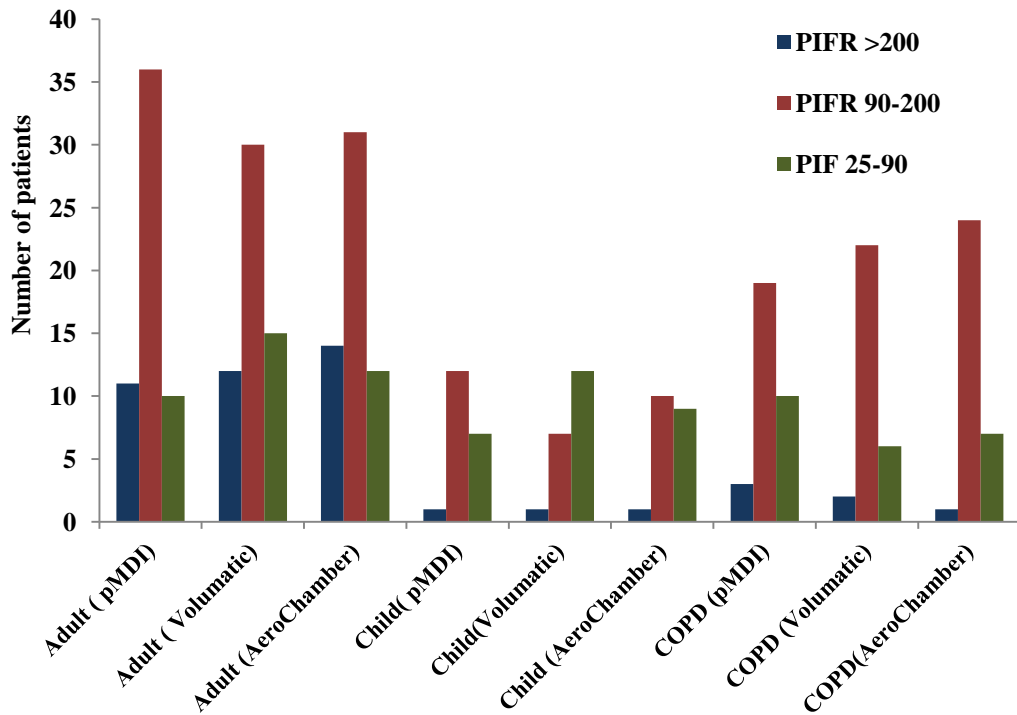
Figure 3.1. Summary of patients categorised with respect of their PIF.
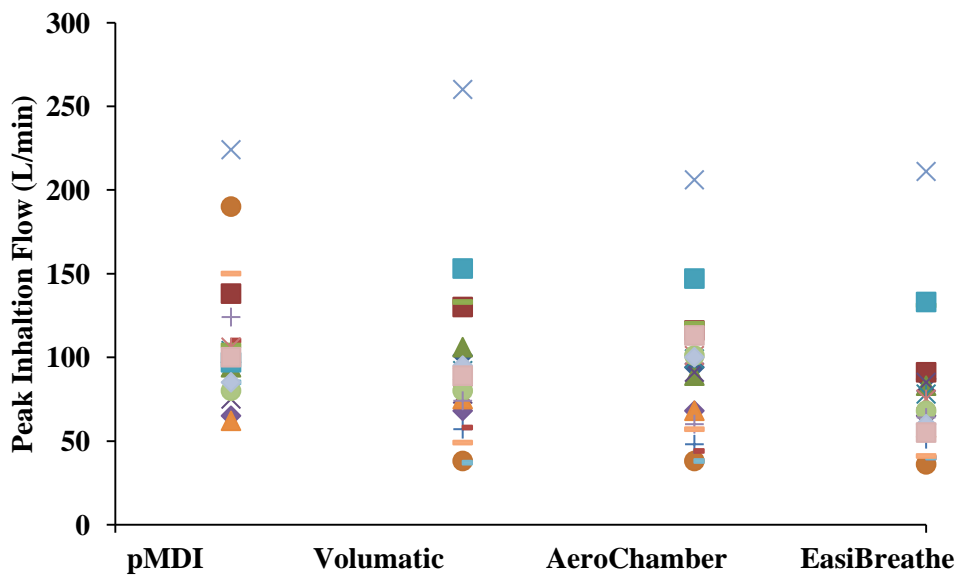
Figure 3.2. Individual Peak inhalation flow (L/min) for the children with asthma when they inhaled through the pMDI, pMDI attached to a Volumatic, pMDI attached to an AeroChamber and an EasiBreathe.
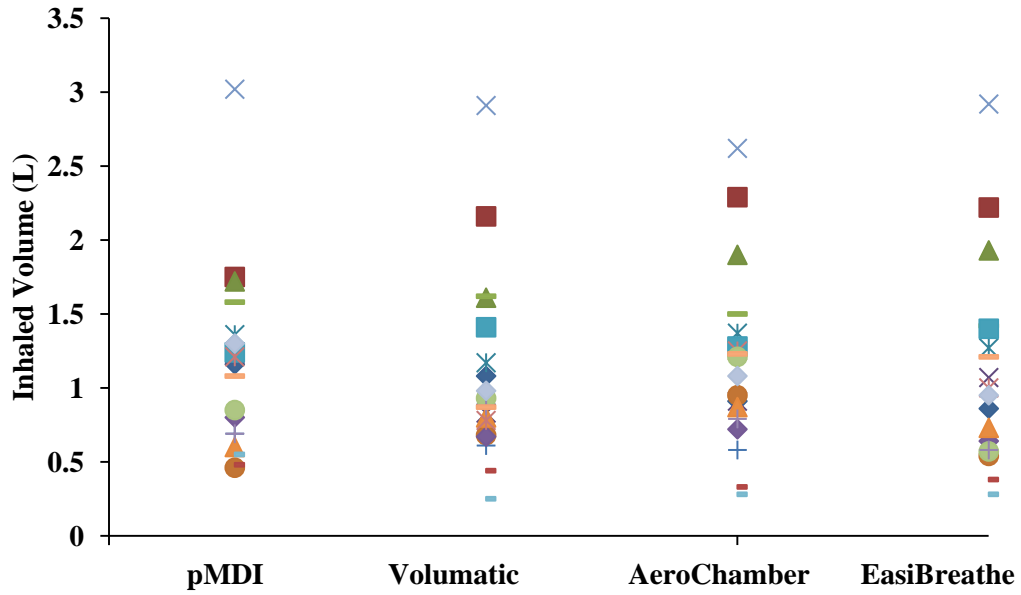
Figure 3.3. Individual Inhaled volume (L) for the children with asthma when they inhaled through the pMDI, pMDI attached to a Volumatic, pMDI attached to an AeroChamber and an EasiBreathe.
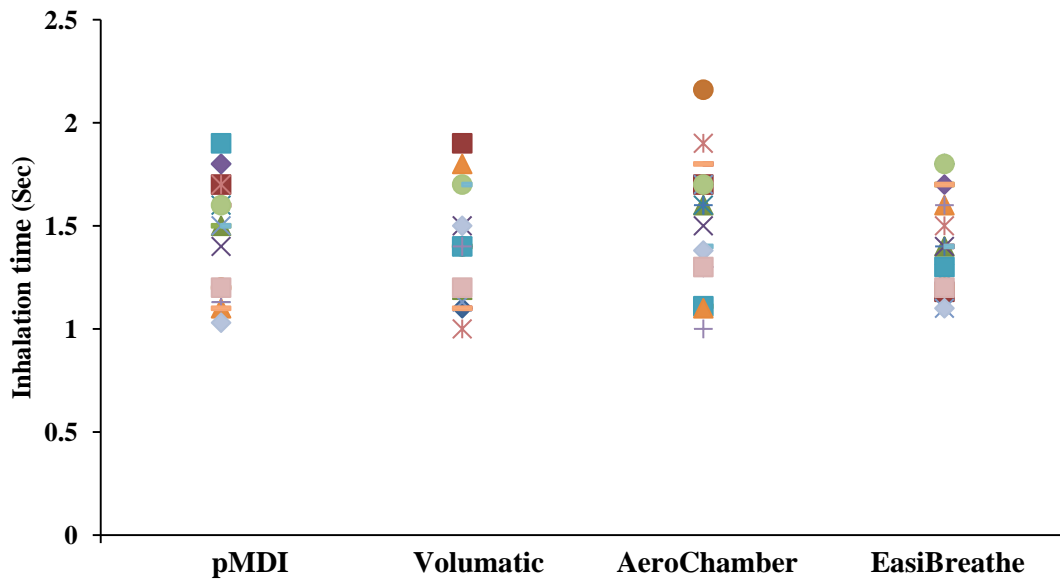
Figure 3.4. Individual durations of the inhalation (Ti) of the children with asthma when they inhaled through the pMDI, pMDI attached to a Volumatic, pMDI attached to an AeroChamber and an EasiBreathe.
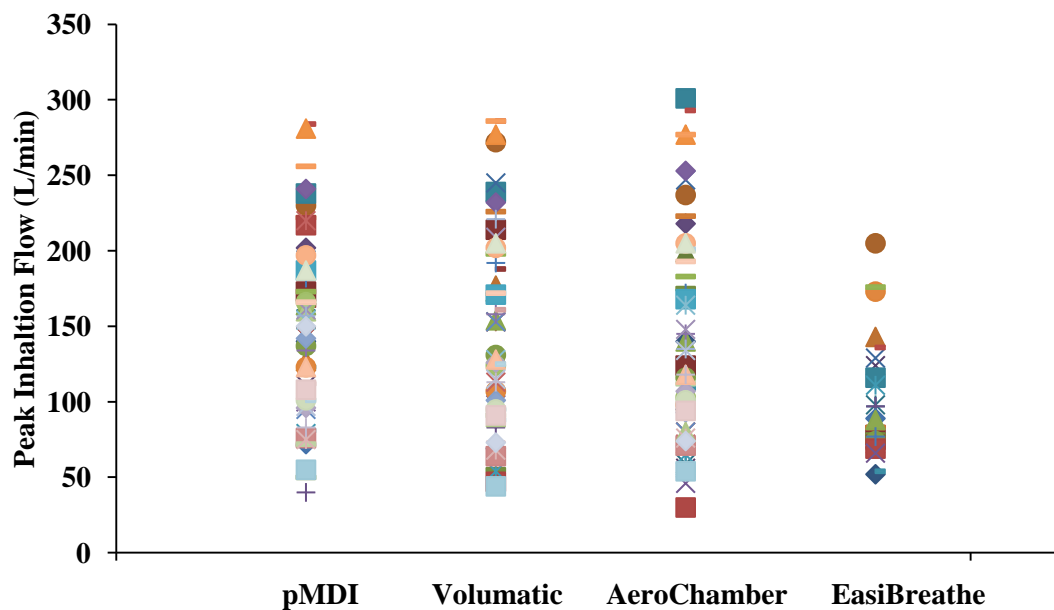
Figure 3.5. The peak inhalation flow (L/min) of each adult with asthma when they inhaled through the pMDI, pMDI attached to a Volumatic, pMDI attached to an AeroChamber and an EasiBreathe.
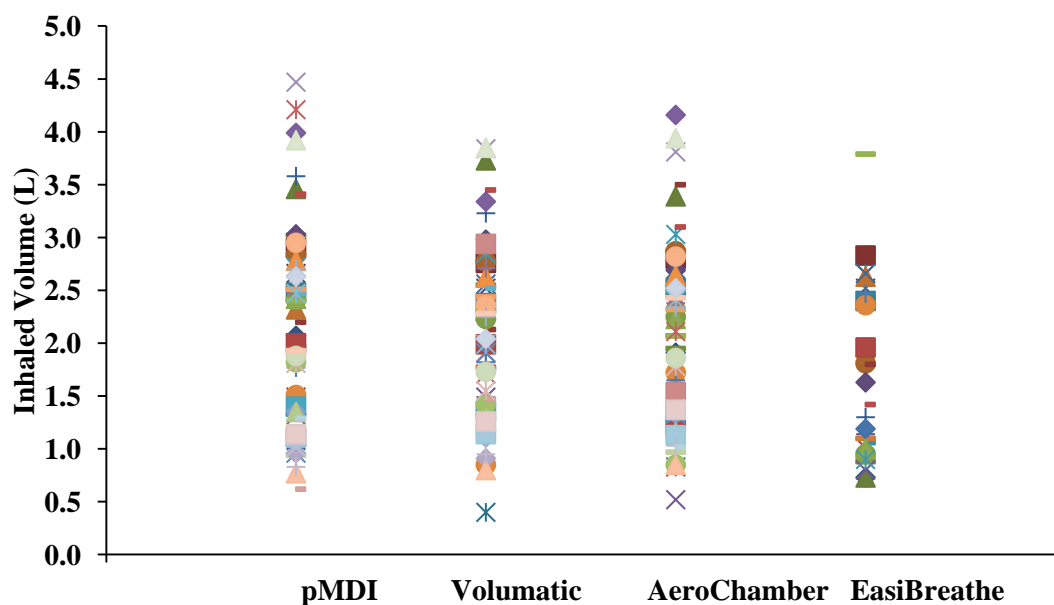
Figure 3.6. Individual inhalation volumes (IV) of the adults with asthma when they inhaled through the pMDI, pMDI attached to a Volumatic, pMDI attached to an AeroChamber and an EasiBreathe.
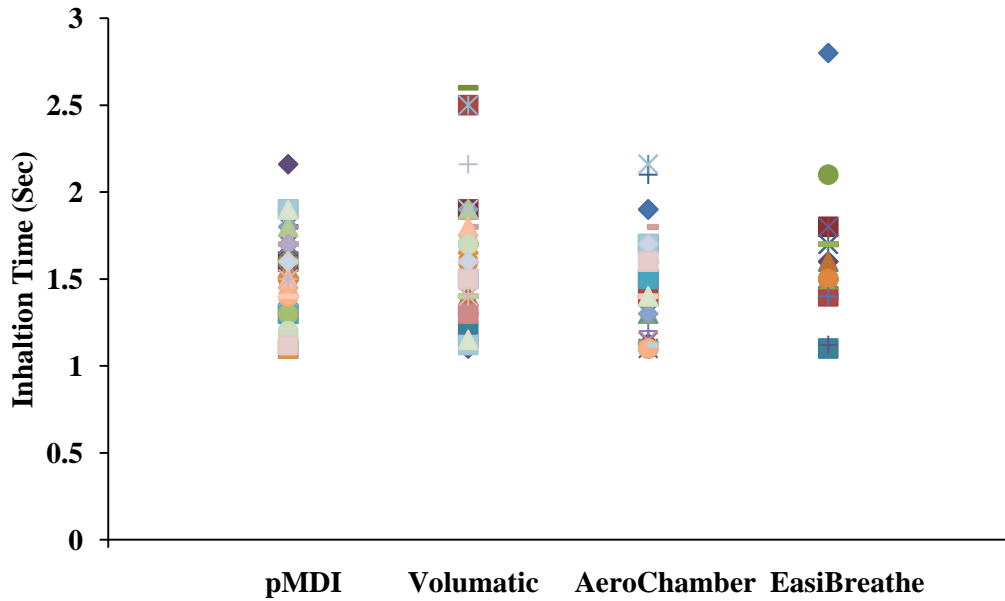
Figure 3.7. The duration of the inhalations (Ti) of each adult with asthma when they inhaled through the pMDI, pMDI attached to a Volumatic, pMDI attached to an AeroChamber and an EasiBreathe.
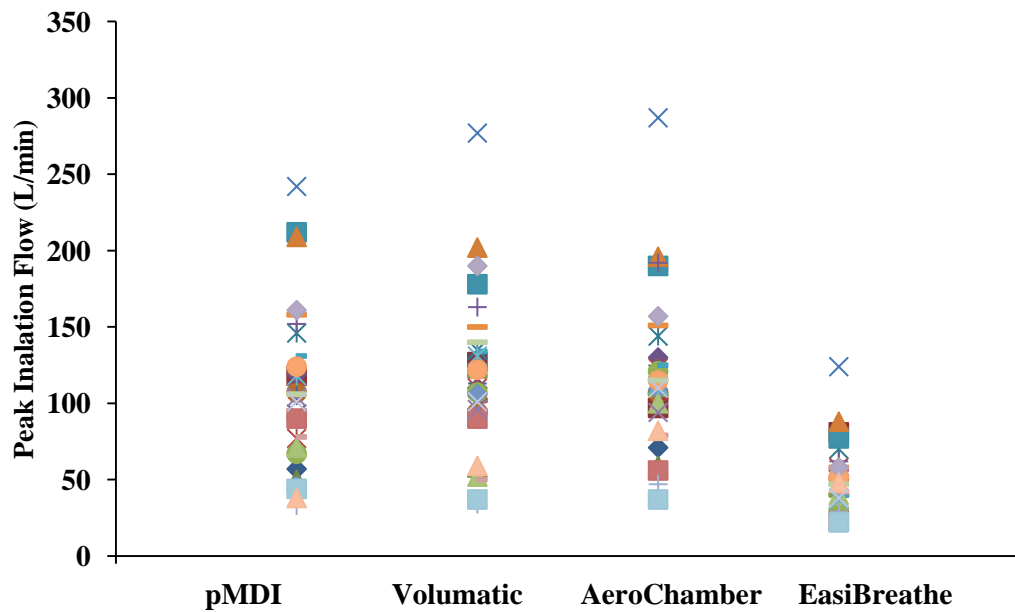
Figure 3.8. Peak inhalation flow (L/min) of each COPD patients when they inhaled through the pMDI, pMDI attached to a Volumatic, pMDI attached to an AeroChamber and an EasiBreathe.
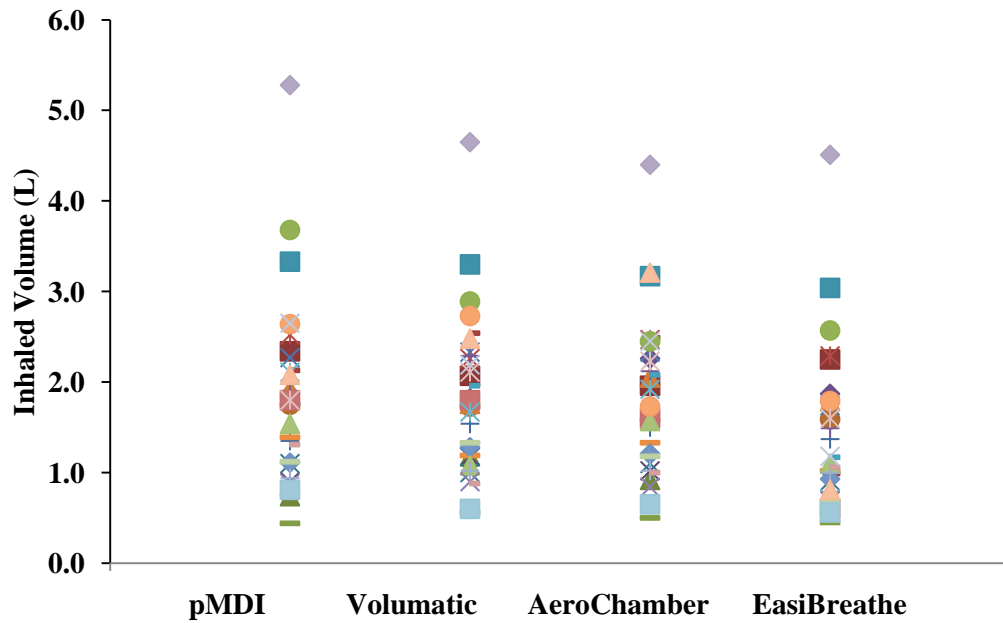
Figure 3.9. Individual inhalation volumes (IV) of the COPD patients when they inhaled through the pMDI, pMDI attached to a Volumatic, pMDI attached to an AeroChamber and an EasiBreathe.
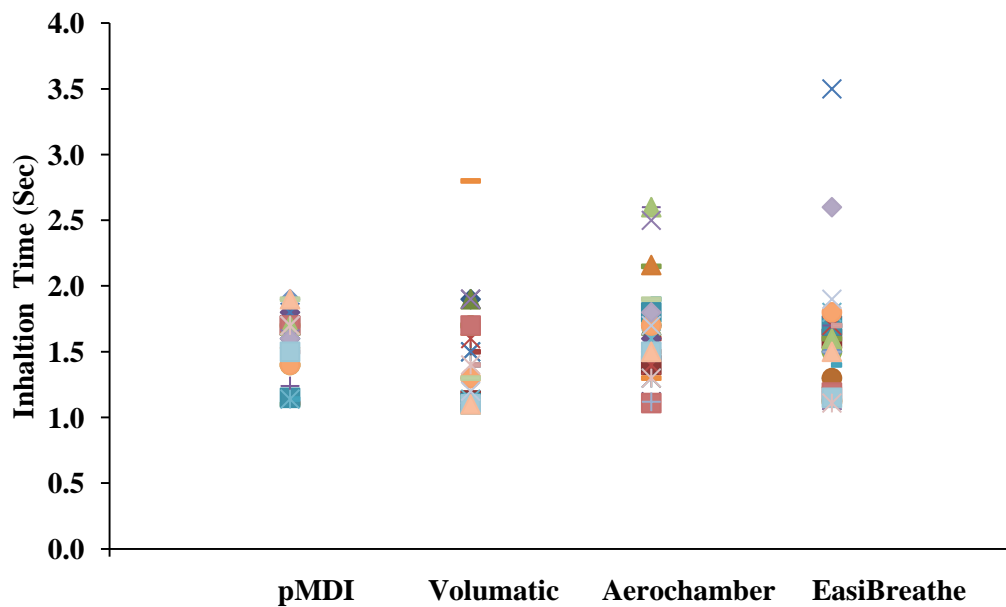
Figure 3.10. The duration of each inhalation (Ti) by the COPD patients when they inhaled through the pMDI, pMDI attached to a Volumatic, pMDI attached to an AeroChamber and an EasiBreathe.

The range of peak inhalation flows and inhaled volumes of the three patient groups with respect to the severity of their disease is presented in Table 3.6 whilst Table 3.7 presents these ranges for the adults with asthma according to their ACQ. Table 3.8 shows the range of the PIF and IV for the children with asthma with respect to their age.

Table 3.6. Range of inhalation parameters through the pMDI in all patients according to the severity of obstruction

	CHILD	ADULT	COPD
PIF (L/min)			
Mild	65 - 224	55 - 217	33-209
Moderate	75 - 150	40 - 281	38-242
Severe	110 - 106	75 - 284	44-146
Very Severe	n/a	n/a	n/a
IV (L)			
Mild	0.5 - 3	1 - 3.5	0.7-5.3
Moderate	1.1- 1.8	0.8 - 4.5	0.8-3.7
Severe	0.5 - 1.2	0.6 - 3.6	0.81-1.80
Very Severe	n/a	n/a	n/a

Table 3.7. Range of inhalation parameters through the pMDI in the adult asthmatic patients according to their asthma control measured by their ACQ

	ADULT
PIF (L/min)	
< 0.7	76 - 284
0.7-1.5	108 - 238
> 1.5	40-280
IV (L)	
< 0.7	1-3.4
0.7-1.5	1.1-2.5
> 1.5	0.6 - 4.5

Table 3.8. Range of inhalation parameters in the children with asthma according to their age

	pMDI	Volumatic	AeroChamber
PIF (L/min)			
5-7 years	62- 190	37-92	38-99
8-10 years	75-150	49-153	57-147
> 10 years	85-224	88-260	89-206
IV (L)			
5-7 years	0.5-1.4	0.3-1.2	0.3-1.4
8-10 years	0.7-1.8	0.8-2.2	0.8-2.3
>10 years	1.2-3	0.8-2.9	1.1-2.6

3.4.3 The Inhalation Characteristics between the patients groups

Figure 3.11 shows a comparison of PIF for each group using each different inhalation method and a summary of the statistical analysis between each inhalation method within each group for the pMDI and spacers are presented in Table 3.9. (Using, the non-parametric test (Wilcoxon test)), and between each group for the different inhalation methods used non-parametric test (using the independent-samples, Mann-Whitney U test) is presented in Table 3.10.
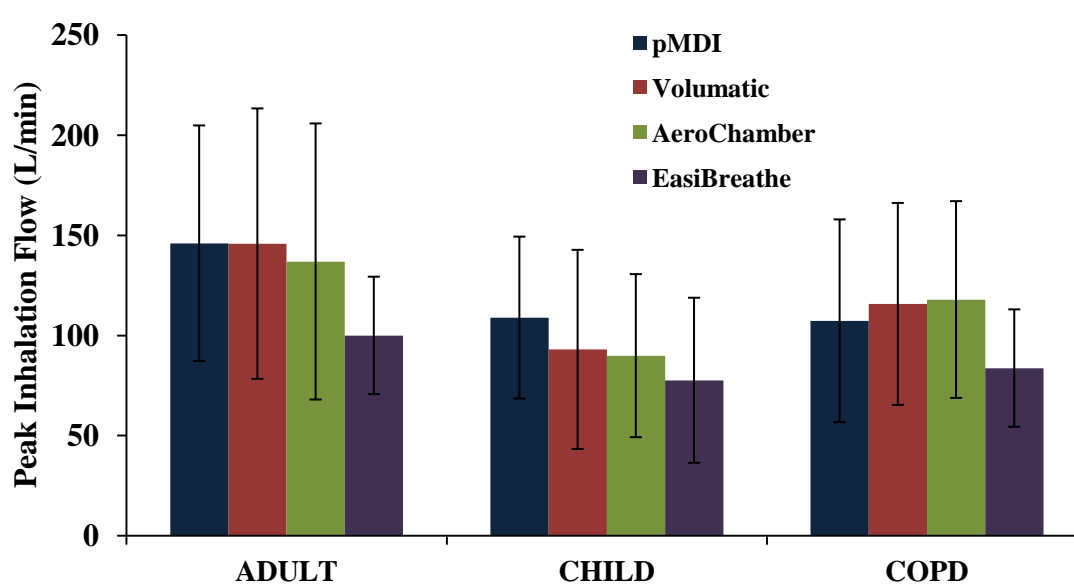
Figure 3.11. Mean (SD) peak inhalation flows for the different group of patients when they inhaled through pMDI, Volumatic, AeroChamber and an EasiBeathe

Table 3.9. Statistical comparison of PIF within each group between each inhalation method.

	pMDI v's Volumatic	pMDI v' AeroChamber	Volumatic v's AeroChamber
CHILD	0.286	0.185	0.445
ADULT	0.429	0.359	0.238
COPD	0.054	0.02	0.422

Table 3.10. Statistical comparison of PIF values between the different groups

	CHILD v's ADULT	CHILD v's COPD	ADULT v's COPD
pMDI	0.000	0.191	0.002
Volumatic	0.0007	0.023	0.067
AeroChamber	0.003	0.016	0.481
EasiBreathe	0.003	0.033	0.226

Figure 3.12 shows a comparison of the inhaled volumes (IV) for each group using each different inhalation method and a summary of the statistical analysis between each inhalation method within each group for the pMDI and spacers is presented in Table 3.11.
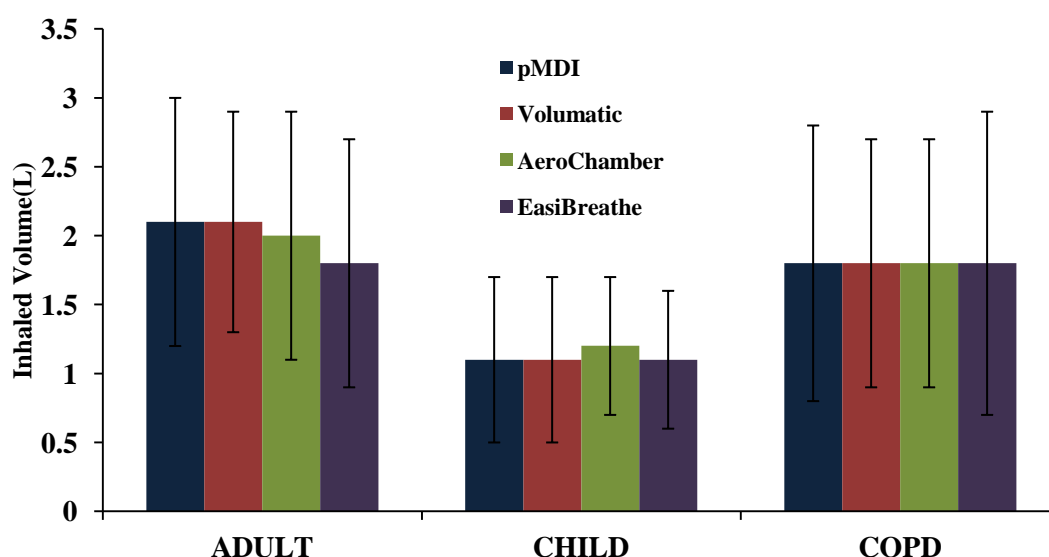
Figure 3.12. Mean (SD) inhalation volumes for the different group of patients when they inhaled through pMDI, Volumatic, AeroChamber and EasiBeathe

Table 3.11. Statistical comparison of inhaled volumes within each group between each inhalation method

	pMDI v's Volumatic	pMDI v' AeroChamber	Volumatic v's AeroChamber
CHILD	0.262	0.681	0.121
ADULT	0.222	0.310	0.541
COPD	0.875	0.430	0.750

Table 3.12. Statistical comparison of inhalation volumes between the different groups

	CHILD v's ADULT	CHILD v's COPD	ADULT v's COPD
pMDI	0.000	0.003	0.079
Volumatic	0.000	0.001	0.077
AeroChamber	0.000	0.004	0.201
EasiBreathe	0.001	0.007	0.507

Figure 3.13 shows a comparison of the inhalation times (Ti) for each group using each different inhalation method and a summary of the statistical analysis between each inhalation method within each group for the pMDI and spacers is presented in Table 3.13 and between each group for the different inhalation methods is presented in Table 3.14
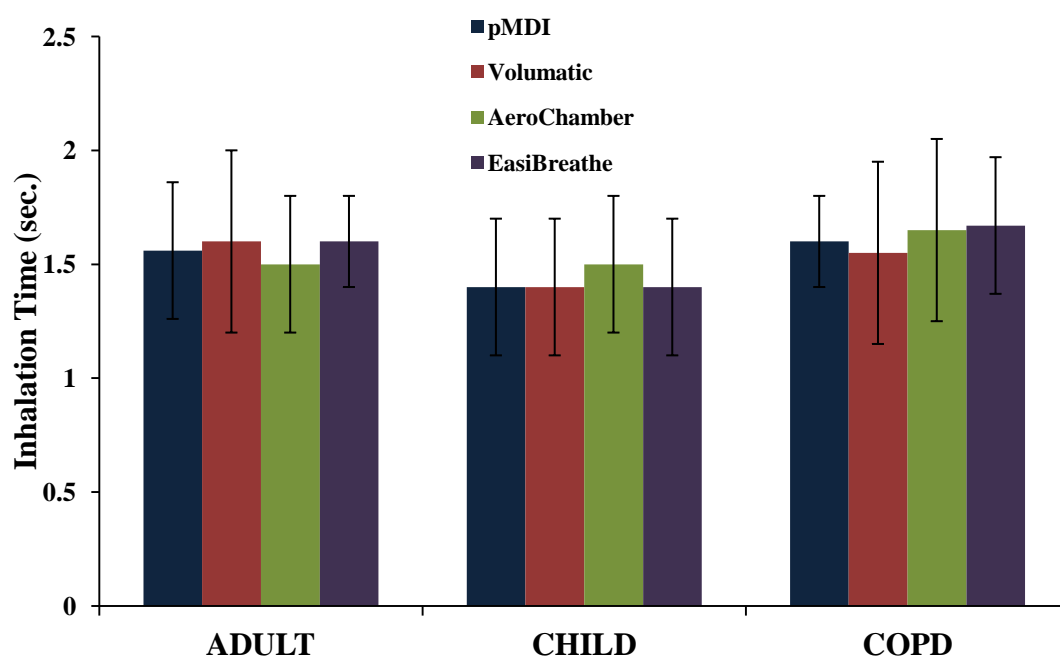
Figure 3.13. Mean (SD) inhalation times for the different group of patients when they inhaled through pMDI, Volumatic, AeroChamber and EasiBeathe

Table 3.13. Statistical comparison of the inhalation times within each group between each inhalation method, values are the *p* values.

	pMDI v's Volumatic	pMDI v' AeroChamber	Volumatic v's AeroChamber
CHILD	0.432	0.329	0.239
ADULT	0.226	0.738	0.975
COPD	0.127	0.456	0.042

Table 3.14. Statistical comparison of inhalation times between the different groups

	CHILD v's ADULT	CHILD v's COPD	ADULT v's COPD
pMDI	0.995	0.214	0.140
Volumatic	0.027	0.472	0.154
AeroChamber	0.842	0.335	0.144
EasiBreathe	0.000	0.005	0.473

3.4.5. Inhalation Characteristics of COPD patients through Respimat®.

The inhalation parameters of the COPD patients when they inhaled using an empty Respimat® are summarised in Table 3.15 and the numbers using different PIF are shown in Table 3.16

Table 3.15. Inhalation characteristics of the COPD when they inhaled through a Respimat®.

	PIF (L/min)	IV (L)	Duration of Inhalation(Sec)
Mean(SD)	49.9(21.1)	1.4(0.9)	1.6(0.5)
Min	22.0	0.4	1.1
Max	124.0	4.5	3.5

Table 3.16. Summary of COPD patients categorised with respect to their PIF.

PIF (L/min)	COPD Patients n=32(%)
> 200	None
200-90	1(3.12%)
90-25	28(87.5%)
< 25	3(9.37%)

3.4.6 Quality of Life Questionnaires

(a) CHILD

➢ The Paediatric Asthma Quality of Life (PAQLQ) and Questionnaire the Paediatric Asthma Caregivers Quality of Life (PACQLQ)

The mean (SD) Paediatric Asthma Quality of Life (PAQLQ) and the Paediatric Asthma Caregivers Quality of Life (PACQLQ) were 4.35 (1.05) and 4.7 (1.19). The symptoms, Activity and Emotional domains of the PAQLQ were: 3.7(1.1), 4.5(1.5), 4.9 (1.1). Individual values are presented in APPENDIX B-4 (refer to enclosed DVD)

(b) ADULTS

➢ Asthma Control Questionnaire–(ACQ) and Asthma Quality Of Life Questionnaire – (AQLQ)

The mean (SD) ACQ scores were 2.1(1.0), Table 3.17 presents the frequencies and percentages of the asthmatic adults in different ACQ score. Previously Table 3.7 presents the ranges for PIF and IV with respect to the ACQ scores of these adult asthmatics. A summary of the mean (SD) of AQLQ scores (overall and its three domains: symptoms, Activity Limitation, Emotional and Environment) are presented in Table 3.18. (Individual values can be found in APPENDIX B-5, B-6 refer to the enclosed DVD).

Table 3.17. ACQ categorises of the adult asthmatics.

ACQ Categories	Frequencies
≤ 0.75 (well controlled)	5 (8.8%)
0.75-1.50 (not well controlled	14 (19.2%)
≥ 1.50 (uncontrolled)	38 (66.6%)

Table 3.18. Mean (SD) (AQLQ) of the asthmatic adults.

ASTHMA QUALITY OF LIFE QUESTIONNAIRE – (AQLQ). DOMAINS	
Domains	Mean (SD) Score-AQLQ Domains for one visit
Overall AQLQ	4.40 (1.12)
Symptoms	3.8(1.2)
Activity Limitation	3.9 (1.1)
Emotional Function	3.2 (1.3)
Environment	3.5(1.5)

(C) COPD

➢ The SGRQ Scores

The SGRQ scores (overall and its three domains: Symptoms, Activity and Impacts) are presented in Table 3.19. The detailed SGRQ scores of all COPD patients are presented in APPENDIX B-8 (refer to the enclosed DVD).

Table 3.19. Descriptive Statistics of the SGRQ scores FOR COPD Patients.

SGRQ (n=32)		Symptoms score	Activity score	Impacts score	Total score
Mean (SD)		70.2 (24.2)	73.6 (19.5)	50.2 (21.6)	60.6 (18.5)*
Percentiles	**25**	58.3	60.7	34.7	43.5
	50	75.5	76.1	52.4	62.1
	75	90.1	91.2	69.47	78.3

*SGRQ scores ranges from 0 to 100, zero scores indicate no impairment, with higher scores indicating worse health status.

3.5 Discussion

Subjective assessment of each patient's inhalation technique was not performed because this was a pilot study to identify inhalation parameters and the methodology did not allow an electronic measurement of the point of co-ordination.

The results provide substantial information about the inhalation parameters of asthma patients (both adults and children) and COPD patients when they use pMDIs and when they are attached to spacers. Poor co-ordination and slow flow are common errors made by patients when they use a pMDI (Al-Showair et al., 2007a; Hardwell et al., 2010). Not using a slow flow is a more common mistake made by different group of patients when they inhaled through a pMDI (Al-Showair et al, 2007a).

This study shows that the majority of patients inhaled too fast (>90L/min) when using their pMDI. The results revealed that 65% of children with asthma inhaled > 90L/min as well as 82% of the adult 68% of the COPD patients. The COPD findings are in accordance with Al-Showair et al (2007). In this 2007 reported study (using the IN-Check to measure flow) 59.5% of COPD patients with mild severity demonstrated an incorrect flow and their PIFR was > 90L/min with a mean PIF >120l/min before training. Another study reported that the majority of adults with asthma, children with asthma and COPD patients used a high flow rate >100 l/min when they used their pMDI (Chrystyn, 2009).

The study in this Chapter confirms that not using a slow flow is not only problem with pMDIs but also when they are attached to spacers and to some extent when the EasiBreathe is used. However the children did decrease their flows when using spacers whilst the adults with asthma and COPD patients did not. This could be due to the constant training they receive when using their spacers. The lack of a statistical difference is due to the small number of children together with the large variability of

the results. There was no change in their inhaled volumes when all patients used their pMDI or spacers suggesting that they all used a similar complete inhalation during each manoeuvre. The prolonged inhalation times of the children when they used spacers are probably due to their training and since their volume did not change then their flows were slower. Again the lack of a statistically significant change is due to the small number of subjects and the variability of the results.

Inhalation parameters of children with asthma when using pMDIs have not been reported before as well as when all asthmatics and COPDs use a pMDI attached to a spacer and when they use an EasiBreathe. Also similar data about adults with asthma and COPD patients is very limited. Previously Broeders et al (2003) have reported that the mean (SD) inhalation flows in adults asthmatics, mild COPD, moderate COPD and severe COPD patients when they use a pMDI are 149.6 (19.2), 127.9 (5.5), 134.0 (8.1) and 142.1 (14.7) L/min. The results reported for the adult asthmatics in this Chapter are similar whilst those of the COPD patients were lower. Age and disease severity should not affect inhalation flow because this is heavily reliant on technique rather than the capability of the individual and could be influenced by the amount of training (especially children) and attention to details (in COPD patients). This would account for the significantly reduced flows in the children and COPD compared to the adults with asthma. It is this latter group that should be targeted for extensive technique training.

The peak inhalation flows when the pMDI was attached to either a Volumatic or an AeroChamber were similar to those of the pMDI. The mean (SD) inhaled volume of asthmatic children asthmatic adults and COPD patients through the pMDI were 1.14(0.5), 2.1(0.9), 1.8(1.0) L. These values compare to 2.7 (1.2) L in adult asthmatics and 2.9 (0.7), 2.6 (0.2) and 2.3 (0.2) L in mild, moderate and severe

COPD patients when they inhaled through a pMDI (Broeders et al., 2003a). Also Farr et al (1995) reported mean (SD) inhalation volumes inhalation volumes ranging from 2.3 (0.3) to 3.2 (0.17) L, in healthy volunteers, depending on the inhalation manoeuvre used. The results in this chapter suggests that the inhalation volumes are related to age for the children. When the children with asthma used the pMDI attached to the Volumatic 5 of those 5-7 years used a volume of < 750ml. Hence with one inhalation these would not be able to inhale the complete volume of the Volumatic. This would be the volume that enters the mouth rather than into the lungs. It is advisable therefore that these patients should use the traditional tidal breathing method when they use a Volumatic. It has been recommended that as soon as a child can use a single deep inhalation though the AeroChamber (Roller et al., 2007) then they should be encouraged to switch from tidal breathing to one complete inhalation. Although all children with asthma used a minimum volume of 280 ml with the AeroChamber and this is almost twice its volume then each child should be individually assessed. The child with the low volume was 5 years old and the smallest subject in the study.

The duration of an inhalation Ti (Sec) is an inhalation parameter that has largely been ignored. Overall these were less than 2 seconds. It has been recommended that adult patients should be trained to inhale over 5 seconds and children 2 to 3 seconds (Laube et al, 2010). If patients use the same inhalation manoeuvre with respect to a gentle exhalation followed by a full inhalation then if the volume does not change and the duration of the inhalation increases then flow will be reduced. This theory is investigated during the studies in Chapter 5.

When using the EasiBreathe the inhalation parameters were similar to those of the pMDI. Flows were slightly slower which could be due to the higher resistance in the Easibreathe. The resistance was not measured but the air channels of this device are smaller than those of the pMDI. No patient used a flow of < 20 L/min which is the threshold for this device to breath actuate.

The Respimat is designed to emit a soft mist aerosol over 1.6 seconds (Newman et al., 1998; Hochrainer et al., 2005). Overall the COPD patients used a slower flow rate through the Respimat and only one patient inhaled > 90 L/min. However these flows are much faster than those of highly trained volunteers (Newman and Newhouse, 1996; Newman et al., 1998) whereas the volumes are similar. This suggests that the healthy volunteers may not have made a full inhalation. In this study 23 of the 32 (71.9%) patients inhaled over < 1.6 seconds and so these would have stopped their inhalation while the dose was still being emitted. The duration of the inhalation is critical parameter when using the Respimat®.

In summary, most patients performed an inadequate inhalation technique because of high inhalation flows when using their "real life" pMDI technique. Inhaled volumes and inhalation duration were low. This was a pilot study and the methodology did not lend itself to make subjective assessments of their technique. This preliminary pilot study highlights the value of using electronic methodologies to measure these parameters and incorporate an objective measure of co-ordination. The volumes indicate that most patients can empty a spacer using a single full inhalation but caution should be exercised when switching small and young children from tidal breathing to one single full inhalation.

Conclusion:

The study indicates that characterisation of the inhalation flow profile to identify aspects of the inhalation could be useful to identify the areas to focus on when training a patient to use their pMDI. Overall flows were too fast and inhalation times were short.

Chapter 4: Inhalation characteristics of children with asthma (Child), adult asthmatic and chronic obstructive pulmonary disease patients (COPD) using a pressurised metered dose inhaler

4.1 Introduction

The pressurized metered dose inhaler (pMDI) is the most widely used delivery system and commonly used in the management of asthma and COPD compared to other devices (Lenney et al., 2000; Broeders et al., 2003a). In 1965 the problems patients have using the correct pMDI technique were first report (Saunders, 1965). Subsequent subjective observations of patients using their pMDI have reported that these problems have yet to be solved (Orehek et al., 1976; Paterson and Crompton, 1976; Epstein et al., 1979; Shim and Williams, 1980; Crompton, 1982b; Allen and Prior, 1986; Pedersen et al., 1986; Horsley and Bailie, 1988; Crompton and Duncan, 1989; Manzella et al., 1989; Hilton, 1990; Larsen et al., 1994; van Beerendonk et al., 1998; Lenney et al., 2000; Hesselink et al., 2001; Molimard et al., 2003; Melani et al., 2004; Sestini et al., 2006; Melani, 2007; Melani et al., 2011). These have been confirmed by limited objective measurements of inhalation parameters (Goodman et al., 1994; Broeders et al., 2003a) and an Aerosol Inhalation Monitor (Sarvis et al., 2004; Hardwell et al., 2010).

Not using a slow inhalation followed by good co-ordination between the start of an inhalation and dose actuation are the most common errors. Other problems are not shaking the pMDI, failure to exhale, the cold-freon effect, not inhaling as much as possible and breath holding (Crompton, 1982b). Only 8% of adult asthmatics used their pMDI with a slow flow and good co-ordination (Al-Showair et al., 2007a).

When used correctly, only about 10%-20% of the nominal dose reaches the targeted airways (Newman, 1985). However, only a small amount is needed to produce a useful clinical effect and despite the consistent problems with pMDI inhaler technique these products have and continue to provide significant healthcare benefit.

Although the guidelines (BTS/SIGN., 2009; GINA, 2011) do recognise this they do appreciate that disease control could be improved without escalating the dose by better inhalation technique and compliance. It has been shown that good inhaler technique is associated with better asthma control (Giraud & Roche, 2002; Al-Showair et al, 2007a), reduced inhaled corticosteroids (Kamps et al., 2003) and significantly less hospital admissions as well as acute exacerbations (Melani et al., 2011). Thus patients with poor technique get sub-optimal benefit from their inhalers and this could translate into escalating doses and hence prescription item and other healthcare costs. It has been estimated that half the patients do not get the full therapeutic benefit from their inhalers due to poor inhaler technique (Crompton & Duncan, 1989). Improving inhalation technique could be one method of achieving the GINA challenge which is to reduce hospital admissions due to asthma by 50% over the next 5 years (Fitzgerald et al., 2011). A complete healthcare package that includes inhaler technique training in Finland has shown significant healthcare benefits and reduction in healthcare costs (Haahtela et al., 2006).

To compliment traditional subjective assessment of inhaler technique objective measurements could be used to target the steps of the inhalation manoeuvre that the patient does not perform as recommended. Figure 4.1 describes an inhalation profile when a subject uses a pMDI.

This profile identifies when the patient depressed the pMDI canister (co-ordination) where TsIn is the time between the start of the inhalation and actuating a dose. Also the peak inhalation flow (PIF), the duration of the inhalation (Ti) and the inhalation volume (IV) can be identified. Linking these to spirometry the ratio of the inhaled volume to the forced vital capacity could be used to identify if the patient exhaled and that during the inhalation they inhaled as much as possible
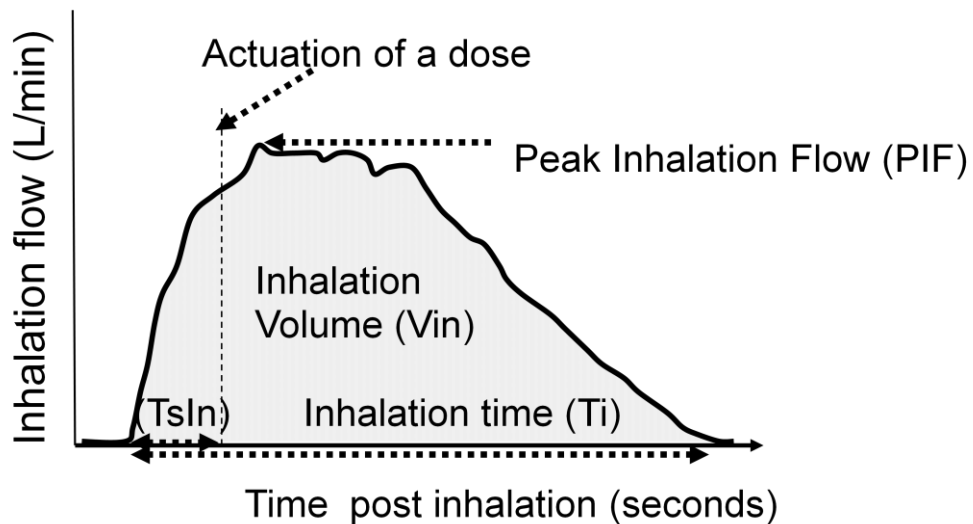
Figure 4.1. The inhalation flow with respect to time when using a pMDI.

The aim of this study was to measure electronic profiles of patients when they inhaled through their pMDIs using their normal, untrained, real life inhalation technique. Using these objective methods the errors made with respect to co-ordination and peak inhalation flow have been identified and an assessment of their inhalation volume has been made. Correlations of these parameters to spirometry have also been made.

4.2 Aim and Objectives

4.2.1 Aim

- Identify the inhalation parameters of patients (children with asthma, adults with asthma and COPD patients) when they inhale through a pMDI.

- Use the inhalation parameters to identify inhalation technique errors with respect to flow, co-ordination and inhaled volume.

- Evaluate if there are correlations between the inhalation parameters and the indices of spirometry.

4.2.2 Objective (s):

➢ Measure the inhalation profiles of children with asthma (CHILD), asthmatic adults (ADULT) and COPD patients (COPD) when they inhale through a pMDI using their 'real life' technique.

➢ Identify peak inhalation flow rate (PIF), inhalation volume (IV), length of inhalation (Ti) and the time of dose actuation with respect to the start of an inhalation. (TsIn).

➢ Use the inhalation parameters to identify inhalation technique problems

➢ Correlate the inhalation parameters to spirometry.

➢ Identify the levels of control (ACQ and AQLQ in asthmatics; SGRQ in COPD).

4.3 Methods

4.3.1 Study design

NRES research ethics approval from the Yorkshire and Humber Research Ethics Committee – Bradford was obtained (ref number 09/H1302/64). Stable asthmatic (adult and children) and COPD patients who were attending an out-patient NHS clinic and were prescribed a pMDI were invited to take part. The study objectives and procedure were described to the patients (including the parents/guardians of asthmatic children) using relevant patient information sheets [APPENDIX A1-A-2 and A-3]. All gave signed informed consent. [APPENDIX A 5].

The NHS Hospitals were:

➢ Airedale General Hospital, Steeton, West Yorkshire, UK.

➢ Leeds General Infirmary, Leeds, UK.

➢ Bradford Royal Infirmary, Bradford, West Yorkshire, UK.

➢ St Luke's Hospital, Bradford, West Yorkshire, UK.

(a) Inclusion Criteria:

➢ Male or female

➢ Stable asthma or COPD

➢ Asthmatic: children aged 5-17 years and adults 18-70 years

➢ COPD patients > 55 years

➢ Prescribed a pMDI

➢ Signed informed consent form (including the parent/guardian of asthmatic children).

 (b) Exclusion Criteria:

➢ Limited ability to understand / implement the study procedures and instructions

➢ Other pulmonary diseases (e.g. TB, pneumonia)

➢ Acute exacerbation or oral short course of high dose prednisolone during the last 4 weeks.

➢ Patient participating in another clinical research study at the time of or in the past 3 months.

➢ pregnant

(C) Design

Each patient's gender, age, height and weight were obtained together with their current medication. Their spirometry (PEF, FEV_1 and FVC) was measured using a MicroLoop Spirometer (Cardinal Health) and their % predicted values were calculated (Gore et al., 1995).

The patients were asked to complete the following;

➢ 18-55 years: Asthma Control Questionnaire (ACQ) and Juniper Asthma Quality Of Life Questionnaire (AQLQ) (Juniper et al 1999d; Juniper et al., 2006) [Appendix A-6 and A-7 respectively].

> 4-17 years: Paediatric Asthma Quality Of Life Questionnaire (PAQLQ) (Juniper et al., 1996a) and Paediatric Asthma Caregiver's Quality Of Life Questionnaire(PACQLQ) [APPENDIX A-8, A-9] (Juniper et al., 1996)

> COPD patients completed the St George's Respiratory Questionnaire (SGRQ) [APPENDIX A-10].(Jones et al., 1991)

Each patient, made two inhalations using their normal inhalation technique through an empty pMDI that was attached to an inhalation profile recorder. From these inhalation profiles the peak inhalation flow (PIF), inhalation volume (IV), the time between actuation and the start of an inhalation (TsIn) and the duration of the inhalation (Ti) were obtained. The inhalation profile with the slowest peak inhalation flow was chosen for the final data analysis.

Co-ordination was defined as GOOD if TsIn was 0-0.2 seconds (Farr et al., 1995), EARLY if < 0 seconds and LATE if > 0.2 seconds. Some patients did not actuate a dose during their inhalation (DNA). Flow was classified as SLOW if < 90 L/min (Newman et al, 1980, Newman et al, 1982; Farr et al, 1995; Pauwels et al, 1997) and FAST if > 90L/min with those > 200 L/min further classified as VERY FAST. Those with good co-ordination and slow flow were defined as using a GOOD technique. Also a IV/FVC ratio > 60% (Farr et al, 1995) suggested that they used a complete inhalation.

The measurements were made during a single visit and patients were free to withdraw from the study at any time. They could also be withdrawn from the study by their doctor or at the discretion of the investigator(s) if they violated the study plan, were unable to follow the protocol procedures and / or for any other safety or clinical reasons.

4.3.2 Statistical Analysis

The statistical analysis of the study data was carried out using the Statistical Package for the Social Sciences (SPSS for window version 17) software. The study data was first classified into scale, categorical (nominal) or ordinal categories, as appropriate, and an SPSS dataset was then set up for the analysis. The statistical analysis was performed and presented as follows

➢ Descriptive statistics: mean and standard deviation.

➢ For scale data; normal distribution of the data was examined using histograms and statistical tests for normality; the Kolmogorov-Smirnov and Shapiro-wilk tests

➢ Comparisons (differences) of measurements through different inhalers within the same group were performed using the related (paired)-samples t-test (for parametric data) and the Wilcoxon test (for non-parametric data)

➢ Comparisons (differences) of measurements between different the groups were performed using the independent-samples t-test (for parametric data) and the Mann-Whitney U test (for non-parametric data).

➢ Correlations between the ACQ and the inhalation parameters and between the spirometry indices and the inhalation parameters were carried out. The data was first tested for normality (as described above) to determine the use of either Pearson's (Normal data) or Spearman's rho (non parametric) tests

4.4 Results

4.4.1 Patients

Table 4.1 describes the 181 patients that completed this study.

Table 4.1. Demographic data of the patients. Value are means (SD) unless stated otherwise.

Characteristics	CHILD	ADULT	ADULT + CHILD	COPD
Number (n)	20	130	150	31
Age (years)	8.9(3.3)	39.7(9.2)	35.6(19.2)	67.2(11.6)
Sex (M/F)	14/6	33/97	47/103	16/15
Height (cm)	133.4(20.6)	167.1(9.2)	162.6(16.1)	167.3(10.9)
Weight (Kg)	35.8(17.7)	75.5(14.8)	70.2(20.3)	77.7(12.3)
FEV_1 (L)	1.74(0.58)	2.58(0.77)	2.47(0.80)	1.27(0.61)
FEV_1 (% pred)	53.9(13.1)	77.9(21.1)	74.7(21.9)	55.2(34.0)
FVC (L)	1.88(0.61)	3.13(0.95)	3.00(1.00)	2.06(0.81)
FVC (% predicted)	47.0(21.4)	78.3(22.1)	74.2(24.4)	57.4(19.9)
PEF (L/min)	201.3(70.7)	339.6(105.2)	321.1(111.6)	178.9(94.1)
PEF (% pred)	52.0(15.1)	74.4(23.3)	71.4(23.6)	40.2(21.0)

Classification of the severity of their obstruction according to their predicted FEV_1 is presented in table 4.2.

Table 4.2. Severity of patients.

	CHILD	ADULT	CHILD+ADULT	COPD
Mild	10	63	73	5
Moderate	7	45	52	7
Severe	3	22	25	19
Very Severe	N/A	N/A	N/A	0

The mean (SD) ACQ of the adult asthmatics (n=130) was 1.66 (0.93) with 22 below

0.7, 40 between 0.71 and 1.49, and 68 above >1.5. Their mean (SD) AQLQ was 4.35

(1.23). The mean (SD) PAQLQ of the children was 4.73(1.19) and PACQLQ

was 4.35 (1.05). The mean (SD) SGRQ of COPD patients was 60.6(18.5)

4.4.2 Inhalation parameters and coordination

A summary of the pMDI inhalation characteristics of the patients is presented in

Table 4.3.

Table 4.3. Mean (SD) inhalation parameters.

	CHILD	ADULT	CHILD+ADULT	COPD
Profile with slowest PIFR				
PIF (L/min)	70.5(36.4)	131.4(60.8)	123.2(61.7)	70.9(28.1)
IV (L)	0.88(0.60)	2.04(0.91)	1.99(0.96)	1.05(0.56)
Duration (Ti)	1.25(0.46)	1.68(0.82)	1.62(0.79)	1.44(0.65)
IV/FVC ratio (%)	50.0(29.7)	65.9(23.1)	67.4(24.7)	57.3(32.4)

The PIFs of each individual from the slowest profile are presented in Figure 4.2 -4.4.

Those for the inhalation volume are shown in Figure 4.5-4.7 and the inhalation times

in Figure 4.8-4.10 with the time between actuation and the start of an inhalation

(TsIn) in figure 4.11.
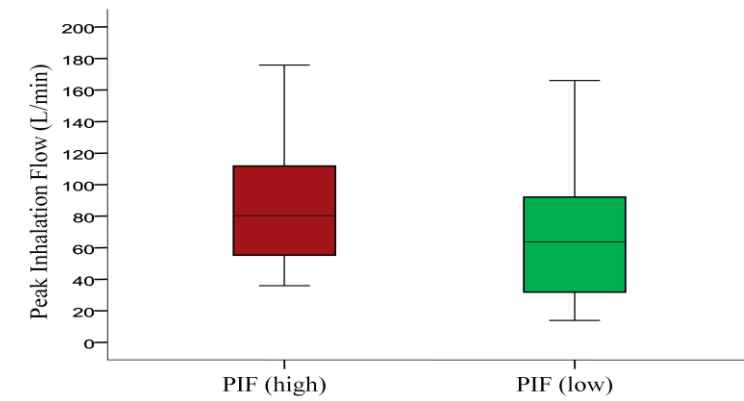
Figure 4.2. The distribution of the peak inhalation flow, from the fast and slow inhalation profiles, through the pMDI by children with asthma.
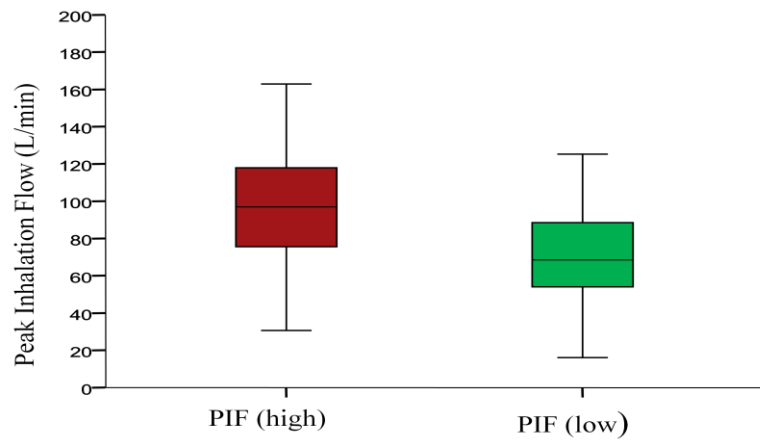
Figure 4.3. The distribution of the peak inhalation flow, from the fast and slow inhalation profiles, through the pMDI by the COPD patients.
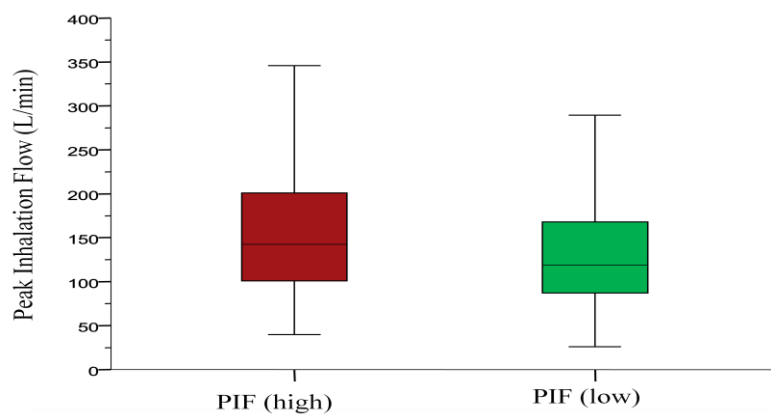
Figure 4.4. The Peak inhalation flows, from the fast and slow inhalation flow profiles, through the pMDI for the adults with asthma.
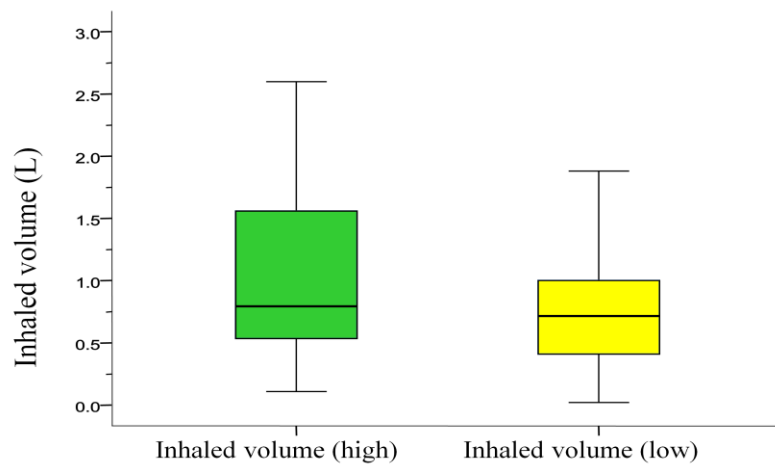
Figure 4.5. The inhaled volume, from the high and low inhalation profiles, through the pMDI by the children with asthma.
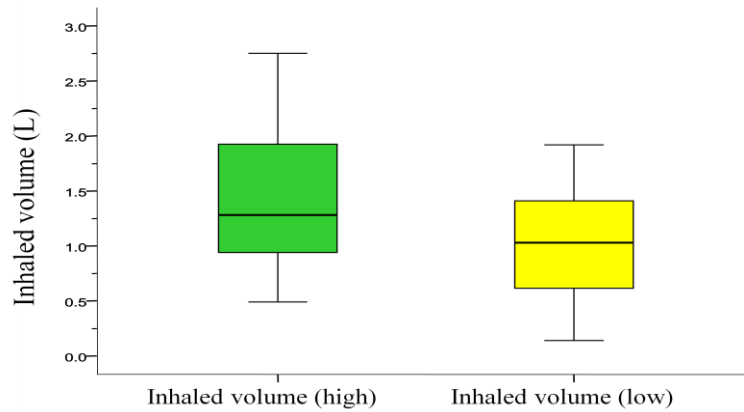
Figure 4.6. The inhaled volume, from the high and slow inhalation profiles, through the pMDI by the COPD patients.
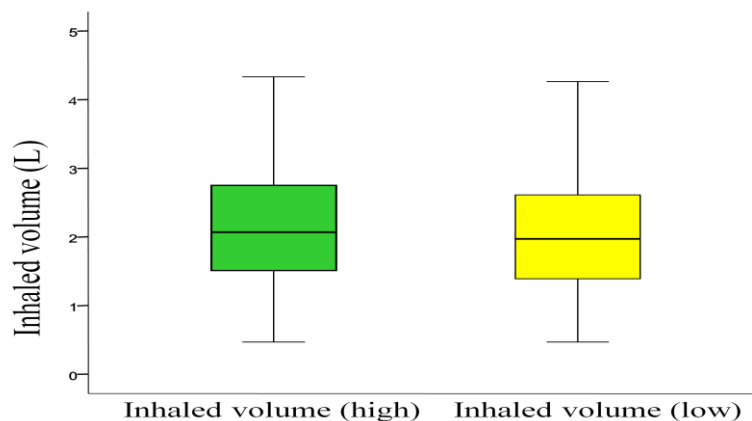
Figure 4.7. The inhaled volume, from high and slow inhalation flow profiles, through the pMDI by adults with asthma.
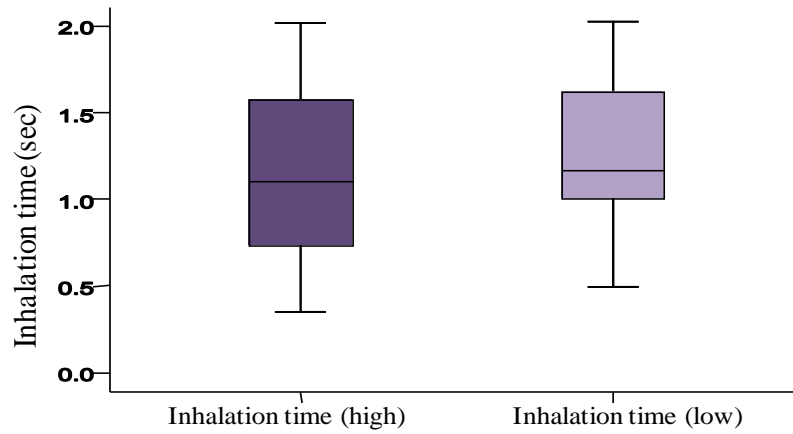
Figure 4.8. The inhalation times, from the high and low inhalation flow profiles, for children with asthma.
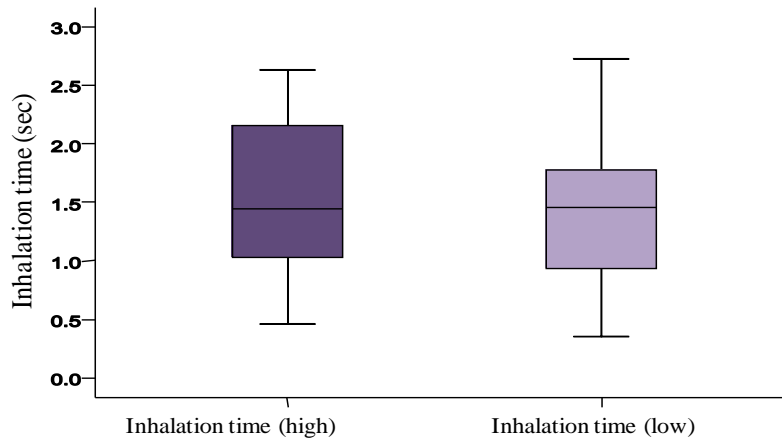
Figure 4.9. The inhalation times, from the high and low inhalation profiles, for COPD patients.
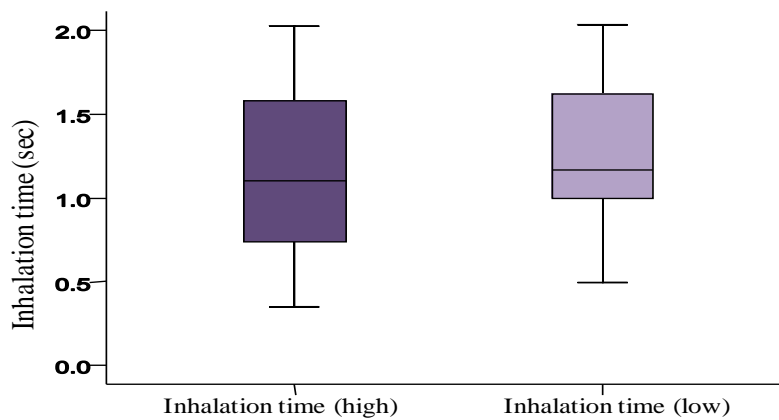
Figure 4.10. The inhalation times, from high and low inhalation flow profiles, for the adults with asthma.
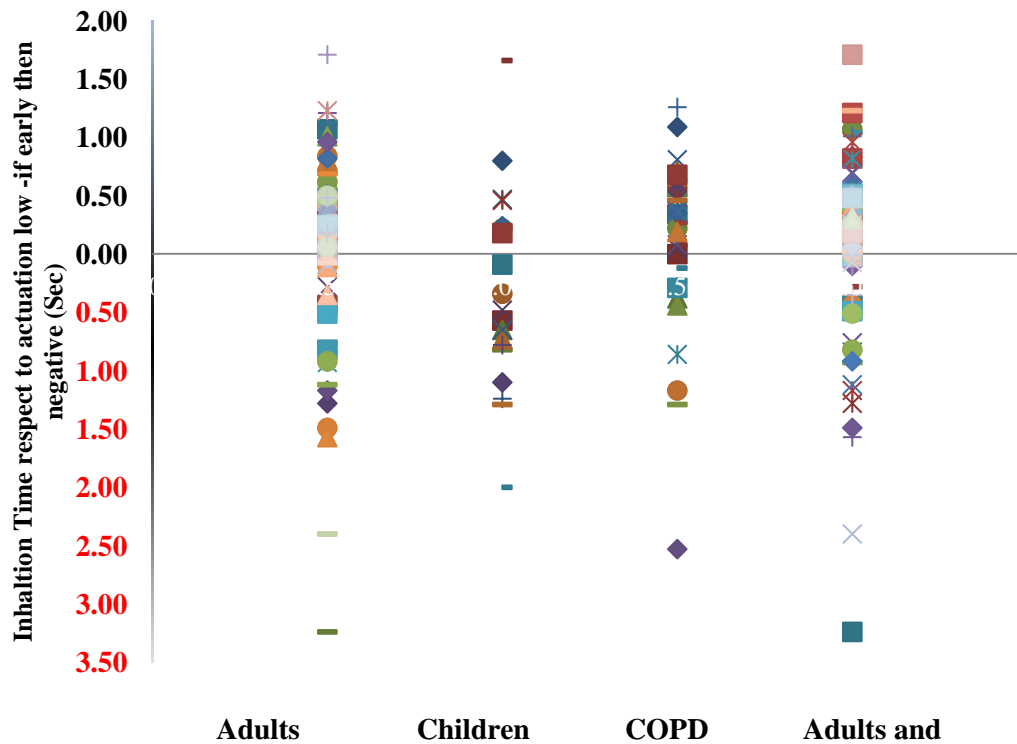
Figure 4.11. Inhalation times between actuation of the dose and the start of an inhalation (TsIn) for the different group of patients from slow the inhalation profiles.

Using the inhalation parameters from the profile with the slowest PIF to categorise aspects of the inhalation technique into flow, co-ordination, technique and a complete inhalation is presented in Table 4.5.

A comparison between each group presented in figure 4.12, 4.13, and 4.14 and a Summary of the comparison between the groups is presented in Table 4.4.
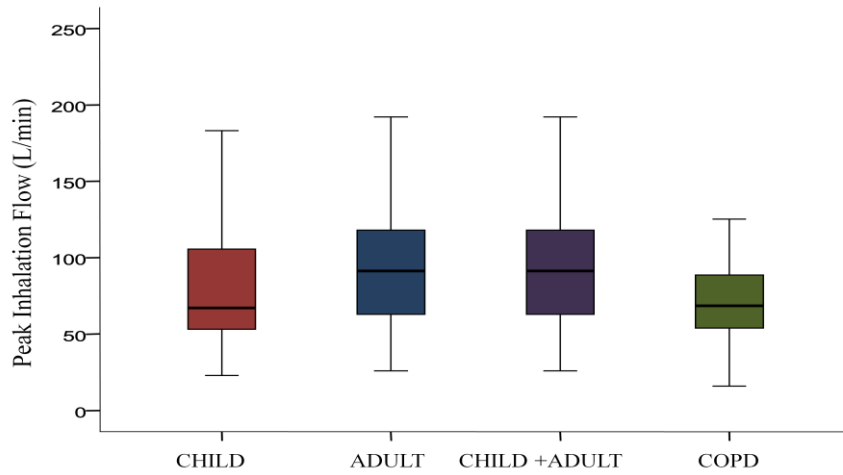
Figure 4.12. Peak inhalation flow (PIF) for different group of patients.
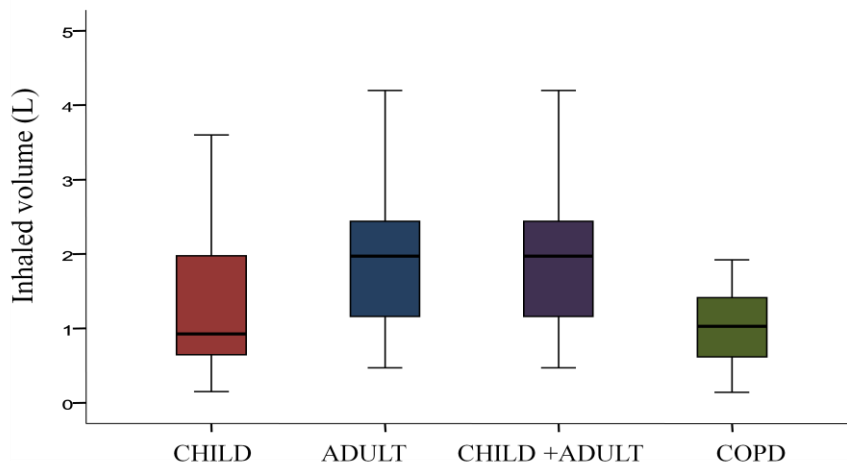
Figure 4.13. Inhaled volume (IV) for different group of patients
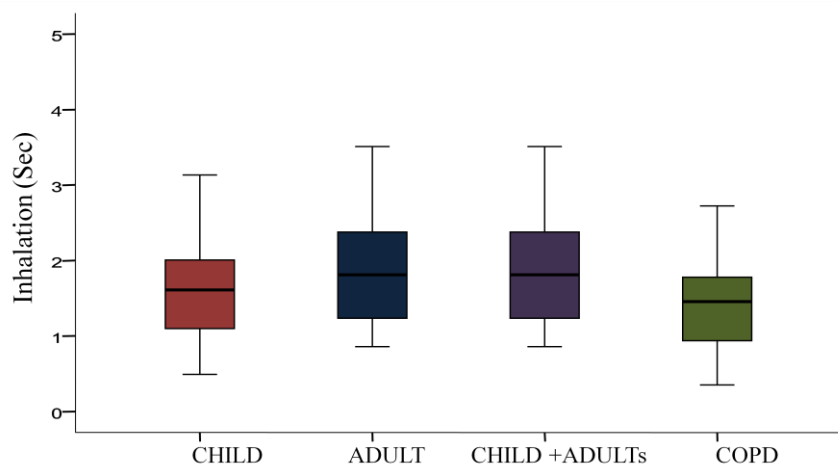
Figure 4.14. Inhalation time for different group of patients

A Summary of the comparison between the groups is presented in Table 4.4.

Table 4.4. Statistical summary between each group (Mann-Whitney U test for non-parametric data).

	CHILD vrs ADULTS	CHILD vrs COPD	ADULTS vrs COPD
PIF (L/min)	*p*<0.001	*p*=0.794(ns)	*p*<0.001
IV (L)	*p*<0.001	*p*=0.151(ns)	*p*<0.001
Ti (Sec)	*p*=0.016	*p*=0.375(ns)	*p*=0.159

Table 4.5. Classification of inhalation technique.

	CHILD	ADULT	CHILD+ADULT	COPD
(a) Flow				
SLOW	15	37	52	24
FAST	5	72	77	7
VERY FAST	0	21	21	0
(b) Co-ordination				
GOOD	5	53	58	10
EARLY	4	27	31	13
LATE	9	45	54	8
*DNA	2	5	7	0
(c) Good Technique				
GOOD	3	6	9	7
POOR	17	124	141	24
(d) IV/FVC ratio				
>60%	7	84	91	15
<60%	13	46	59	16
(e) Good technique and IV/FVC ratio >60%				
	0	2	2	3

*DNA: did not actuate a dose during their inhalation

4.3.3 Correlation between ACQ and PMDI technique

There was no link between asthma control and inhalation parameters. Of the adult asthmatics that used a slow inhalation (n=37) only 5 had an ACQ <0.7 whereas 6 had an ACQ of 0.7-1.5 and the remaining 26 had >1.5. Figure 4.15 and 4.16 shows the relationship between the ACQ for the adults with asthma with peak inhalation (low) and inhalation volume (low). Of those with good co-ordination (n=53) 12 had an ACQ of < 0.7, 21 between 0.7 and 1.5 and 20 >1.5. The six adult asthmatics with good technique (slow flow and good co-ordination) had ACQ scores of 1.57, 1.86, 1.43, 2.7, 2.17 and 1.50. Two of these asthmatics with good technique had a IV/FVC ratio of > 60% and their ACQ scores were 2.7 and 2.17.
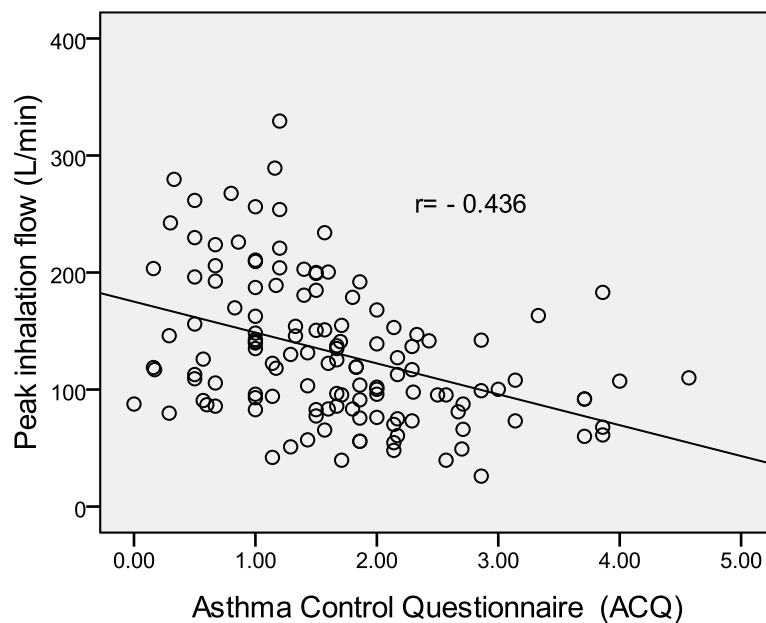
Figure 4.15. Correlation between the peak inhalation flow (low) and the ACQ for adults with asthma (p<0.01).
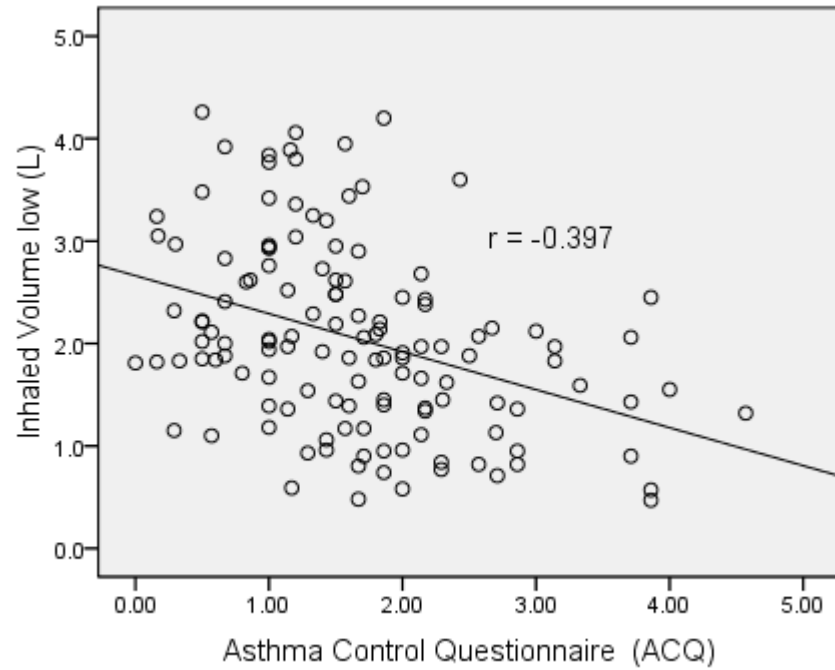
Figure 4.16. Correlation between the IV and the ACQ for adults with asthma (p<0.01).

4.3.4 Correlation between spirometry and inhalation parameters

The inhalation parameters from the profile with the slowest PIF were chosen for the correlations.

There was no correlation between PEF and PIF for any of the groups. Associations between FEV_1 and the inhalation parameters as well as FVC and the inhalation parameters were significant with the latter being more strongly correlated.

The only significant correlation between spirometry and the inhalation parameters was between FVC and PIF as well as FVC and IV for the adult with asthma group as shown in figure 4.17-4.18
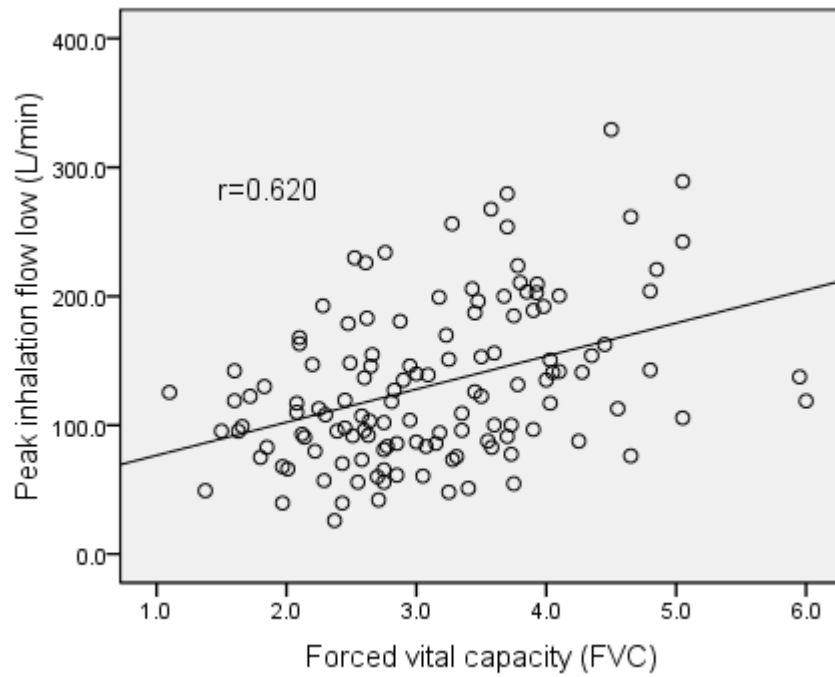
Figure 4.17. Relationship between the FVC and PIF for adults with asthma ($p<0.001$).
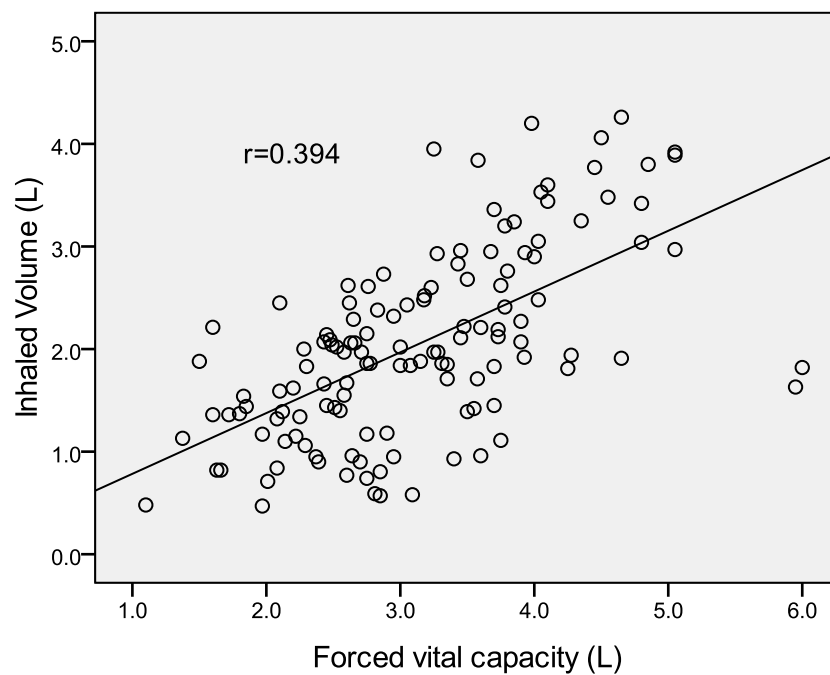
Figure 4.18. Relationship between the FVC and IV for adults with asthma p<0.001.

4.5 Discussion

The results in this chapter provide substantial data about the inhalation characteristics of all patients when they use their pMDI. The metered dose inhaler (MDI) is the most widely used inhaler to deliver drug to the airways (Everard et al., 1995) and the efficiency of the pMDI, in terms of the extent and distribution of lung deposition, is influenced by many factors (Goldberg and Lourenco, 1973; Newman et al., 1981a; Ganderton, 1997). The inhalation technique by patients is one of the main factors that affect the fraction of the inhaled aerosol depositing in the lung and the subsequent distribution of the inhaled dose in the lungs (Canadian Asthma Consensus Group, 1999). Inadequate pMDI use adversely affects airways distribution and results in poor drug delivery, decreased disease control and increased inhaler use. Many studies have found that using the correct inhalation technique through pMDIs results in a significant increase in bronchodilator response (Newman et al ,1980), and misuse of pMDIs is correlated to reduced asthma control (Giraud and Roche 2002; Al-Showair et al, 2007a), increased corticosteroid use (Kamps et al., 2003) and hospitalisations (Melanie et al, 2003). Efficient inhalation technique by patients is crucial for the success of therapy. In realty, the majority of asthmatic and COPD patients misuse their pMDI and several studies have confirmed that patients fail to use the correct technique when using their pMDIs (Paterson and Crompton, 1976; Epstein et al., 1979; Larsen et al., 1993; Larsen et al., 1994; Kamps et al., 2000; Molimard et al., 2003; Melani et al., 2011).

There is a growing appreciation of the fact that patients find it particularly difficult to use the correct inhalation technique, particularly where device actuation and inspiration are concerned (Price et al., 2003). Many previous studies have attempted to measure inhalation technique using direct observation. These methods will have

limitations and, so throughout this study an inhalation profile manager system has been used to obtain reliable quantitative inhalation measurements in order to assess technique.

To signify a good inhalation technique coordination between inhalation and device actuation, should be between > 0 and < 0.2 seconds (Farr et al., 1995) and an inhalation flow of < 90 L/min was defined as slow flow (Farr et al, 1995; Pauwels et al, 1997; Al-Showair et al, 2007). Although many patients fail to exhale before an inhalation (Melani et al., 2011) the definition of a complete inhalation with respect to the inhaled volume has yet to be fully defined although there is a suggestion that a IV/FVC ratio of > 0.6 could indicate this (Goodman et al., 1994; Farr et al., 1995).

This study has confirmed that a high percentage of patients have poor co-ordination and not using a slow flow is the main problem. Fifty three of the 130 adults with asthma used good co-ordination hence 60% demonstrated poor co-ordination. In children with asthma, as expected, more had poor co-ordination (75%) but there were only 20 subjects which could have influenced this. COPD patients were not much better with 68% having poor co-ordination. Again the number (n=31) is much lower than the adults asthmatics. These values for poor co-ordination are similar to those previously reported (Crompton, 1982b; Nimmo et al., 1993; Cochrane et al., 2000) but higher than others (Broeders et al., 2003a; Molimard et al., 2003; Melani et al., 2004; Sestini et al., 2006; Melani et al., 2011). Of most significance 5 adults with asthma and 2 children with asthma that did not depress the pMDI canister. These would receive no dose irrespective of how good the inhalation manoeuvre was. Furthermore 7 adults pressed the canister, to release a dose, at least one second before the start of their inhalation (one patient pressed 3.24 seconds before and another 2.4 seconds before). Also two children depressed >1 second before the start

of their inhalation (one was 3.24 seconds) and three COPD subjects (all >2 seconds). Hence those that did not actuate or inhaled too early are likely to receive no lung deposition. The total of asthmatics (adults and children) that did not actuate or actuated too early is 16 out of a total of 151, hence 10.6%. The three COPD subjects reflect 9.7% although the number of these subjects is small. The results suggest that approximately 10% would have received no drug which is the most significant clinical error that can be made by these patients.

Using a high PIF decreases lung deposition, with increased deposition in the mouth and central zones of the lung (Dolovich et al., 1981; Newman et al., 1981a; Newman et al., 1982; Newman et al., 1994; Newman et al., 1995a). This may affect the fraction of the dose reaching the peripheral regions of the lungs, subsequently affecting the clinical efficacy of the inhaled therapy (Newman et al., 1981b; Newman, 1985). Using a slow inhalation flow has been shown to improve asthma quality of life (Al-Showair et al, 2007). Broeders et al (2003) has reported that the mean of 12 asthmatics and 36 COPD subjects was in the range of 117 – 149 L/min and Al- Showair reported that in 163 COPD subjects the mean was 110 L/min. The latter method did not use electronic methods and was constrained by a maximum flow of 120 L/min due to measuring instrument used (IN- Check Dial). The PIF values of the adult asthmatic are similar to those previously reported whilst the COPD PIF values are slower and there is no previous report with children. Overall the flows in the children with asthma and in the COPDs were the best with 15 out of 20 (75%) children and 24 out of 31 (77%) using a flow < 90 L/min. It is amongst the adult asthmatics that flow is too fast. Overall 93/130 (72%) used a fast flow with 21 (16% of the total) inhaling > 200 L/min.

The inhalation volumes of the children and COPD subjects were, as expected, lower than those of the adult asthmatics. The values in the COPD subjects are much lower than those previously reported (Broeders et al, 2003). This also applies to the asthmatic adults (Broederes et al., 2003) which is also much lower than that reported in healthy volunteers (Farr et al., 1995). In the children the overall mean IV/FVC ratio was less than 50% which could suggest that there was a tendency not to make a full inhalation. Such a ratio would be irrelevant in COPD because of the severity of any obstruction. However the mean value for this ratio was 51% which could suggest that they also did not make a complete inhalation. In the adult asthmatics this ratio is around 66% which does indicate that overall these patients were making a full inhalation.

The strong correlations between inhaled volume and the forced vital capacity of the adult asthmatics have not been previously reported. However these strong correlations did not occur for the children with asthma or the COPD subjects. This would be due to the size of the children and the reduced lung volumes of the COPD patients especially when measuring FVC where there is a tendency for airways to collapse during a forced exhalation maneuver. The correlation between inhaled volume and forced vital capacity warrants further investigation because if a ratio that indicates a full inhalation can be identified then this could be incorporated into future electronic inhaler technique aids to indicate how complete the inhalation was. From the results there is a suggestion that a ratio of > 0.66 indicates a full inhalation. A similar correlation to the inhalation parameters were noted for the FEV_1 (as would be expected due to the FVC correlations) but they were not as significant as the FVC.

Studies have shown that only about 10% of patients use an ideal technique with their pMDI (Allen and Prior, 1986; Larsen et al., 1994; Al-Showair et al., 2007a; Hardwell

et al., 2011). However some other observational studies suggest that between a quarter (Goodman et al., 1994) and a third (Molimard et al., 2003) do not make any errors when they use their pMDI. Only 8% of patients used their pMDI with a flow < 90 L/min and with good co-ordination. In this study 3 /20 (15%) children with asthma, 6/130 (4.6%) asthmatic adults and 7/31 (23%) COPD subjects met these criteria for a slow flow and good co-ordination. When the criteria for an ideal technique were extended to an IV/FVC ratio of > 60% then only 2 adult asthmatics meet these criteria. Hence when electronic measurements are used only 2 out of the total of 151 patients, hence 1.3% used an ideal technique. Although these are very precise electronic measurements they do highlight the potential for designing simple and portable electronic methodology to help identify the problems patients have using their pMDIs. The values obtained would provide valuable feedback on the specific inhalation steps to focus on during training sessions.

These results were available when the ERS / ISAM Consensus statement was in the draft stage (Laube et al, 2011). These results informed the recommendation, in the Consensus Statement, that the inhalation time of an adult should be towards 5 seconds and for a child to be 2-3 seconds (Laube et al, 2011).

However the inhalation times that have been measured fall below these recommended. Theoretically if the inhaled volume does not change and the patient prolongs their inhalation (as demonstrated by the results in this study) then the resultant inhalation flow will decrease. By focusing on increasing the inhalation time will naturally slow the inhalation flow. This may be easier for the patients to understand than instructing them to use a slow inhalation. This could then be extended with information to depress the canister soon after the start of a slow inhalation. This instruction could reduce their tension and stress about the co-

ordination step and enable them to make a relaxed inhalation with their pMDI. Some studies have shown that flow does slow down after training (Broeders et al, 2003; Sarvis etal, 2004; Al-Showair et al 2007b,) whereas others have demonstrated no effect (Hardwell et al, 2011). However patients do revert back to their old habit of a poor technique soon after training (Shim & Williams, 1980). A new approach to focus on prolonging the inhalation time may provide more long lasting effect with improved inhalation technique and hence needs to be investigated.

The correlations between the ACQ and the inhalation parameters are interesting and link to the six asthmatics with slow flow and good co-ordination. The lowest ACQ of these 6 asthmatics was 1.43 indicating that they all had poor asthma control. The correlation between ACQ and flow suggest that as asthma control is poorer then their flows are slower. This could be due to them concentrating more on their technique because their asthma control is not good. Alternatively the results may indicate that although their inhalation technique is good their compliance is poor

Conclusion

The methodology used in Chapter 3 was extended to include a measure of the co-ordination between the start of an inhalation and the release of a dose. Only a few patients used a slow flow with good co-ordination and again the duration of the inhalations were short. The correlation between the inhaled volumes and the forced vital capacity could be a useful indicator for an objective assessment of a 'full inhalation'. The results suggest that an electronic aid to check a pMDI technique could provide the necessary information for the trainer to focus on when training patients how to use their pMDI

Chapter 5: Improved metered dose inhaler technique when a co-ordination Cap is used

5.1 Introduction

The pressurised metered dose inhaler (pMDI) has been the most widely used inhaler over the past 40 years (Crompton, 2006) and the problems patients had using the correct inhaler technique when it was introduced are the same as they are today (Saunders, 1965; Paterson and Crompton, 1976; Molimard et al., 2003; Melani et al., 2004; Melani et al., 2011). It has been shown that poor pMDI technique is related to poor asthma control (Orehek et al., 1976; Giraud and Roche, 2002; Kamps et al., 2003; Al-Showair et al., 2007a) and hospitalisation (Melani et al., 2011). The recommended inhalation procedure for a pMDI involves several steps (see Table 2.11, section 2.3.1.1) (Laube et al., 2011), of these good co-ordination and a slow inhalation flow maintained for as long as possible are particularly important for good asthma control (Al-Showair et al., 2007a). Lung deposition is reduced when there is poor co-ordination between the actuation of the dose and the start of inhalation (Newman et al., 1991b) and when a fast inhalation flow is used (Newman et al., 1982; Hindle et al., 1993). Only 8% of patients use a good inhaler technique with their pMDI (Al-Showair et al., 2007a) and although inhalation technique training can be useful, (Al-Showair et al., 2007a) in some cases it has little effect (Broeders et al., 2003a) or improvements are temporary (Shim and Williams, 1980). Breath actuated inhalers solve the problem of poor co-ordination (Newman et al., 1991b) but the choice is limited to use with salbutamol and beclometasone.

A flexible co-ordination cap, shown in Figure 5.1 (i-Breathe, Teva Pharmaceuticals), has been designed to fit onto a pMDI, with an airtight seal, such that an inhalation cannot start until the canister is pressed. Pressing the canister causes slits in the co-ordination cap to open (as it becomes compressed), and this allows the inhalation to be made. The pMDI is converted into a breath actuated device. In this study, we have

measured the inhalation parameters of asthma patients using a pMDI to identify if these parameters change when the co-ordination cap is fitted. We have extended this to determine if a short training session to increase the patients' inhalation times helps to decrease their inhalation flow.
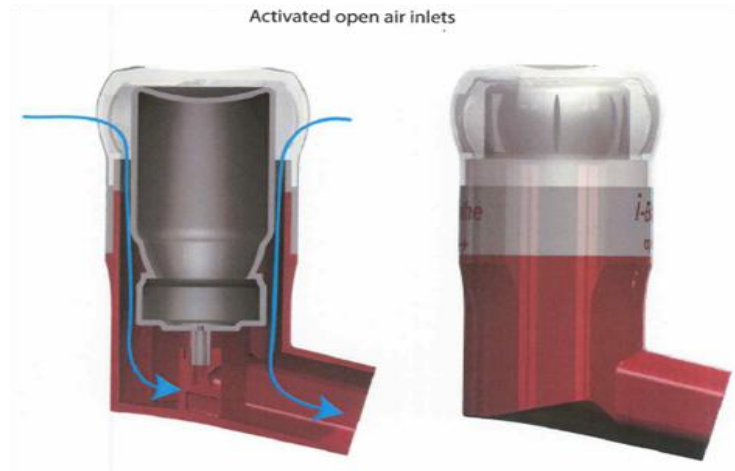
Figure 5.1. The I-Breathe inhaler (Teva Pharmaceuticals, Ire).

5.2 Aims and Objectives

5.2.1 Aims

To identify if there is a change in the inhalation parameters when a patient uses a pMDI when a co-ordination cap is fitted and whether a simple instruction to prolong the inhalation time alters the inhalation parameters.

5.2.2 Objectives

➢ Obtain demographic and spirometry data from mild asthmatics

➢ Measure the resistance of a pMDI and when the co-ordination cap is fitted on the pMDI

➢ Measure inhalation profiles when asthmatic patients use a pMDI, the pMDI with the co-ordination cap and the pMDI with the co-ordination cap after an instruction to prolong their inhalation time to 5 seconds.

➢ Correlate pMDI inhalation parameters to spirometry.

5.3 Methods

5.3.1 Patient demographics and baseline characteristics

Ethical committee approval was received from the Yorkshire and Humber Research Ethics Committee – Bradford (ref number 09/H1302/64) and from the University of Huddersfield (SASEC/ 10/01).

5.3.1(a)Inclusion Criteria

➢ Asthma

➢ 18-45 years old

➢ Prescribed a pMDI

5.3.1(b)Exclusion criteria

➢ Acute exacerbation or short course of oral prednisolone in the previous 4 months

➢ Not able to understand the inhalation procedure instructions

➢ Other pulmonary diseases (e.g. TB, pneumonia)

➢ Pregnant

All patients provided written, informed consent prior to participation.

5.3.2 Study design and inhalation parameters

Patients' demographic data and medication usage were recorded. Their spirometry was measured using a ONE FLOW (Clement Clarke International, UK) Spirometer and they each completed the Asthma Control Questionnaire (ACQ) (Juniper et al., 1999b).

An empty pMDI was adapted such that electronic data could capture a patient's inhalation flow profile as shown in figure 4.1 section - 4.1.

From this profile the peak inhalation flow (PIF in L/min), the inhalation volume (Vin in L) and the length of the inhalation (Ti in seconds) were determined. A ratio

of Vi/FVC was calculated to indicate a deep inhalation. The time between the start of an inhalation and pressing the canister was defined as TsIn (seconds).

Slow flow was defined as PIF < 90L/min (Newman et al., 1980; Newman et al., 1981a; Hindle et al., 1993; Pauwels et al., 1997; Broeders et al., 2003a) and good co-ordination as TsIn of 0–0.2 seconds (Newman et al., 1980; Newman et al., 1981a; Goodman et al., 1994; Farr et al., 1995; Gabrio et al., 1999; Broeders et al., 2003a). A deep inhalation was defined as a Vi/FVC ratio of > 0.6 (Farr et al., 1995).

All procedures were carried out during a single visit. Inhalation profiles were measured for each of the following inhalation procedures.

➢ pMDI: patients inhaled through an empty pMDI. The inhalation procedure they used was their normal real life manoeuvre.

➢ pMDI+CAP: Patients used the empty pMDI fitted with the co-ordination cap. Again they used their normal untrained inhalation technique. They were informed that the cap would not allow them to inhale until it was depressed. During use, if the patient did not keep the canister depressed then the slits in the cap would close and not allow any further inhalation. If this occurred the patient was instructed that they should keep the canister depressed until the end of their inhalation. This instruction was only given once.

➢ pMDI+CAP+TRAIN: Each patient was then trained to increase the length of their inhalation to 5 seconds. This was done by the trainer demonstrating a slow inhalation whilst they counted to 5 and this was then practised once by the patient. Patients then used the pMDI fitted with the co-ordination cap after this training, and inhalation profiles were measured.

For each inhalation manoeuvre two separate inhalations were made. The inhalation parameters for the profile with the slower PIF were chosen for data analysis.

5.3.3 Patient satisfaction

Following the inhalations, a 5 point Likert scale was used to obtain patient satisfaction about using a pMDI with the co-ordination cap. Patients were also asked if they perceived any advantages or disadvantages when using the co-ordination cap with their pMDI.

5.3.4 Resistance of devices

The resistance of the pMDI with and without the co-ordination cap was determined by measuring the pressure change corresponding to flows from 10-100 L/min as described by Clark and Hollingworth (Clark and Hollingworth, 1993).

5.3.5 Statistical analysis

A series of repeated measures analyses of covariance (ANCOVA) models was derived to assess the effect of pMDI+CAP and pMDI+CAP+TRAIN (the inhalation procedures) on the use of a pMDI, with respect to the primary outcome measure of PIF; and the secondary outcome measures of Vin and Ti, and controlling for all measured factors and covariates. All covariates were centred to avoid altering the main effect of the condition in any cases where covariate variability was large compared to condition variability. An additional series of controlled (ANCOVA) models was derived using the outcome measure Vin standardised by FVC. In these models FVC was not included as a covariate.

An uncontrolled multivariate general linear model was also performed on baseline data, considering the relationship between the single predictor FVC and a linear combination of the three outcome measures, with follow-up univariate models derived as appropriate

5.4 Results

The measured resistance of the empty pMDI without the co-ordination cap was 0.0135 $(cm\ H_2O)^{1/2}(min\ L^{-1})$ and 0.0243 $(cm\ H_2O)^{1/2}(min\ L^{-1})$ for the pMDI with the co-ordination cap while the canister was depressed.

Patients' baseline characteristics and spirometry measurements (n=71 patients, 52 females and 19 males) are listed in Table 5.1.

Table 5.1. Mean (SD) Patient demographics and baseline characteristics.

Characteristic	n=71
Age (years)	31.96 (13.5)
Weight (Kg)	74.44 (12.8)
Height (cm	167.45 (9.7)
PEF	
Actual (L/min)	355.5 (108.1)
% predicted	74.8 (23.3)
FVC	
Actual (L)	3.46 (1.04)
% predicted	82.4 (22.0)
FEV_1	
Actual (L)	2.81 (0.85)
% predicted	78.31 (21.03)
ACQ	1.32 (0.71)

Sixteen patients had an ACQ below 0.75, 30 patients between 0.75 and 1.5, and 25 above 1.5.

There was no statistical difference between the parameters for the inhalation profile with the slowest and the faster PIF. Figure 5.2 shows a distribution of the PIF values of each individual from the profile with the slow inhalation whilst figures 5.3 and 5.4 show inhaled volume and inhalation time distributions.
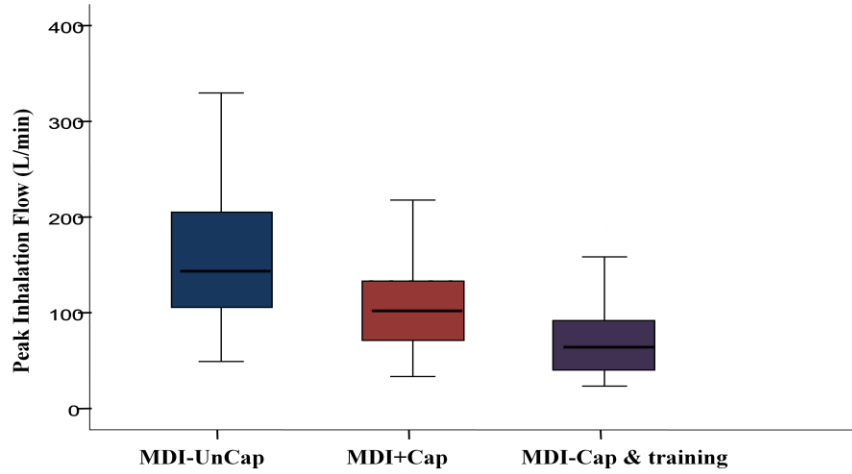
Figure 5.2. The distribution of the individual PIF values for each inhalation manoeuvre.
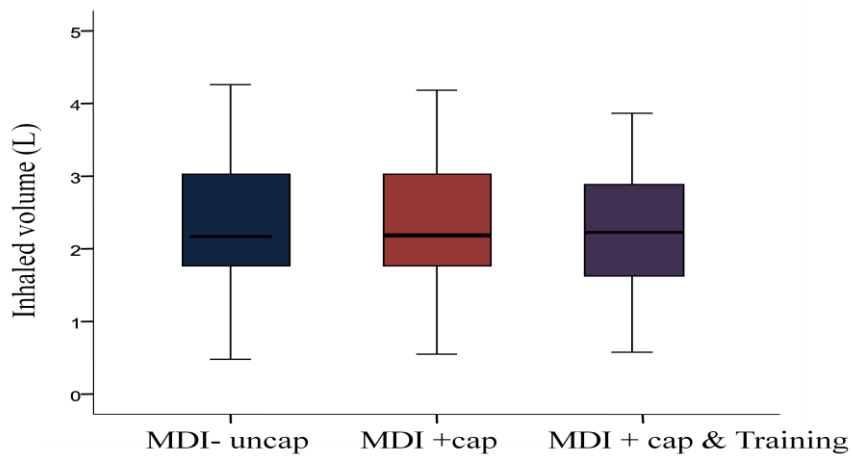
Figure 5.3. The distribution of the individual inhaled volumes for each inhalation manoeuvre.
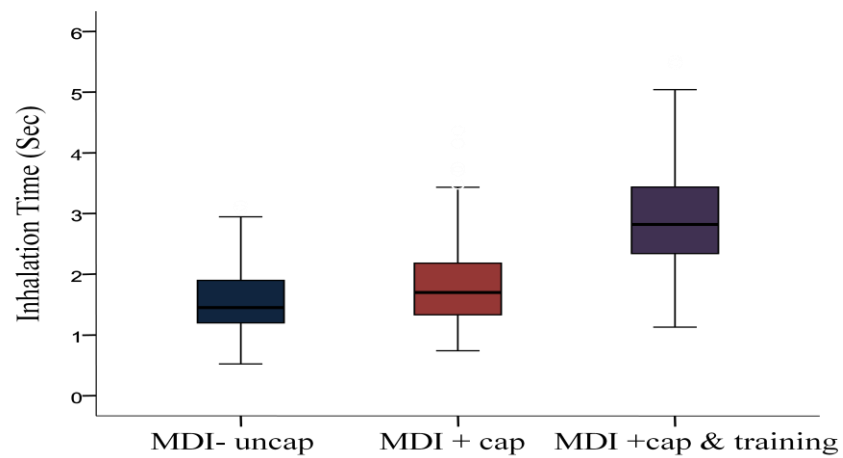
Figure 5.4. The distribution of the individual inhalation times for each inhalation manoeuvre.

Table 5.2 shows a summary of their inhalation parameters for the inhalation profile with the slowest PIF. Individual PIF, Statistical analysis revealed pair wise differences corrected for multiple comparisons (p< 0.001) between the PIF and Ti for each inhalation procedure but not for Vin.

Table 5.2. Mean (SD) inhalation parameters for patients using a pMDI with or without the co-ordination cap. PIF, peak inhalation flow; IV, volume of inhalation; Ti, time of inhalation; FVC, forced vital capacity.

Parameter	Profile with slowest PIF			
	MDI alone	With Cap	With cap after training	*p* value
PIF, L/min	155.6 (61.5)	112.3 (48.4)	73.8 (34.9)	<0.001
IV, L	2.33 (0.84)	2.26 (0.86)	2.30 (0.79)	0.681
Ti, sec	1.60 (0.60)	1.92 (0.80)	2.99 (1.03)	<0.001
Vi/FVC	0.70 (0.21)	0.67 (0.22)	0.68 (0.18)	0.847

Table 5.3. Shows the number of patients using a slow flow and Table 5.4 those that used a full inhalation.

Table 5.3. The number (and percentage) of patients who performed a slow (correct) inhalation (< 90 L/min), fast inhalation (90–200 L/min) and a very fast inhalation (> 200 L/min).

PIF (L/min)	pMDI,	pMDI+CAP	pMDI+CAP+TRAI
< 90 (slow)	12 (16.9)	25 (35.2).	50 (70.4)
90–200 (fast)	41 (55.8)	42 (59.2)	21 (29.6)
>200 (very fast)	18 (38.0)	4 (5.6)	0

Table 5.4. Patient with a deep inhalation with respect to their Vi/FVC ratio.

Ratio Vi/FVC	pMDI, n (%)	pMDI+CAP, n (%)	pMDI+CAP+TRAIN, n (%)
< 0.6	19 (26.8)	26 (36.6)	21 (29.6)
> 0.6	52 (73.2)	45 (63.4)	50 (70.4)

When using the pMDI alone Figure 5.5 shows the TsIn values. Negative values are compared to an early inhalation (actuation before inhalation).
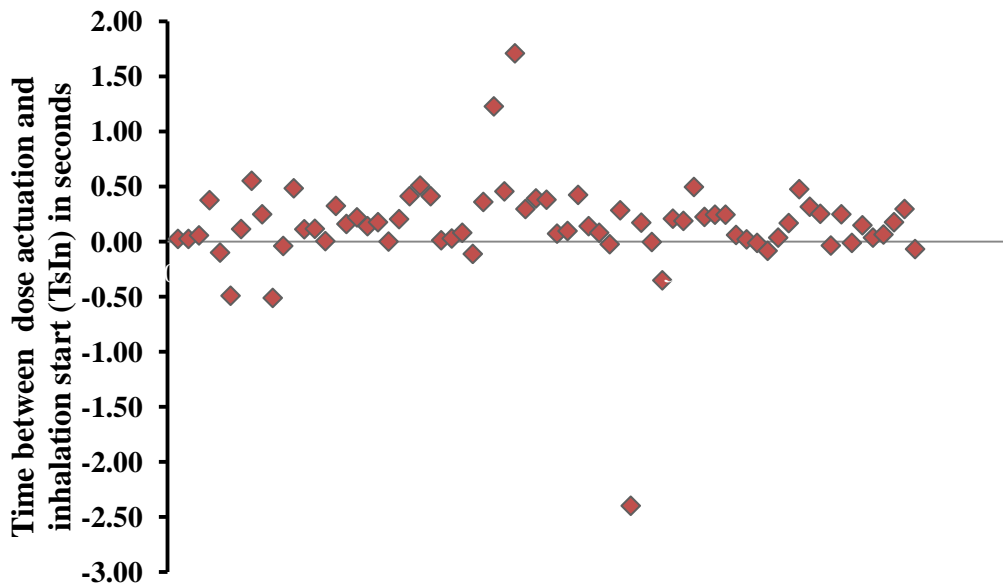
Figure 5.5. The co-ordination time (TsIn) in seconds for each patient.

Seven patients had a negative TsIn (ranging from -0.1 to -2.41 seconds) indicating early actuation and 22 a late actuation (TsIn 0.25-1.71 seconds) whilst 42/71 (59%) used the pMDI with good co-ordination (TsIn 0-0.2 sec). Of these 42 patients with good co-ordination only 2 had a PIF < 90 L/min: therefore 2/71 (2.8%) demonstrated good inhalation technique when using the pMDI without the co-ordination cap.

Patients were asked on a scale of 1 to 5 how satisfied they would be to use the co-ordination cap with their pMDI in daily life (1 unsatisfied, 5 very satisfied). 7 gave a score of 3, 21 a score of 4 and 33 were very satisfied (score of 5). 17 of the 71 patients had to be instructed to keep the canister depressed throughout the duration of their inhalation the first time they used the pMDI fitted with the co-ordination cap. The inhalation profile was repeated when this occurred. They did not repeat this problem for all the remaining inhalations.

An uncontrolled general linear model (GLM) assessing the effect of FVC on baseline outcome measures indicated a significant association between FVC and the outcome measures assessed jointly ($p< 0.001$). Subsequent follow-up univariate GLMs identified significant associations between FVC and PIF ($p=0.006$); and between FVC and Vin ($p=0.001$). The association between FVC and Ti was not statistically significant. Figures 5.6 and 5.7 highlight that PIF ($p=0.006$) and IV ($p<0.001$) were significantly correlated with FVC. Ti was not significantly correlated with FVC ($p=0.073$).
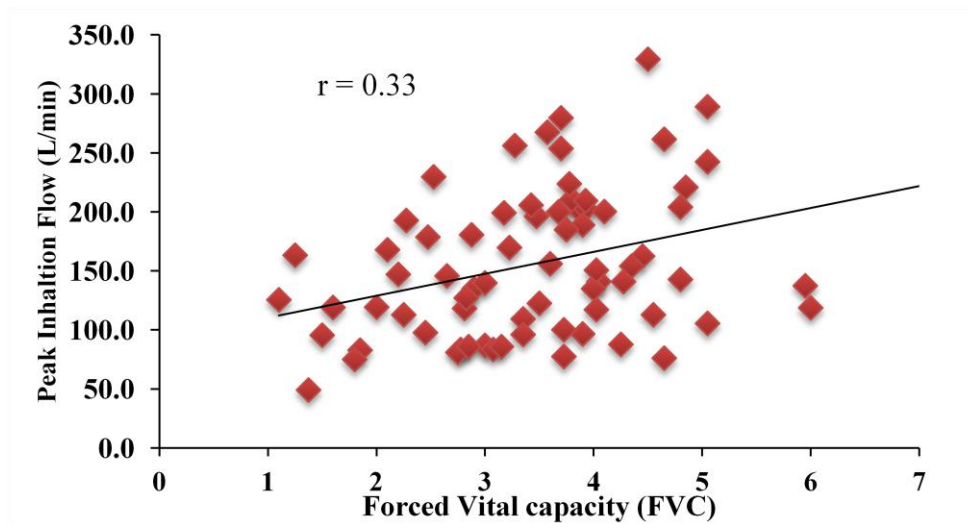
Figure 5.6. The correlation between peak inhalation and forced vital capacity.
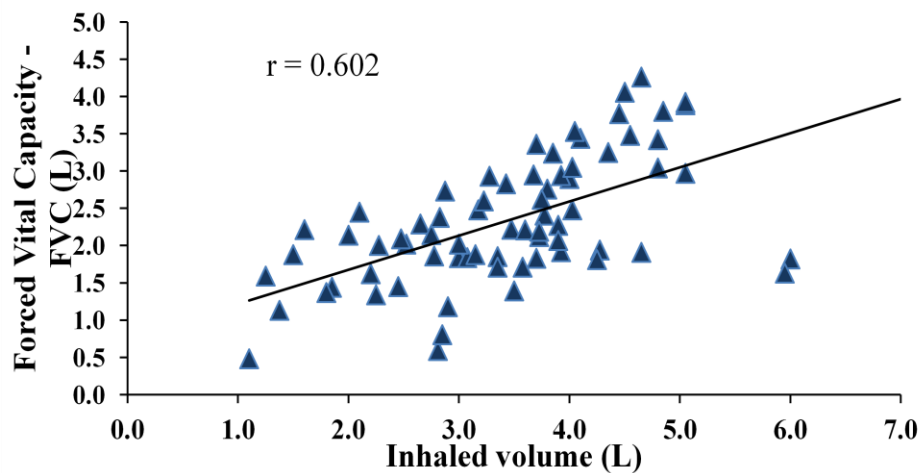
Figure 5.7. Correlation between inhaled volume and forced vital capacity.

5.5 Discussion

Overall in this study 59% of the patients used their pMDI with good co-ordination and 73.2% had a IV/FVC ratio of > 0.6 indicating a full inhalation but only 16.9% used a slow inhalation. These and the consistent inhalation volume for each procedure indicate that overall the pMDI technique of these patients was good. The proportion of patients with poor co-ordination is consistent with previous reports which used subjective methods (Hesselink et al., 2001; Molimard et al., 2003; Melani et al., 2004; Melani et al., 2011). The results confirm previous studies that show that not using a slow inhalation is the commonest mistake made by patients (Hesselink et al., 2001; Al-Showair et al., 2007a). Despite the overall good pMDI inhalation technique of these patients and that they were mostly mild asthmatics only 16 had good asthma control (ACQ < 0.70) (Juniper et al., 2006). The study results highlight the potential of solving co-ordination problems with the cap and that using a simple instruction to increase the inhalation period towards 5 seconds ensures that most patients would use a slow flow with good co-ordination. Since asthma control is related to inhaler technique (Giraud and Roche, 2002; Al-Showair et al., 2007a; Melani et al., 2011) and hospitalisations (Melani et al., 2011) then use of the cap and a simple instruction to extend the duration of the inhalation to 5 seconds would improve inhalation technique. These improvements could improve patients' asthma control and thus contribute to the GINA challenge to reduce hospitalisations by 50% over a 5 year period (Fitzgerald et al., 2011).

The very highly significant slower inhalation flow with the cap fitted compared to the pMDI (alone – without the cap) would be due to the increased resistance caused by the cap. This would also have been the reason for the slightly longer inhalation time.

(The small difference between the inhalation times explains the lack of any statistically significant difference). The lower flows and longer inhalation times with unchanged inhaled volumes suggest that new pMDI or new drugs formulated in pMDI should be designed with resistance to airflow to naturally reduce the speed of the inhalation flow. This phenomena occurs with dry powder inhalers.

After the short inhalation technique training that focussed on increasing the inhalation times towards 5 seconds patient inhalation time did increase by approximately 1 second to almost 3 seconds, and since the inhalation volume was unchanged then there was a further very highly significant reduction in the inhalation flow. This training lasted less than one minute and resulted in a highly significant increase in the inhalation time. Although the training was targeted to increase their inhalations to 5 seconds the increase from 2 to 3 seconds and the no change in the inhaled volumes substantially reduced the inhalation flows.

The first set of measurements using the pMDI alone showed that only 2 (3%) of the patients used a slow inhalation flow with good co-ordination that was consistent with previous values (Al-Showair et al., 2007a). Without training this increased to 25 (35%) patients with slow flow and good co-ordination because of the cap. This was further increased to 50 (70%) patients when the co-ordination cap was used together with the simple instruction to lengthen inhalation (as near to 5 seconds as possible). In clinical use this would represent a large increase in the number of patients with good inhaler technique. Previous studies have shown the clinical benefit of a breath actuated inhaler (Price et al., 2003) and that poor inhaler technique is due to a fast inhalation. (Hesselink et al., 2001; Al-Showair et al., 2007a). With the co-ordination cap the focus could be on the exhalation and inhalation steps, thereby keeping the training simple without worrying the patient about the co-ordination.

When patients used the co-ordination cap they were informed to use their normal inhalation technique. They were informed that if they did start their inhalation before depressing the canister they would notice an initial vacuum which was released when they pressed the canister. It was emphasised that this was not an error.

On first use, 17 of the patients did not keep the canister depressed throughout the duration of their inhalation. This meant that the slits in the cap closed and patients were not able to maintain their inhalation. This could be regarded as a critical error. When patients had to be instructed to keep the canister pressed, they did not repeat this problem. In their open comments no patient mentioned this as a disadvantage. This could be due to the strong feedback mechanism of not keeping the canister depressed. Nevertheless if this co-ordination cap became available for use by patients then the information about keeping the cap depressed is an important step that should be highlighted in the Patient Information Leaflet and included in counselling.

We used a ratio of the inhalation volume to the forced vital capacity of 0.6 to indicate a deep inhalation (Goodman et al., 1994; Farr et al., 1995) but this value was greater in most of the patients. Greater lung deposition occurs when exhaling to residual volume compared to functional residual volume (Hindle et al., 1993; Juniper et al., 2006). However it has been shown that when using a slow flow and inhalation at different stages of the vital capacity does not affect lung deposition (Newman et al., 1982; Newman, 1985). Receptors for inhaled bronchodilators are distributed throughout the lungs, but they have their greatest effect in the conducting airways due to the presence of smooth muscle surrounding the airways (Carstairs et al., 1985; Mak and Barnes, 1990). Corticosteroid receptors are also present throughout the airways and inflammation has been shown to exist in all regions of the lungs

especially in asthma (Hamid et al., 1997; Tulic and Hamid, 2006). For these reasons, good penetration of the aerosol dose is required. Patients should exhale before an inhalation and the inhalation should continue as long as possible (Laube et al., 2011) but many patients make errors with these two simple inhalation steps (Molimard et al., 2003; Melani et al., 2004; Melani et al., 2011).

Previous correlations of inhalation parameters to spirometry have concentrated on peak inhalation flow, and peak expiratory flow and not been successful (Engel et al., 1990; Brown et al., 1995; Broeders et al., 2003a; Derom et al., 2007). Our results (Like those in the previous chapter) showed that FVC is a likely predictor of inhalation parameters when patients use their pMDI. We did not include FEV_1 because it was correlated to FVC and our preliminary statistical analysis identified its use rather than the FEV_1. The strong positive correlations enable the use a ratio of > 0.6 (inhaled volume: forced vital capacity) to indicate that when patients make a full inhalation.

The methods we have used could easily be incorporated into a simple portable electronic aid that can be used in the clinic to identify the errors that are made by a patient when they use their pMDI so that a focus on these can be made during any inhaler technique training session.

The study was a repeated measure design rather than the traditional parallel study design that could have been used to identify the effect of the cap and also the 5 second inhalation period. The benefits of the repeated measures design include improved efficiency (because fewer subjects are required) and the elimination of variability due to individual differences in overall performance, thereby allowing treatments to stand out. Against this are possible training effects and other carry over

effects which would not occur in a parallel design of a traditional randomised control trial (RCT)

Conclusion

A co-ordination cap together with a simple instruction to lengthen the inhalation time when a patient uses a pMDI ensures that they use the recommended slow inhalation flow with good co-ordination. The cap transforms a traditional pMDI into a breath actuated inhaler whilst the increased resistance to airflow naturally helps to reduce the inhalation flow. Training the patient to extend the duration of their inhalation did not alter their inhaled volume so inhalation flows were reduced. Seventy percent of patients used the correct pMDI technique with the cap and the simple instruction for their inhalation phase to last 5 seconds.

Chapter 6: Inhalation profiles of asthmatic children, asthmatic adults and COPD patients when they use different dry powder inhalers

6.1 Introduction

Dry powder inhalers (DPIs) are breath-controlled devices, and due to their many advantages they have over pMDIs, then these devices have increasingly replaced pMDIs as the most common devices (Lavorini and Corbetta, 2008). However in the UK the pMDI is still more widely used although there is a gradual shift towards DPI use. DPIs do not require the need to coordinate actuation and the start of an inhalation like the pMDI device which is a mistake that most patients make (Broeders et al., 2003a).

Before a dose is inhaled from a DPI it has to be prepared for inhalation. Each type of device has its unique dose preparation requirements. When a dose has been prepared for inhalation the formulation does not have the potential for lung deposition. This is because the drug particles are either attached to a carrier with large particles (usually lactose) or are formulated into spherical aggregates. This is to improve powder flow which is essential for accurate inhaler filling during manufacture and for dosing metering accuracy prior to an inhalation. During an inhalation each patient's inhalation reacts with the resistance created by the internal design of the DPI to create a turbulent energy that breaks up (de-aggregates) the formulation. Hence the emitted drug particles have the potential for lung deposition (Clark and Hollingworth, 1993; Chrystyn and Price, 2009a). Each type of DPI has its unique resistance with some having low resistance, others medium and some high (Laube et al., 2011). Since the turbulent energy is determined by the inhalation flow and the internal resistance of the device then inhalation flow should not be considered in isolation unless flows with the same DPI are compared (Azouz and Chrystyn, 2012). To attain a set pressure change (the turbulent energy) then the inhalation flow through an inhaler with low resistance must be higher than that through a DPI with

higher resistance (Azouz and Chrystyn, 2012). When comparing different devices during patient use then the pressure change should be the focus and not the inhalation flow. When comparing patient use through the same DPI then it is feasible to compare inhalation flow. This is due to the greater turbulent energy caused by a faster inhalation through the same DPI. To ensure adequate de-aggregation then the patient should use a forceful and deep inhalation (Borgstrom, 2001; Newman and Busse, 2002; Laube et al., 2011).

It has been shown that the inspiratory effort and thus the inspiratory flow achieved by patients through each DPI will significantly affect the emitted dose which is related to the clinical efficacy (Engel et al., 1989; Nielsen et al., 1997; Chrystyn, 2003). Studies have highlighted that some patients have problems achieving a fast inhalation rate during routine use of their DPI (Pedersen et al., 1986; Broeders et al., 2001; Chrystyn, 2009). Asthmatics children (Amirav et al., 2005) and elderly COPD patients (Chrystyn , 2009) with acute exacerbations (Engel et al., 1990; Broeders et al., 2004) are most likely to have problems achieving sufficient turbulent energy inside a DPI due to them only being able to use slow flows. Therefore, the choice of an appropriate dry powder inhaler for particular patients should be based on the objective measurements of their PIF against a certain resistance (Janssens et al., 2008).

For each DPI there will be a minimum turbulent energy threshold for sufficient de-aggregation to occur during an inhalation (Laube et al, 2011). From this viewpoint, more attention needs to be directed to the minimum acceptable PIF achieved through each DPI rather than to the optimal PIF of each device. Also it has been suggested that the initial acceleration rate during an inhalation in a DPI is more important than PIF in the generation of the fine particle dose (Everard et al., 1997; Kamin et al.,

2002). Similarly, inhaled volume is also considered as an important parameter of the inhalation profile and can govern the quality of the emitted dose (Kamin et al., 2002) particularly in a capsule formulation (Chrystyn, 2009; Alaboud et al., 2010) because of the needed to empty the capsule.

There is very little data of the turbulent energy (measured as a pressure change), inhalation volume and the acceleration rate when patients routinely use DPIs. A method has been designed to measure inhalation parameter of patients when they use different DPIs.

6.2 Aim and Objectives

6.2.1 Aim

The main aim of this study was to identify the inhalation characteristics of different groups of patients (children with asthma, asthmatic adults and COPD patients) when they inhaled through different DPIs (Aerolizer, Accuhaler, Novolizer, Spiromax, Turbuhaler, Clickhaler, Easyhaler and Handihaler

6.2.2 Objectives

The primary objectives were to measure inhalation flow profiles when patients inhale through different DPIs. From these profiles the inhalation parameters can be obtained.

The secondary objectives were to obtain each patient's demographic features and measure their spirometry as well as the level of their disease control. Also to investigate if there are any correlations of these to the inhalation parameters

6.3 Method

6.3.1 Study Population

This was a randomised, open label study completed during one visit.

6.3.1.1 Patient Recruitment

Asthmatic adults /children and COPD patients attending an outpatient appointment and receiving regular care at the respiratory clinic (see below for the list of hospitals involved) and fulfilling the protocol's patient definition criteria were invited to take part in this research study. For children their parent / carer were included in the invitation. The study objectives and procedures were explained to the patients using the participant information sheets [APPENDIX A-1, A-2, and A-3 (refer to the enclosed DVD)]. After their agreement to take part in the study, a signed informed consent form [APPENDIX A- 5 (refer to the enclosed DVD)] was obtained prior to performing any protocol related procedures. This study was designed to be completed during one visit.

The NHS Teaching Hospitals involved were:

➢ Leeds General Infirmary (LGI), Leeds.

➢ St. Luke's Bradford Hospital.

➢ Bradford Royal Infirmary Hospital, Bradford.

➢ Airedale General Hospital, Steeton.

This study was approved by the NRES Committee Yorkshire and the Humber -

Bradford and the Research and Development Department within each of the

involved NHS Hospitals (refer to the enclosed DVD [APPENDIX])

6.3.1.2 Patients

(a) Inclusion criteria

➢ Male or female, with stable asthma or COPD

> Prescribed a DPI.

> Groups:

  ❖ Child with asthma (CHILD): 5-18 years

  ❖ Adult asthmatic (ADULT): 18-55 years

  ❖ COPD patients (> 55years)

> Signed informed consent form

(b) Exclusion Criteria

> Prescribed inhaled medication for less than 4 weeks prior to enrolment.

> Other pulmonary diseases (e.g. CF, TB, pneumonia)

> An acute exacerbation of asthma or COPD or a short course of high dose oral prednisone during the last 2 weeks.

> Pregnant

> Participation in another clinical research study in the 3 months prior to enrolment.

6.3.2 Study design

A Micro-Loop Spirometer (Cardinal Health, UK) was modified so that adapters could be fitted onto the air inlet end of the spirometer. For each DPI a specially designed adapter was used to ensure airtight seals between the adapter and the spirometer inlet as well as the adapter and the empty DPI. Inhalation flow profiles were measured by asking patients to make their normal (real life) DPI inhalation through the spirometer mouthpiece fitted with the adapter and the DPI. To obtain the inhalation parameters the spirometer was operated in the flow volume mode and only the inhalation phase was used. To obtain complete data from each inhalation flow profile the data of each inhalation was transported into Microsoft Access for data analysis. Flow rates were converted into pressure changes using the resistance of the DPI.

Each patient's age, gender, height and weight were recorded together with their medication. Their spirometry (PEF, FEV_1 and FVC) was measured using a ONEFLOW Spirometer (Clement Clark International). The patients were asked to inhale through the mouthpiece of the Micro-Loop with the empty DPI fitted onto the air inlet of the spirometer. They were informed to make each inhalation as if they were using their DPI.

The empty DPIs used were:

➢ Accuhaler (GlaxoSmithKline, UK) – ACC

➢ Aerolizer (Novartis, Switzerland) – AERO

➢ Clickhaler (UCB Pharma, UK) – CLICK

➢ Easyhaler (Orion Pharma, Finland)- EASY

➢ Handihaler (Boehringer Ingelheim, GmbH) – HANDI

➢ Novolizer (Meda, Sweden) – NOVO

➢ Spiromax (Teva Pharmaceuticals, Israel) – SPIRO

➢ Turbuhaler (AstraZeneca, Sweden) - TBH

The order of inhalation through each different device was randomised. Each patient made three separate inhalations manoeuvres through each DPI. On every occasion they were reminded to mimic their normal inhalation manoeuvre when they used their DPI. The inhalation profile with the highest PIF through each device was chosen for data analysis. The Handihaler was only included for ADULT and COPD patients.

Each patient was given a 5 minute break between each series of inhalations through each different device.

Patients also completed a questionnaire:

> ADULT: Asthma Control questionnaire (ACQ – Juniper et al 1999b) see [APPENDIX 6] and Juniper Asthma Quality of Life - mini version (AQLQ) – see [APPENDIX 7] (Juniper et al., 1999a).

> CHILD: Paediatric Quality of Life – PAQL (Juniper et al., 1996a) and the Paediatric Asthma Caregivers Quality of Life – PACQLQ (Juniper et al.,1996b). [APPENDIX 8and 9].

> St George's Respiratory questionnaire (SGRQ) -see [APPENDIX [10] (Jones et al., 1992).

6.3.3 Inhalation parameters

Table 6. 1.The resistance of the DPIs in $(kPa)^{0.5}(min\ l^{-1})$.

The resistance of the DPIs in $(kPa)^{0.5}(min\ l^{-1})$	
❖ Aerolizer (AERO)	0.0207
❖ Accuhaler (ACC)	0.0249
❖ Novolizer (NOVO)	0.0254
❖ Spiromax (SPIRO)	0.0313
❖ Turbuhaler (TBH)	0.0335
❖ Clickhaler (CLICK)	0.0394
❖ Easyhaler (EASY)	0.0485
❖ Handihaler (HANDI)	0.0495

These resistance values were used to convert inhalation flows into the respective pressure change.

Primary parameters:

> Peak inhalation flow (PIF) in L/min.

> Maximum pressure change (ΔP) in kPa.

> Time to peak inhalation flow (Tp) in seconds.

> Time to 90% of the peak inhalation flow (Tp_{90}) in seconds.

> Inhaled volume at Tp_{90} (IV_{90}) in litres.

> The acceleration rate (Acc) in kPa/sec.

> Inhalation volume (IV) in litres.

> Duration of the inhalation (Ti) in seconds.

Secondary parameters

> Inhalation flow when 150 ml had been inhaled (IF_{150}) in L/min.

> Time when 150 ml had been inhaled (T_{150}) in seconds

6.3.4 Data Analysis

The statistical analysis of the study was carried out using the Statistical Package for Social Sciences (SPSS 17) software. The study data was first classified into scale, categorical (nominal) or ordinal categories, as appropriate, and an SPSS dataset was then set up for the analysis. The statistical analysis was performed and presented as follows

> Descriptive statistics: mean and standard deviation.

> For scale data; normal distribution of the data was examined using histograms and statistical tests for normality; the Kolmogorov-Smirnov and Shapiro-Wilk tests

> Comparisons (differences) of measurements through different inhalers within the same group were performed using the related (paired)-samples t-test (for parametric data) and the Wilcoxon test (for non-parametric data)

> Comparisons (differences) of measurements between different the groups were performed using the independent-samples t-test (for parametric data) and the Mann-Whitney U test (for non-parametric data).

> Scatter plots between the inhalation volume and the pressure change (ΔP) were made for each device

> For the Turbuhaler correlations were determined between the PIF when 150ml had been inhaled and the PIF as well as the PIF_{90}. These correlations were made for each group using the Spearman's rho test.

6.4 Results

6.4.1 Patients

A summary of the patients' demographic data, lung function (presented as $FEV_1\%$ predicted) and disease severity classification according to GINA 2008 and COPD according to NICE 2010 is presented in Table 6.1. Details of the demographic data for each individual are presented in APPENDIX B-15, B-16, B-17 (refer to the enclosed DVD).

Table 6.2. Patient details. All values are mean (SD) unless indicated otherwise.

		CHILD	ADULT	COPD
Number (n)		16	53	29
Sex [M/F] (n)		13/3	11/42	15/14
Ag in years		8.8 (3.08)	48.7(16.02)	64.6(11.2)
Height in cm		132.8(20)	165.703	168.4(10.1)
Weight in Kg		34.8(16.2)	75.4(16.8)	78.0(12.5)
FEV_1 in Litres		1.34(0.67)	2.01(0.6)	1.25(0.8)
FEV_1 % predicted		78.5 (19.5)	72.0(17)	41.5(16.1)
PEF in L/min		182.8(84.7)	301(115.0)	173.3(89.7)
PEF % predicted		65.1(21.57)	71.8(24)	44.9(18.5)
FVC in Litres		1.58(0.73)	2.5(0.8)	2.02(0.6)
Disease severity (n)	Mild	8	17	12
	Moderate	5	22	10
	Severe	3	14	7
	Very severe	N/A	N/A	0

6.4.2 Inhalation characteristics

The inhalation parameters of the patients are summarised in Table 6.2

6.4.2.1 Comparison of the Inhalation Profiles through the different DPIs- Child with asthma

The distributions of the inhalation parameters for the different devices are shown in Figure 6.1- 6.6. Relationships between the inhaled volume and the pressure drop (turbulent energy) at the time of the PIF are presented in Figure 6.7.

Table 6.3. Mean (SD) inhalation parameters of the patients when they inhaled through different DPIs.

	PIF (l/min)	ΔP (kPa)	Tp (sec)	Tp_{90} (sec)	$IV_{(90)}$ (L)	Acc(kPa/sec)	IV (L)	Ti (sec)	IF_{150}(L/min)	T_{150}(sec)
CHILD										
AERO	71.4(21.5)	2.36(1.32)	0.40(0.12)	0.36(0.11)	0.195(0.07)	7.19(6.27)	1.222(0.68)	1.69(0.38)	62.4(22.0)	0.33(0.10)
ACC	53.3(24.2)	2.10(1.70)	0.49(0.19)	0.44(0.17)	0.214(0.11)	5.36(5.52)	1.191(0.76)	1.50(0.46)	50.5(20.3)	0.42(0.22)
NOVO	59.1(22.3)	2.55(1.82)	0.53(0.22)	0.48(0.20)	0.212(0.12)	4.96(3.92)	1.116(0.77)	1.86(0.72)	48.5(15.1)	0.46(0.20)
TBH	44.8(15.9)	2.55(1.78)	0.45(0.20)	0.41(0.18)	0.125(0.04)	6.71(5.91)	1.011(0.73)	1.52(0.17)	41.9(15.5)	0.48(0.19)
CLICK	46.3(13.2)	3.57(1.85)	0.49(0.17)	0.44(0.59)	0.168(0.06)	14.83(17.49)	1.047(0.75)	1.59(0.33)	50.9(20.8)	0.47(0.20)
EASY	45.5(13.2)	5.26(2.89)	0.52(0.18)	0.47(0.16)	0.161(0.06)	11.67(9.38)	1.00(0.46)	1.62(0.23)	42.4(12.7)	0.47(0.17)
ADULT										
AERO	93.7(25.9)	4.04(2.2)	0.33(0.12)	0.29(0.12)	0.236(0.21)	12.60(9.80)	1.964(0.8)	1.53(0.3)	82.7(21.6)	0.24(0.09)
ACC	76.4(23.8)	3.95(2.38)	0.41(0.25)	0.37(0.22)	0.243(0.17)	11.00(8.75)	1.910(0.73)	1.60(0.56)	73.9(24.2)	0.27(0.09)
NOVO	80.2(22.3)	4.64(2.30)	0.37(0.14)	0.33(0.13)	0.196(0.01)	12.84(8.34)	1.861(0.74)	1.59(0.33)	68.2(20.3)	0.33(0.21)
SPIRO	71.9(19.7)	5.44(2.92)	0.43(0.22)	0.39(0.20)	0.210(0.11)	14.10(10.16)	1.77(0.78)	1.58(0.31)	64.9(22.8)	0.35(0.17)
TBH	60.3(16.9)	4.45(2.38)	0.40(0.13)	0.36(0.12)	0.158(0.06)	13.12(13.01)	1.627(0.74)	1.65(0.46)	53.5(16.2)	0.37(0.09)
CLICK	63.2(15.7)	6.57(3.06)	0.40(0.19)	0.36(0.17)	0.175(0.08)	19.58(16.68)	1.677(0.76)	1.61(0.47)	60.0(18.3)	0.43(0.61)
EASY	58.3(14.4)	8.48(4.12)	0.42(0.16)	0.38(0.14)	0.168(0.07)	20.84(15.03)	1.683(0.81)	1.55(0.46)	55.2(12.9)	0.39(0.11)
HANDI	58.6(11.4)	8.72(3.33)	0.44(0.18)	0.40(0.17)	0.193(0.11)	20.91(12.60)	1.720(0.76)	1.56(0.31)	58.7(13.2)	0.34(0.08)
COPD										
AERO	81.7(25.4)	3.13(1.88)	0.43(0.27)	0.39(0.25)	0.229(0.15)	8.68(6.78)	1.706(0.82)	1.71(0.45)	66.9(20.2)	0.31(0.12)
ACC	62.1(22.3)	2.68(1.78)	0.45(0.23)	0.41(0.21)	0.195(0.15)	6.62(7.28)	1.789(0.87)	1.53(0.24)	60.3(20.6)	0.44(0.65)
NOVO	61.0(14.9)	2.53(1.25)	0.42(0.24)	0.37(0.21)	0.169(0.77)	6.90(5.45)	1.616(0.77)	1.61(0.45)	58.5(16.0)	0.35(0.11)
SPIRO	56.2(15.5)	3.32(1.77)	0.42(0.19)	0.37(0.17)	0.147(0.05)	9.18(6.64)	1.609(0.77)	1.60(0.77)	56.9(18.4)	0.38(0.15)
TBH	50.9(15.3)	3.19(1.94)	0.44(0.20)	0.39(0.18)	0.143(0.15)	9.55(7.47)	1.502(0.79)	1.56(0.19)	47.2(14.1)	0.48(0.20)
CLICK	51.1(15.5)	4.40(2.54)	0.48(0.18)	0.43(0.16)	0.159(0.07)	10.43(9.35)	1.483(0.73)	1.63(0.29)	48.9(15.4)	0.43(0.15)
EASY	49.5(15.0)	6.28(3.54)	0.45(0.14)	0.41(0.13)	0.150(0.01)	14.00(9.10)	1.520(0.80)	1.67(0.59)	45.1(11.8)	0.45(0.14)
HANDI	53.4(15.7)	7.59(4.40)	0.42(0.16)	0.38(0.14)	0.150(0.01)	20.90(12.6)	1.55(0.82)	1.64(0.63)	58.8(13.2)	0.41(0.09)

Comparison of the Inhalation Profiles through the different DPIs – Children with asthma
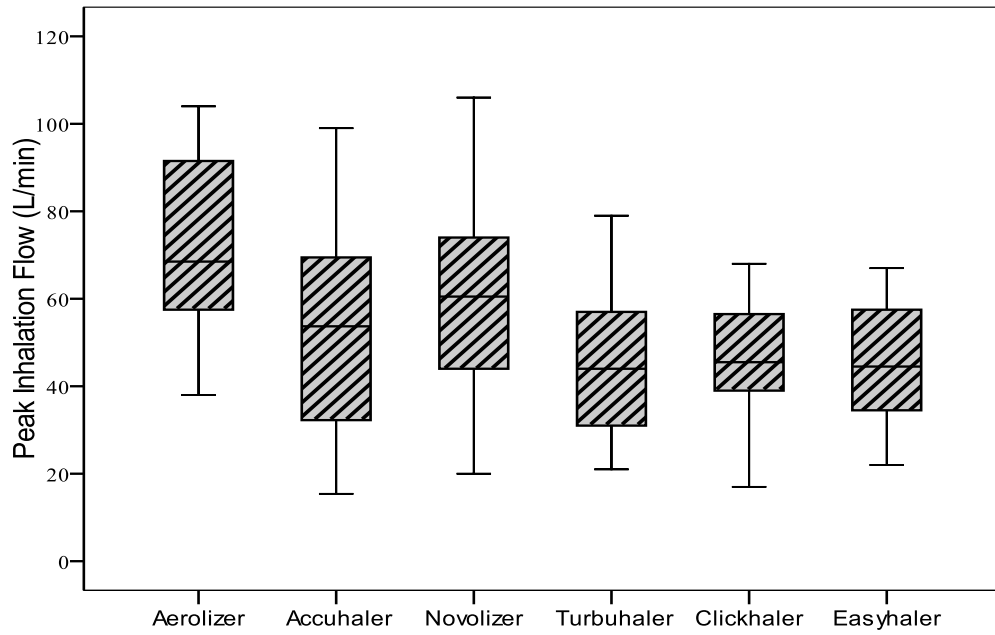
Figure 6.1. The range of peak inhalation flows achieved by the asthmatic children when they inhaled through the different DPIs.
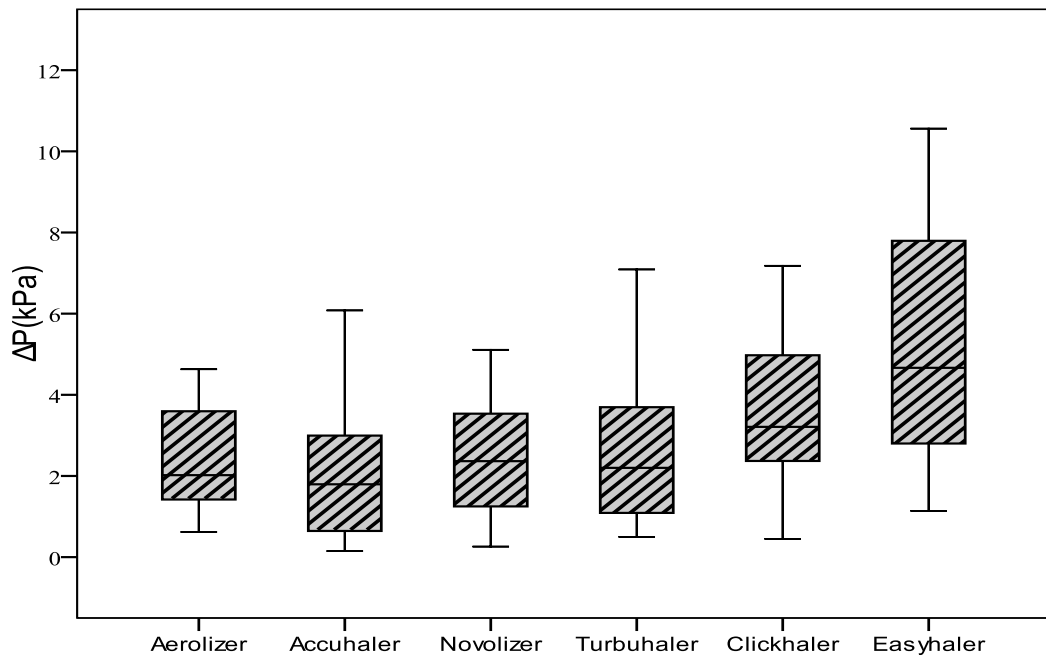
Figure 6.2. The range of the pressure change (ΔP) inside each DPI during the inhalations by the asthmatic children.
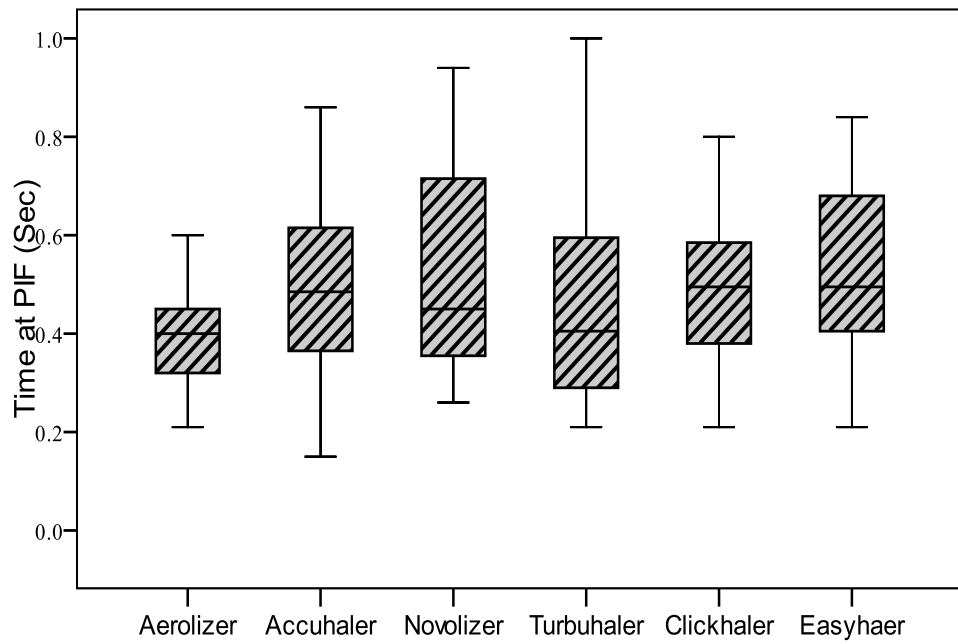
Figure 6.3. The range of the times to PIF for the children with asthma when they inhaled through the different DPIs.
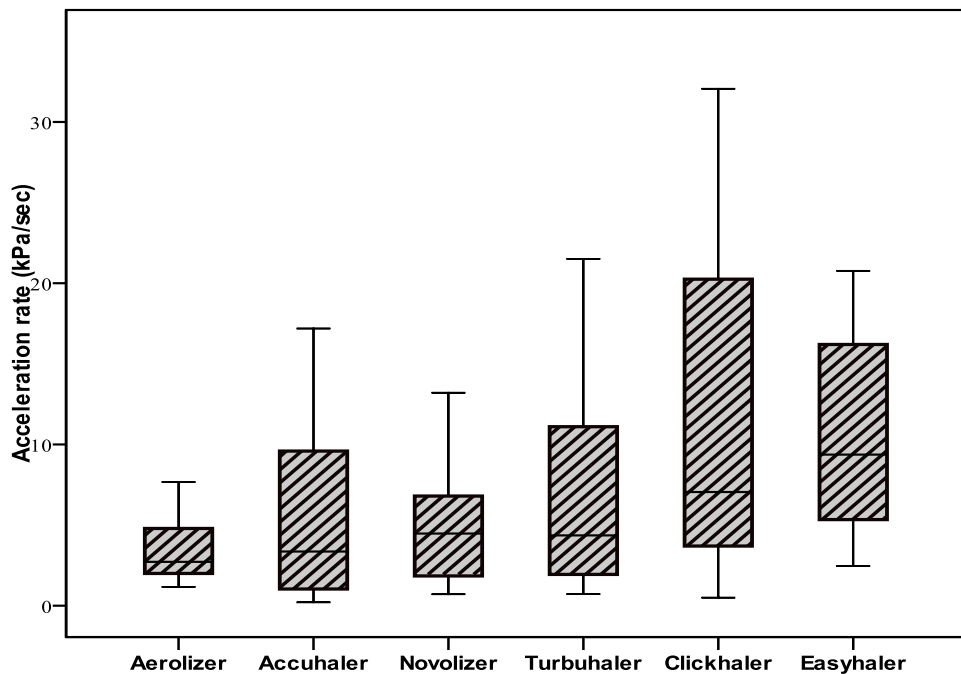
Figure 6.4. The range of the acceleration rates achieved by the children with asthma when they inhaled through the different DPIs.
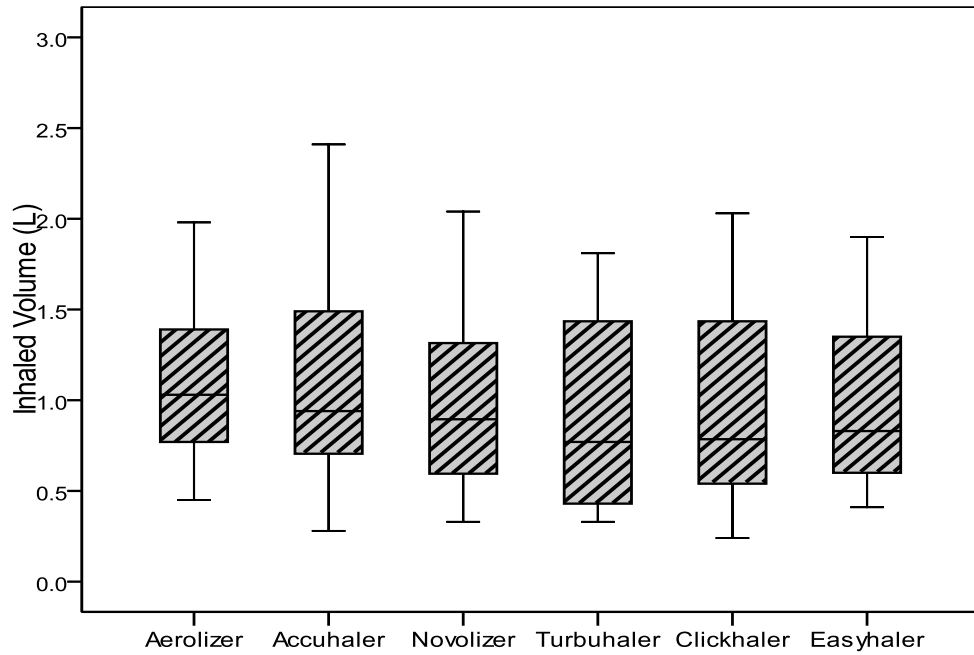
Figure 6.5. The range of the inhaled volumes for the children with asthma when they inhaled through the different DPIs.
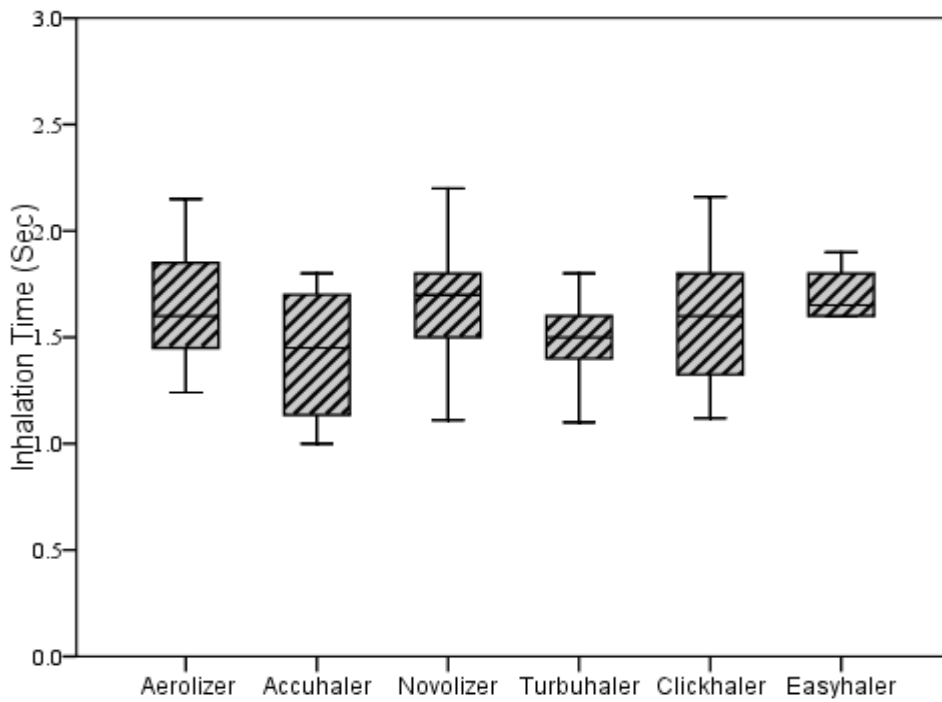
Figure 6.6. The range of the inhalation times for the children with asthma when they inhaled through the different DPIs.

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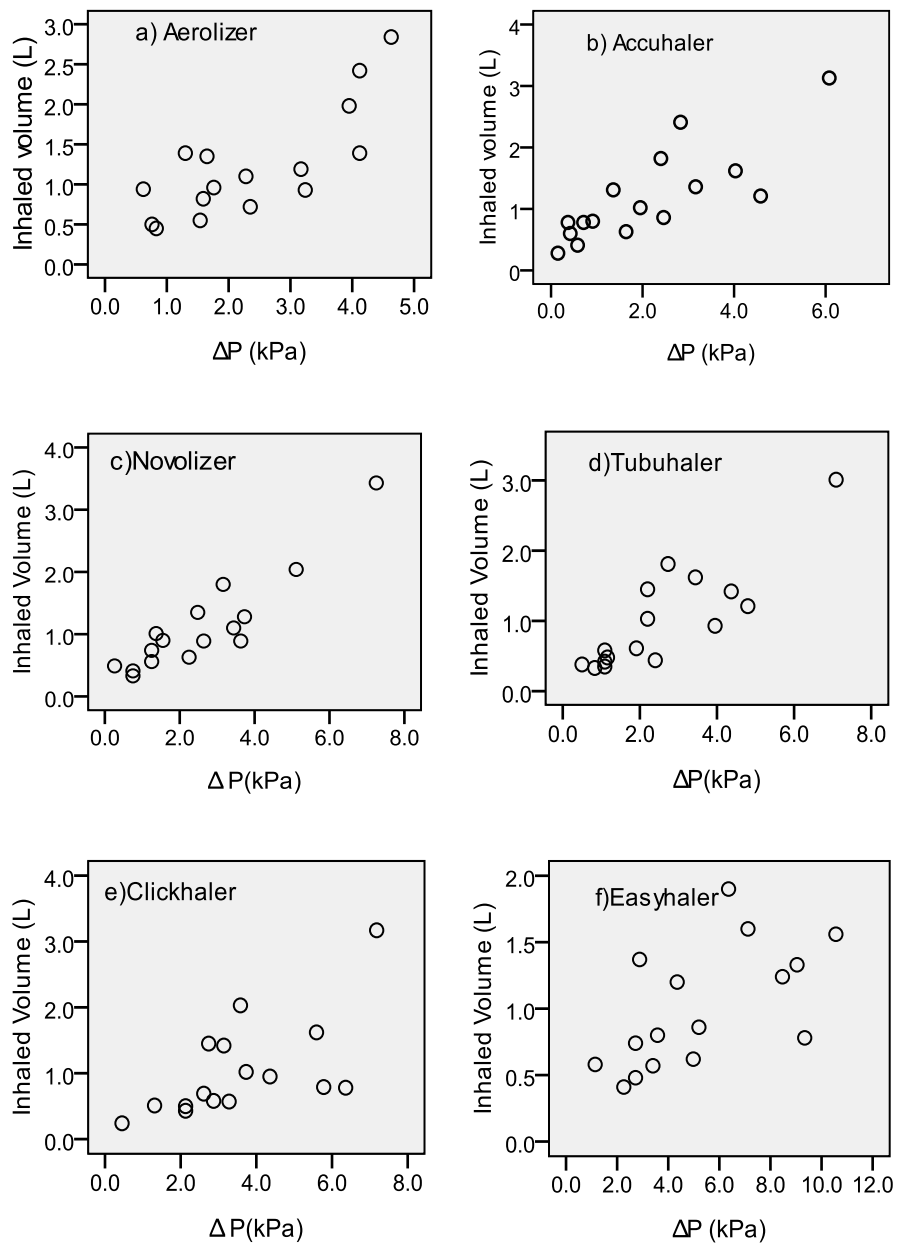
Figure 6.7. Scatter plots between inhaled volume and maximum pressure changes for each of the children with asthma when they inhaled through a) Aerolizer b) Accuhaler) Novolizer d) Turbuhaler, e) Clickhaler, f) Easyhaler.

6.4.2.2. Comparison of the Inhalation Profiles through the different DPIs – COPD

The distribution of the individual inhalation parameters of the COPD patients is presented in Figure 6.8- 6.13. Individual relationship between each patient's inhaled volume and the maximum pressure change is shown in Figure 6.14.
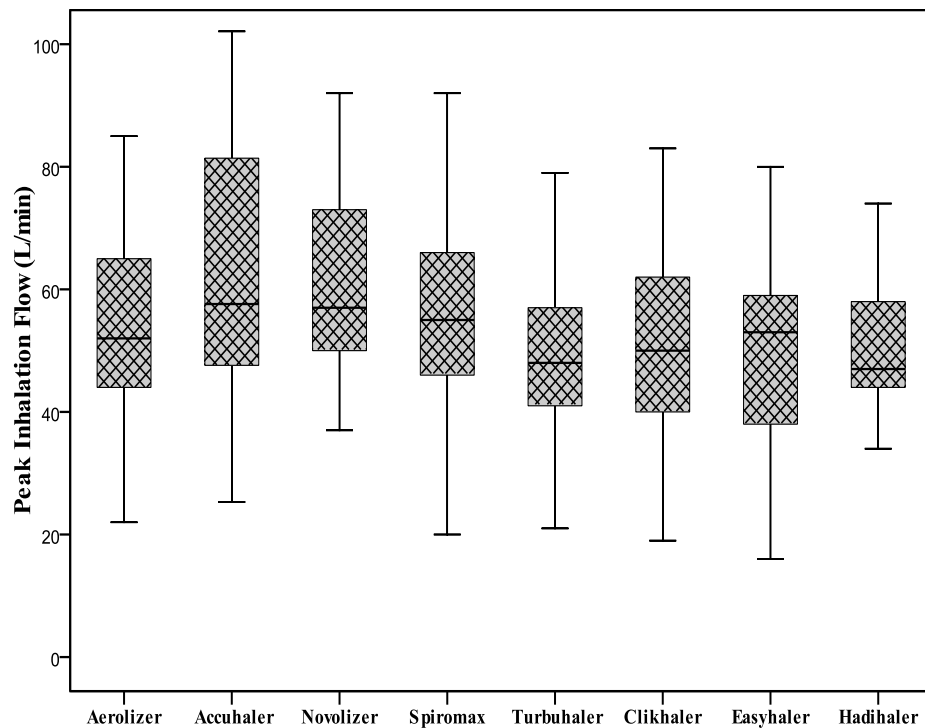
Figure 6.8. The distribution of the peak inhalation flows of the COPD patients when they inhaled through the different DPIs.
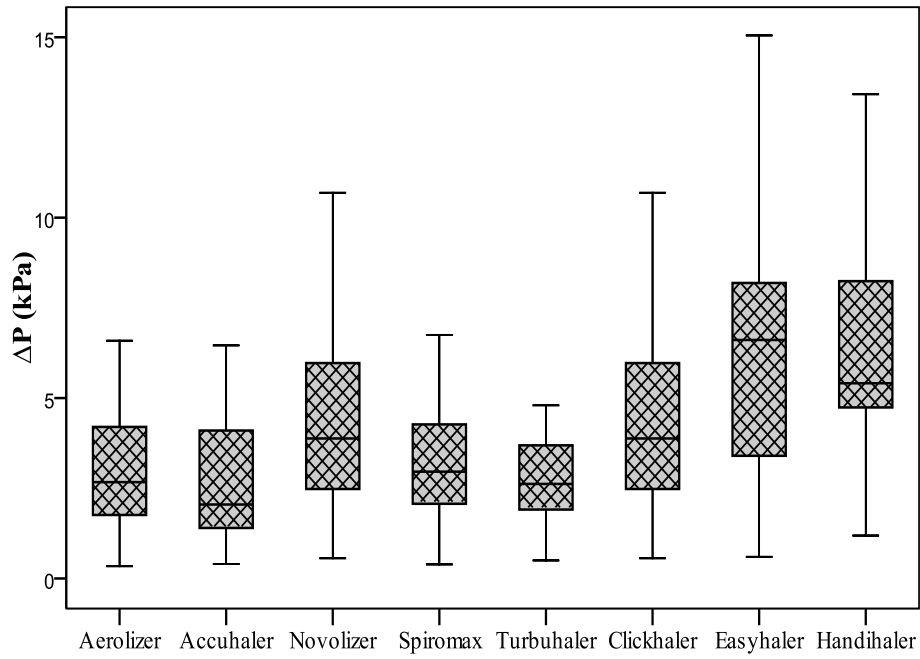
Figure 6.9. The range of the maximum pressure changes that occurred inside each DPI during the inhalations by the COPD patients
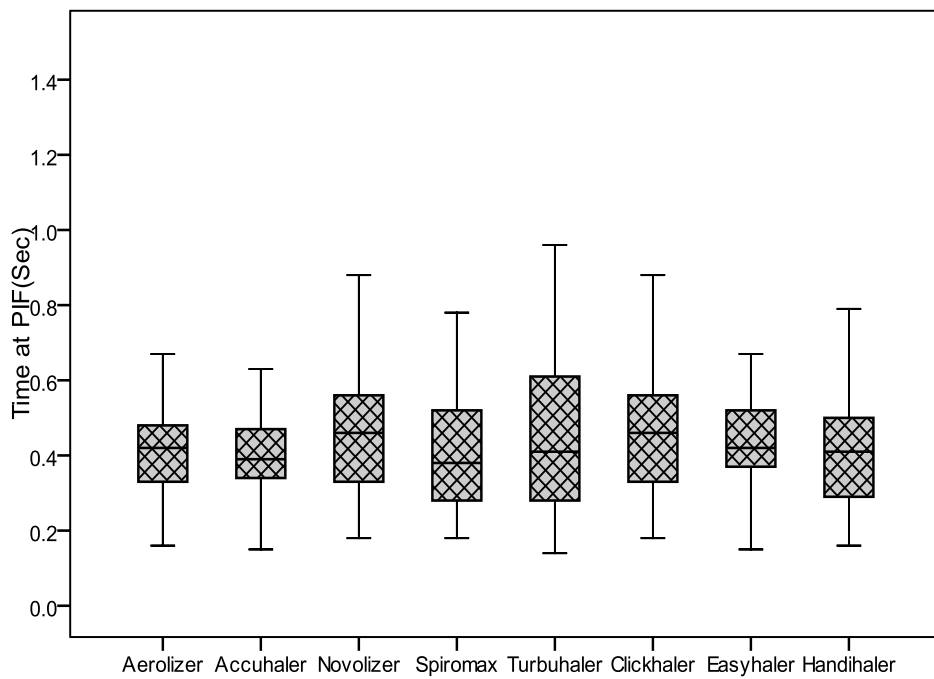
Figure 6.10. The range for the times at PIF achieved by the COPD patients when they inhaled through the different DPIs
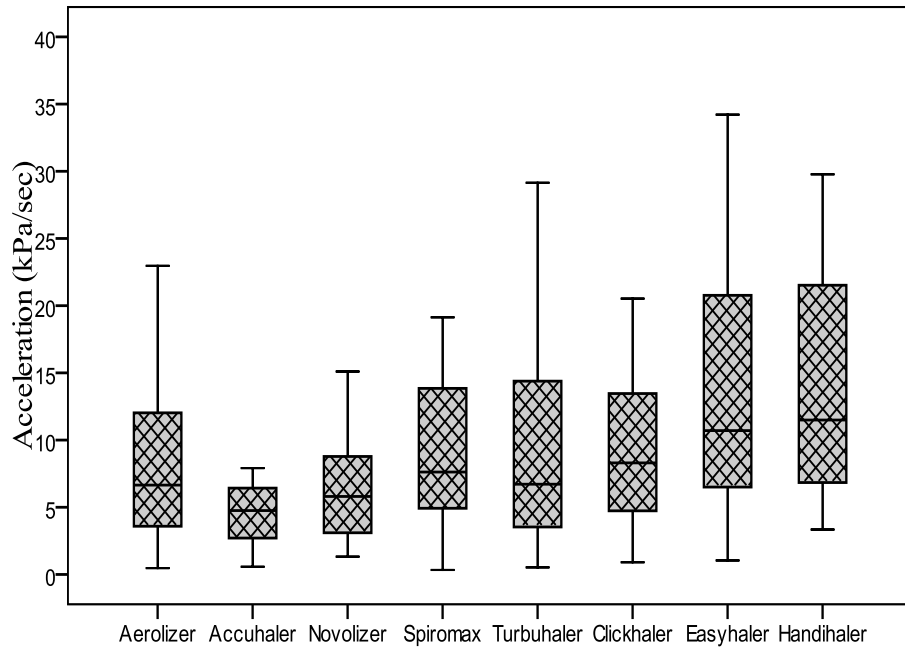
Figure 6.11. The distribution of the acceleration rate achieved by the COPD patients when they inhaled through the different DPIs
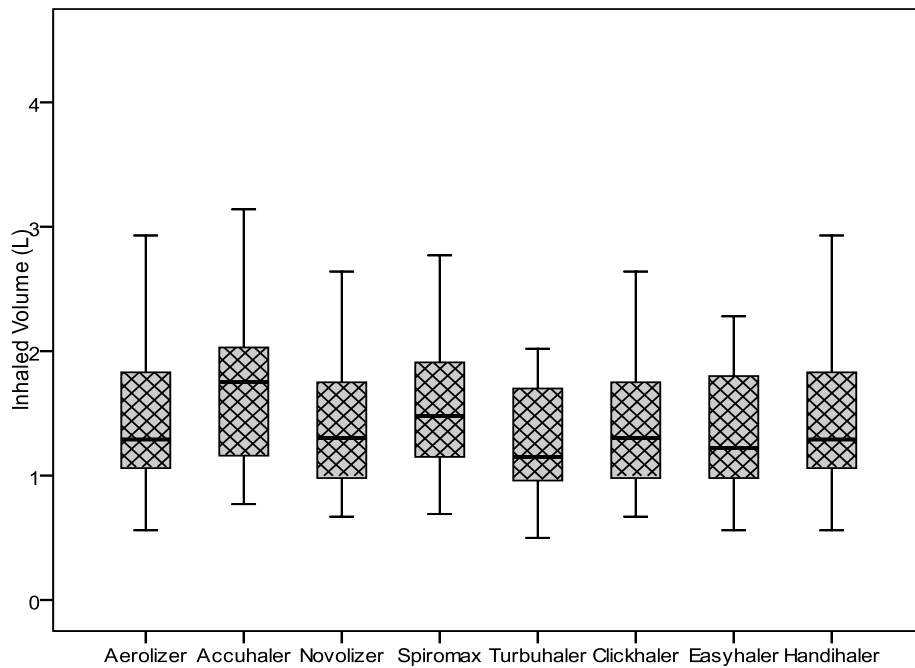
Figure 6.12. The distribution of the inhaled volumes achieved by the COPD patients when they inhaled through the different DPIs
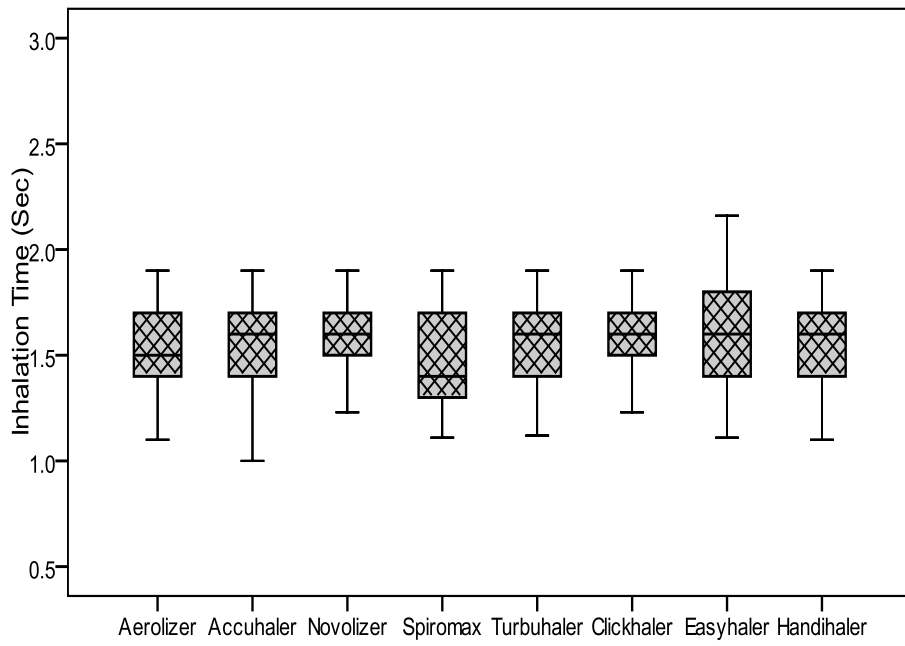
Figure 6.13. The range for the distribution of the duration of the inhalations by the COPD patients when they inhaled through the different DPIs
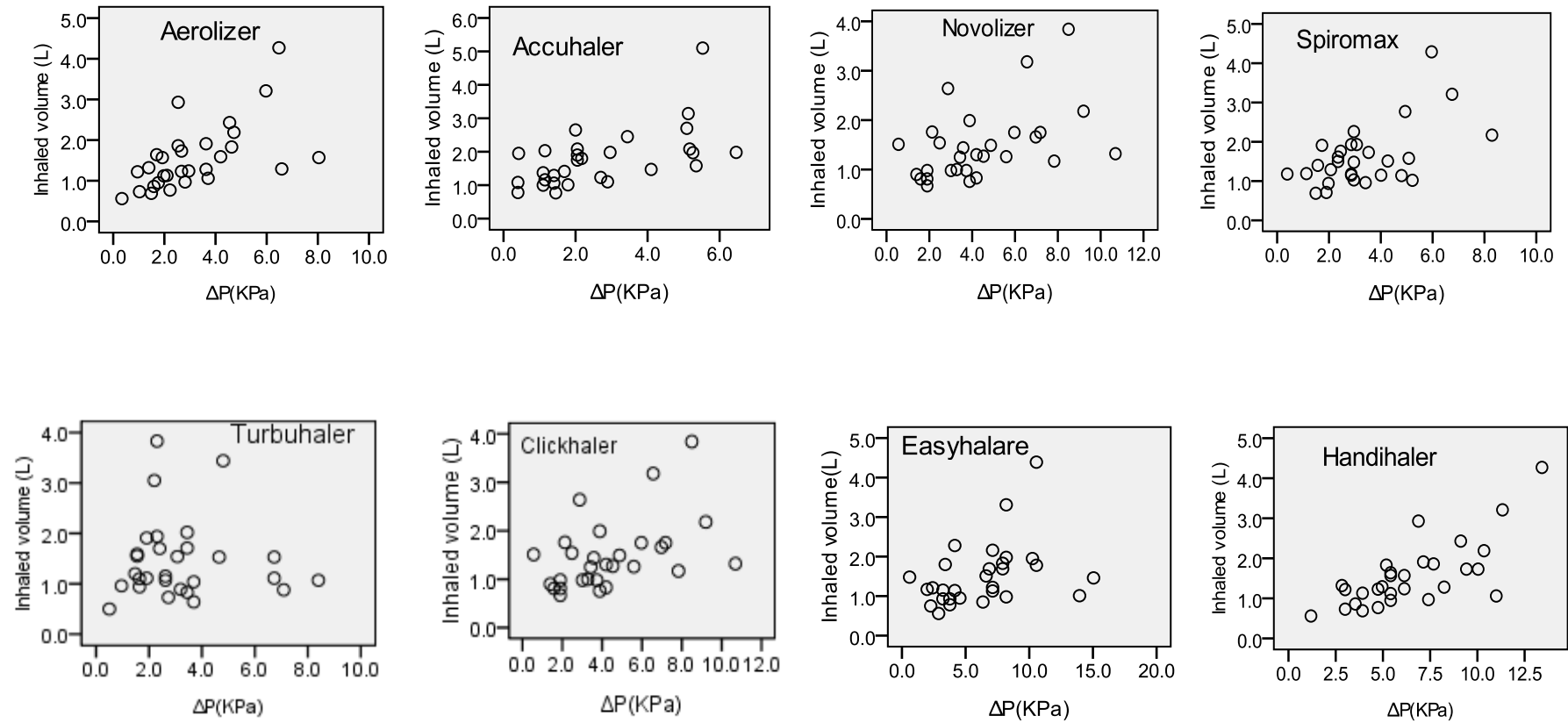
Figure 6.14. Scatter plots between the inhaled volume and maximum pressure change for each COPD patient when they inhaled through, a) Aerolizer, b) Accuhaler, c) Novolizer, d) Spiromax, e) Turbuhaler, f) Clickhaler, g) Easyhaler , h) Handihaler.

6.4.2.3. Comparison of the Inhalation Profiles through the different DPIs –

Asthmatic Adults

The distribution of the individual inhalation parameters of each adult with asthma are presented in Figure 6.15 - 6.20. The relationship between the inhaled volume and the maximum pressure change (ΔP) is shown in Figure 6.21.
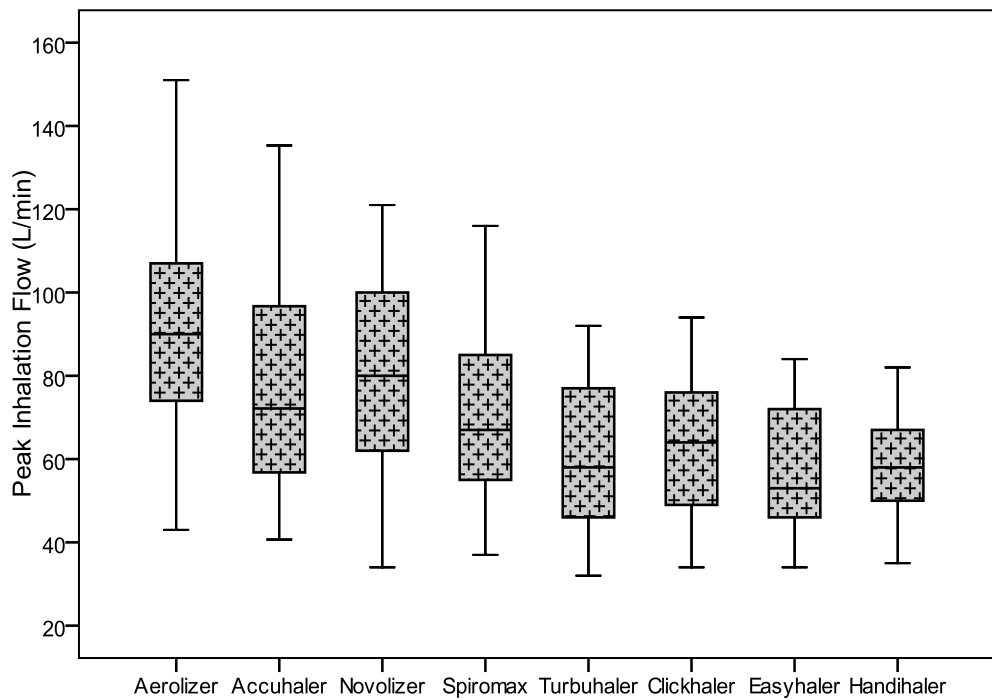
Figure 6.15. The range of peak inhalation flows achieved by the adults with asthma when they inhaled through the different DPIs.
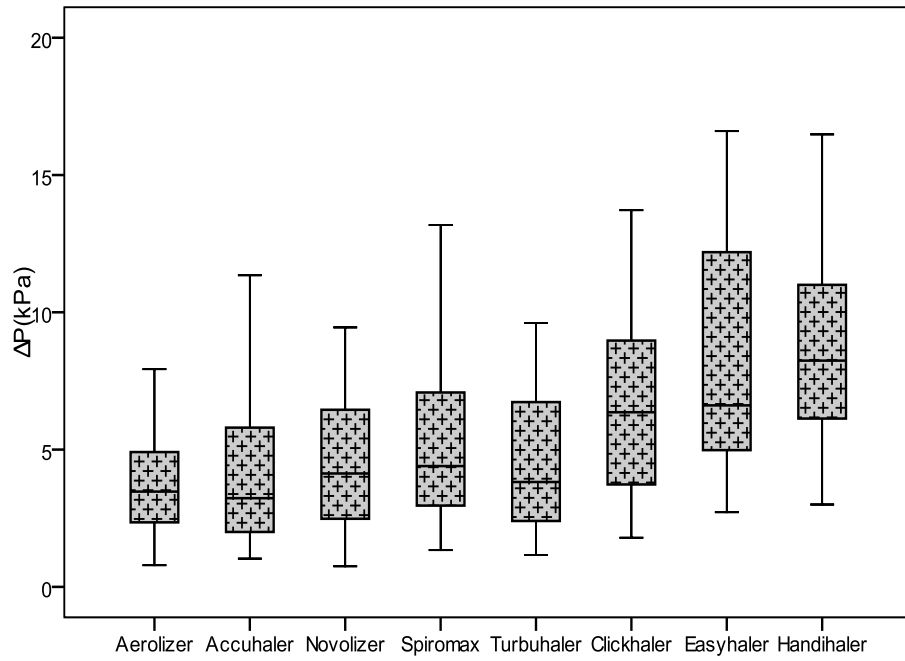
Figure 6.16. The distribution of the maximum pressure change (ΔP) inside each DPI during the inhalation by each adult with asthma
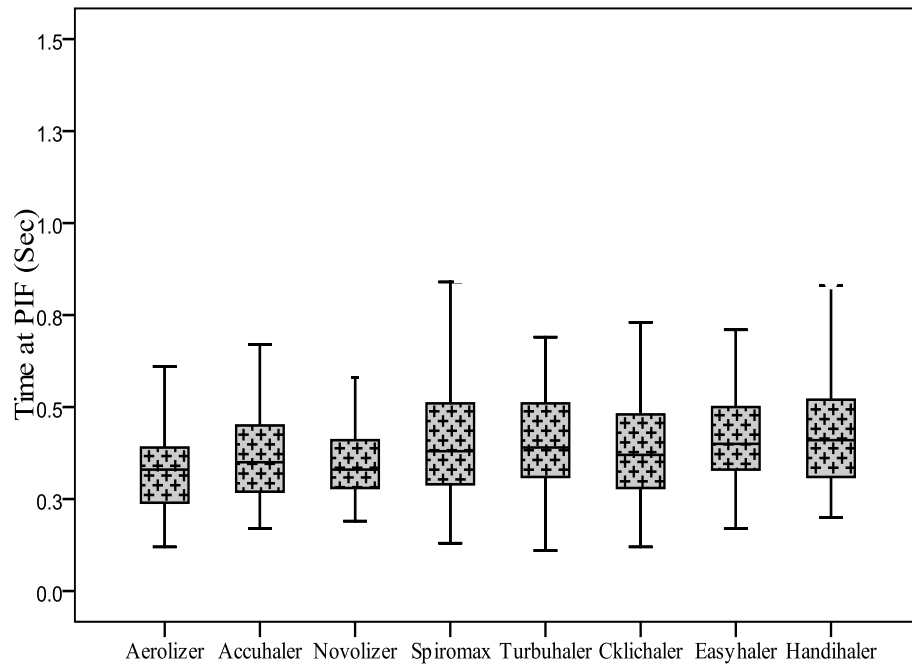
Figure 6.17. The distribution of the time at the occurrence of the PIF when adults with asthma inhaled through the different DPIs
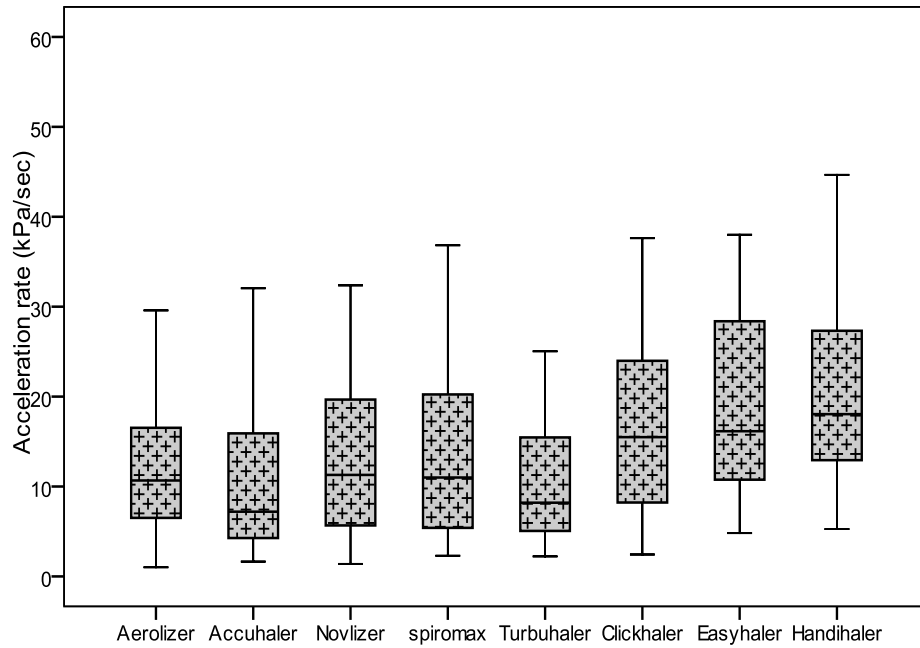
Figure 6.18. The range of acceleration rates (kPa/sec) achieved by the adults with asthma when they inhaled through the different DPIs.
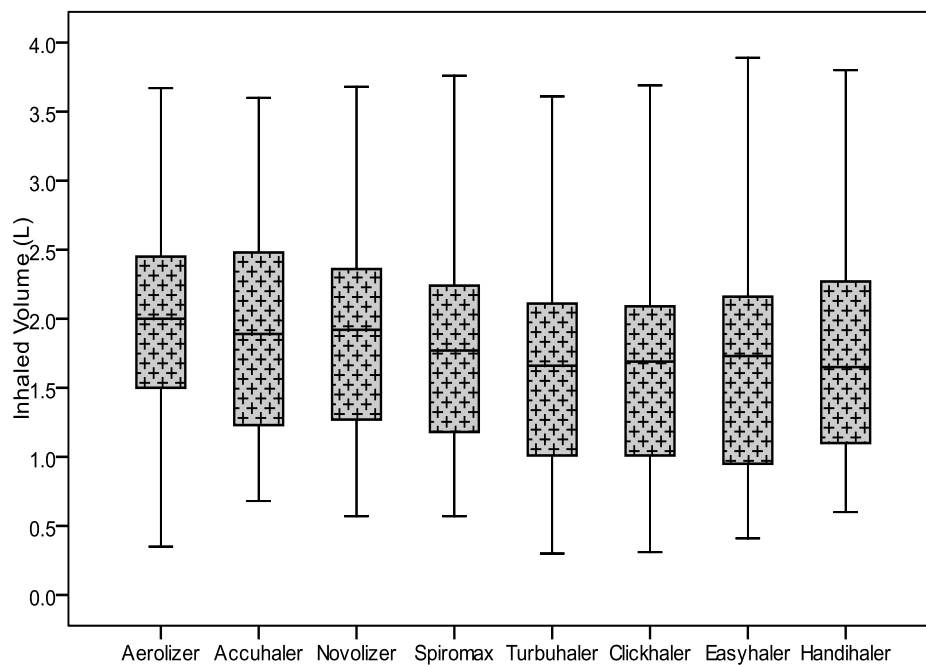
Figure 6.19. The distribution of the inhaled volumes achieved by the adults with asthma when they inhaled through the different DPIs
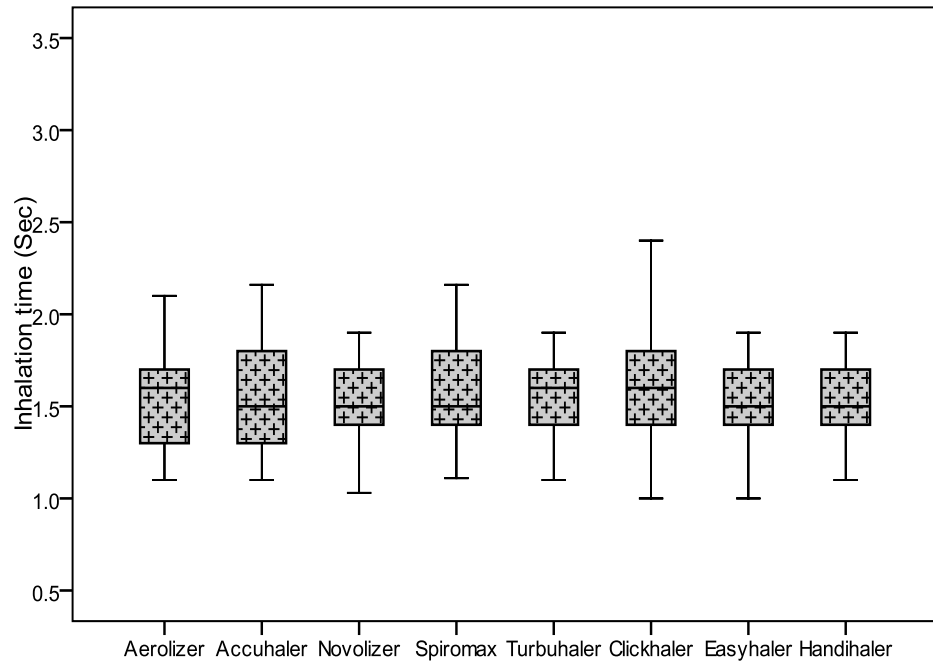
Figure 6.20. The range of inhalation times for the adults with asthma when they inhaled through the different DPIs.
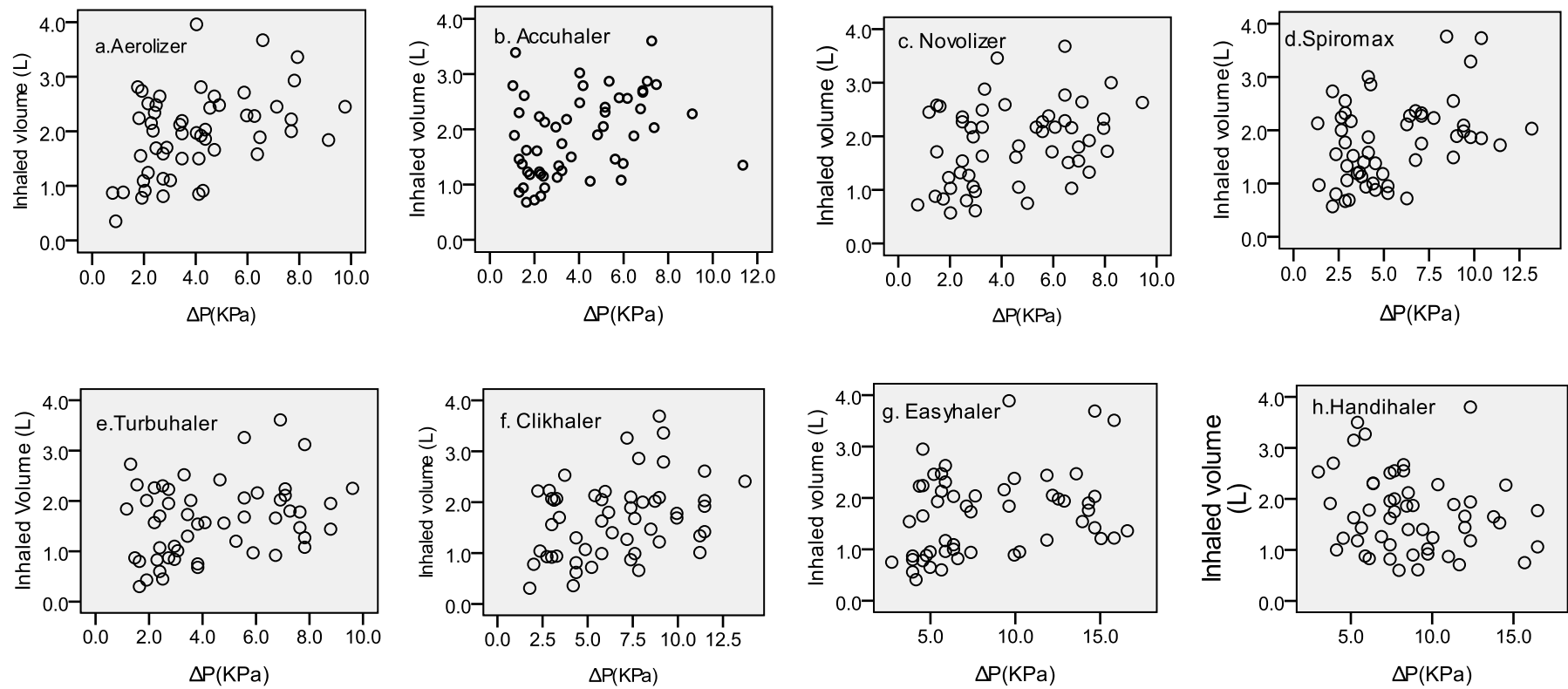
Figure 6.21. Scatter plots between the inhaled volume and maximum pressure change for each adult with asthma through a) Aerolizer, b) Accuhaler, c) Novolizer, d) Spiromax, e) Turbuhaler, f) Clickhaler, g) Easyhaler, h) Handihaler.

6.4.2.5. Subjects with low PIF and >90 l/min

Table 6.3. Shows the number of the patients that achieved PIF values of < 30 L/min, > 60 L/min and > 90 L/min through each the DPI

Table 6.4. The number of patients achieving different flows through each DPI.

	CHILD PIF(L/min)			ADULTS PIF (L/min)			COPD PIF(L/min)		
	<30	>60	>90	<30	>60	>90	<30	>60	>90
AERO	Nil	11	4	Nil	50	25	1	9	Nil
ACC	3	7	1	Nil	33	19	3	12	6
NOVO	1	8	1	Nil	39	22	Nil	13	1
SPIRO	N/A	N/A	N/A	Nil	34	12	1	9	1
TBH	2	3	Nil	Nil	23	1	2	6	Nil
CLICK	2	3	Nil	Nil	32	1	2	8	Nil
EASY	1	3	Nil	Nil	22	Nil	2	5	Nil
HANDI	N/A	N/A	N/A	Nil	21	Nil	1	7	Nil

6.4.2.6 Comparison of inhalation flow parameters for the Turbuhaler

Figure 6.22-6.24 show the relationship between inhalation flows (at 90% of the PIF and the PIF) to the inhalation flow when 150 ml had been inhaled through the Turbuhaler by the children with asthma, COPD patients and Adults with asthma respectively. Statistical comparison of $PIF_{90\%}$ to the inhalation flow when 150 ml had been inhaled revealed no significant difference.
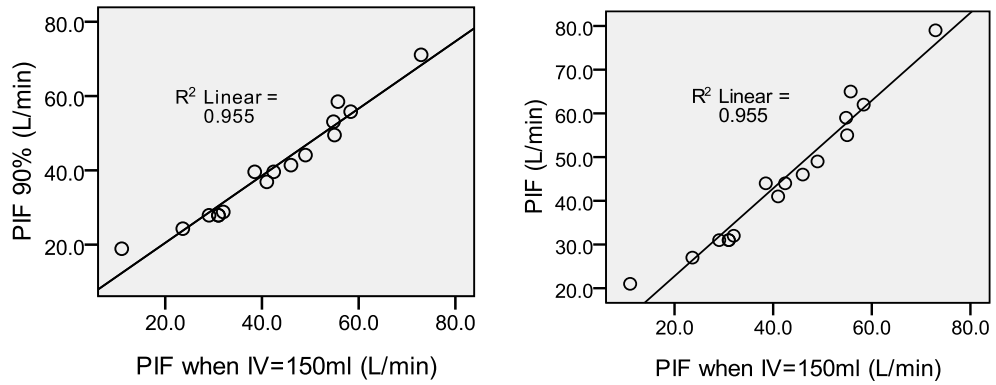
Figure 6.22. The relationship between the inhalation flows and the flow when IV=150 ml through a Turbuhaler by the children with asthma.
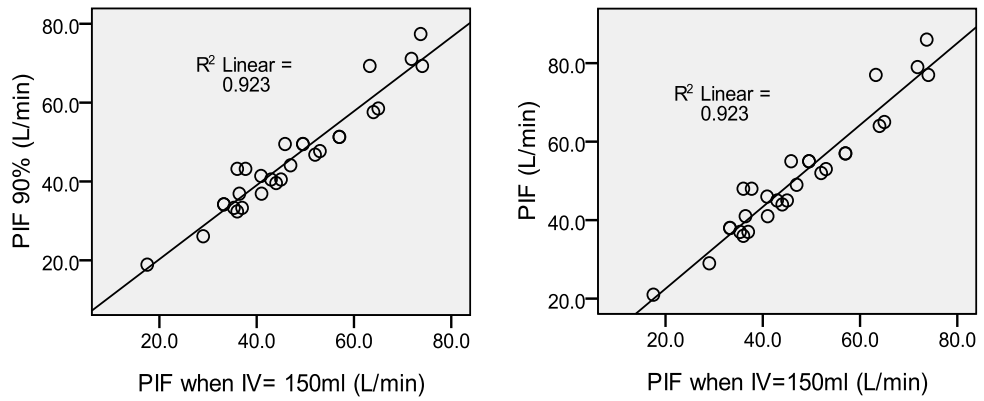
Figure 6.23. The relationship between the inhalation flows and the flow when IV=150 ml through a Turbuhaler by the COPD patients.
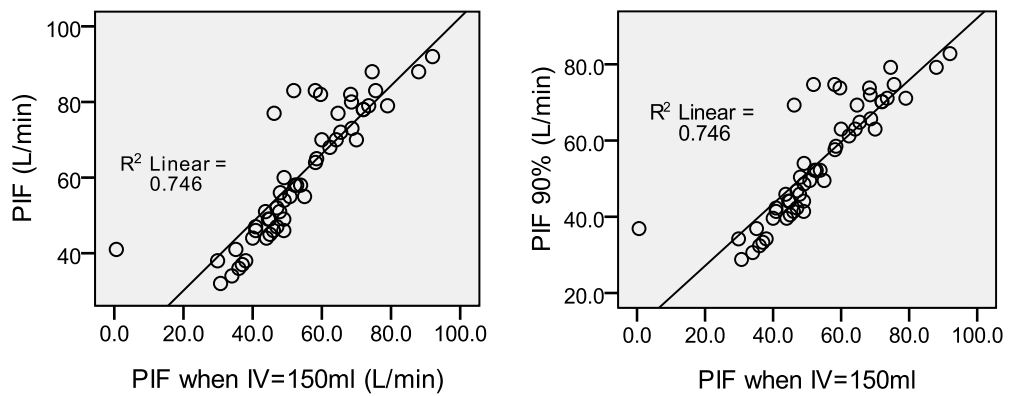
Figure 6.24. The relationship between the inhalation flows and the flow when IV=150 ml through a Turbuhaler by the adults with asthma.

6.4.2.5 Statistical analysis

A summary of the statistical comparisons between the Aerolizer, Accuhaler, Turbuhaler, and Easyhaler within each group is presented in Table 6.4. The non-parametric test (Wilcoxon signed rank test) was used for the comparison

Table 6.5. Statistical summary (values are *p* value).

	AERO v's ACC	TBH v's ACC	EASY'vs ACC	TBH v's AERO	TURB v's EASY	AER v's EASY
PIF						
CHILD	0.004	0.011	0.00	0.00	0.00	0.469
ADULTs	0.000	0.000	0.000	0.001	0.11	0.000
COPD	0.002	0.000	0.000	0.034	0.117	0.010
ΔP (kPa)						
CHILD	0.196	0.026	0.001	0.535	0.000	0.000
ADULTs	0.158	0.012	0.00	0.784	0.000	0.000
COPD	0.002	0.000	0.005	0.000	0.000	0.000
IV						
CHILD	0.408	0.004	0.070	0.011	0.148	0.015
ADULTs	0.487	0.000	0.000	0.000	0.95	0.000
COPD	0.15	0.117	0.10	0.171	0.804	0.459
ACC						
CHILD	0.379	0.26	0.001	0.011	0.000	0.00
ADULTs	0.112	0.378	0.000	0.383	0.00	0.00
COPD	0.033	0.014	0.000	0.787	0.000	0.00
Inhalation Time						
CHILD	0.202	0.325	0.248	0.100	0.231	0.569
ADULTs	0.921	0.511	0.719	0.177	0.225	0.980
COPD	0.202	0.325	0.248	0.569	0.231	0.569
Time at PIF						
CHILD	0.001	0.469	0.115	0.001	0.187	0.001
ADULTs	0.05	0.713	0.136	0.006	0.840	0.000
COPD	0.888	0.161	0.191	0.473	0.770	0.232

Quality of Life Questionnaires

    (a) Children with asthma

The mean (SD) PAQLQ scores (overall and its three domains: symptoms, Activity

Limitation and Emotional Function) and the PACQLQ scores are presented in Table

6.5.

Table 6.6. Mean (SD) PACQLQ and PAQLQ scores.

PACQLQ	
PCAQLQ	**4.33(1.1)**
PAQLQ Domains	
Overall PAQLQ	4.7(1.19)
Symptoms	3.7(1.1)
Activity Limitation	4.5(1.4)
Emotional Function	5.1(1.1)

    (b) Adults with asthma

A summary of the ACQ and AQLQ scores (overall and its three domains: symptoms,

activity limitation, emotional and environment) are presented in Table 6.6. Table 6.7

presents the level of asthma control with respect to the ACQ.

Table 6.7. Mean (SD) scores of (ACQ) and AQLQ for asthmatic Adults.

	Mean(SD)Scores	Minimum	Maximum
ACQ	1.95(1.02)	0.29	4.5
AQLQ	4.6(1.2)	2.0	6.5
Symptom	3.6(1.6)	1.4	5.7
Activity	3.8 (1.3)	0.81	5.7
Emotional	3.2(1.2)	0.9	5.5
Environment	3.4(1.16)	1.1	5.4

Table 6.8. Level of asthma control.

	ACQ Categories	Frequencies
Asthmatic Adults	≤ 0.75 (well controlled)	4(7.5%)
(n= 53)	0.75-1.50 (not well controlled)	19(35.8%)
	≥ 1.50(uncontrolled)	30(56.6%)

(c) COPD patients

Summaries of the SGRQ scores (overall and its three domains: Symptoms, Activity and Impacts) are presented in Table 6.8.

Table 6.9. The SGRQ scores of the COPD Patients.

SGRQ Domains(n=29)		Symptoms score	Activity score	Impacts score	Total score
Mean (SD)		70.27(24.2)	73.68(19.53)	50.20(21.6)	60.66(18.5)
Median		75.55	76.10	52.40	62.10
Minimum		19.90	26.50	8.60	25.30
Maximum		104.50	100.00	85.90	84.20
Percentiles	**25**	58.350	60.75	34.72	43.55
	50	75.55	76.10	52.40	62.10
	75	90.070	91.20	69.475	78.35

*SGRQ scores ranges from 0 to 100, zero scores indicate no impairment, with higher scores indicating worse health status

6.5 Discussion

The inhalation characteristics of children with asthma, asthmatic adults and COPD patients when they inhaled through different dry powder inhalers, that differ by their resistance, that ranging from low to high, have been measured. For these measurements patients were informed that they should use the same inhalation manoeuvre as they would if they were using a DPI.

The data is a substantial addition to the limited information that is available describing the inhalation parameters of patients when they use DPIs. The only data, of this type, that is available is for the Accuhaler and the Turbuhaler and there is no emphasis on the pressure changes that occur in the inhalation channel, of the DPI, during an inhalation and the acceleration rate with respect to a pressure change per time.

The inhalation parameters that have been measured are the peak inhalation flow and when this occurs, the inhalation volume, the pressure change (otherwise referred to as the turbulent energy) that occurs at the point of the PIF and the acceleration of the flow (in kPa/sec). These latter three parameters allow a true comparison to be made between different DPIs rather than PIF. Due to differences in resistance between DPIs when using the PIF the only comparison that can be made between devices is that if the resistance is low then flows will be faster than when the resistance is high (Clark & Hollingworth, 1993).

The PIF, pressure changes and the acceleration rate results obtained for all three groups confirm this. The results also confirm that as expected children with asthma generate significantly lower PIF values than COPD subjects and both these are lower than the rates achieved by adults with asthma. This is due to their reduced inspiratory effort. It has been suggested that a failure to achieve an inhalation flow of 30 L/min

within the first 150 ml of the inhalation affects de-aggregation(Everard et al., 1997) and thus inhalation characteristics about the first 150ml of the inhaled volume were obtained.

Traditionally PIF has been the focus of attention when patients use DPIs. However this is only useful when considering the flows through each DPI (Azouz and Chrystyn, 2012).

This review (Azouz & Chrystyn, 2012) was written after examining the results presented in this Chapter. The statistical analysis (in table 6.4) reveals that the peak inhalation flows, as expected, were very significantly faster when using a low resistance DPI (eg. Aerolizer and Accuhaler) than a high resistance device (Easyhaler and Handihaler). During routine practice this is the parameter that is usually used as the indicator if a patient can use their DPI with a fast inhalation. In contrast the pressure changes (which represent the turbulent energy) are (very highly) significantly greater for the high resistance devices. The acceleration rates mirror the pressure change results. De-aggregation occurs due to the turbulent energy created in the inhalation channel, of a DPI, during an inhalation. It is wrong therefore to recommend a low resistance DPI if the measured inhalation flows are slow when using a high resistance inhaler. This is a common misconception amongst practitioners.

All DPIs have flow dependent dose emission and some more than others (Palander et al, 2000) but even with relatively low flows they do emitted some dose. A more important issue is that for each DPI there will be a minimum threshold turbulent energy (corresponding to a measured pressure change) for efficient de-aggregation of the dose. It has been shown that below 30L/min the turbulent energy generated inside a Turbuhaler is not sufficient to efficiently de-aggregate the dose (Nadarassan et al.,

2010) and that the clinical effect sharply decreases (Pedersen et al, 1980). This flow corresponds to a maximum pressure change of 1.02 kPa in a Turbuhaler. This flow is also considered to be the minimum for the Accuhaler (Nielsen et al., 1998) whilst that for the Clickhaler (Newhouse et al., 1999) and Easyhaler (Koskela et al., 2000) are slightly lower. Nevertheless taking 30L/min as the gold standard for the minimum flow the results show that when patients use their normal real life inhalation technique then no adult asthmatic inhaled below this flow. Three COPD inhaled below this flow with an Accuhaler and of these only two of them achieved low flows with the Turbuhaler, Clickhaler and an Easyhaler. Three of the 16 children with asthma did not achieve 30L/min through the Accuhaler. These were all boys aged 5, 7 and 12 years old. The 5 and 12 year old did not achieve this flow through the Turbuhaler but there were 4 others with flows of either 31 or 32 L/min. The same 2 children failed to achieve 30L/min with the Clickhaler but only one of them (the 12 year old) with the Easyhaler.

Overall the percentage of numbers exceeding the recognised minimum flow of 30L/min flow with the Turbuhaler is higher than values previously reported. Nsour et al (2001) reported 14 out of 74 COPD patients had problems achieving this flow and their predicted FEV_1 was similar to the patients in this study. Also another COPD study has shown that 23/163 patients inhaled < 30L/min (Al-Showair et al, 2007). In contrast others have shown no patients inhaled below this rate (Dewar et al., 1999; Broeders et al., 2003a). In children with asthma 25 out of 72 did not achieve this recognised minimum flow with the Turbuhaler and were mostly 3 or 4 years old (Agertoft & Pedersen, 1998) which confirmed previous results about pre-school children using a Turbuhaler (Pedersen et al, 1990). No child in this study was aged < 5 years. Previously it was reported that 5 out of 24 adults asthmatics did not achieve

30L/min with a Turbuhaler (Hawksworth et al., 2000). These patients did have more severe asthma (57% predicted FEV_1 compared to 71.9% in this study). However in 20 severe asthmatics that were highly trained no patient inhaled used low flows (Tarsin et al, 2006). Previously, when using an Accuhaler no COPD patient (Broeders et al, 2003; Al-Showair et al, 2007) achieved < 30L/min with only 2 out of 129 children (a 5 and a 10 year old) not obtaining this flow (Nielsen et al, 1998). When using the Easyhaler 4 children (aged 4, 6, 10 and 16 years) failed to achieve 30L/min (Malmstrom et al, 1999) but their response to the bronchodilator was similar to when they inhaled using a pMDI attached to a Volumatic spacer (Malmstrom et al, 1999). Furthermore only 2 out of 93 COPD subjects achieved these low flows through an Easyhaler (Malmberg et al, 2010).

Although only one of the 29 COPD subjects in this study did not exceed 30 L/min with the Handihaler others have shown a third of the patients did not produce flows above this rate (Al-Showair et al, 2007). The Aerolizer has low resistance and so the minimum flow for efficient de-aggregation will be faster. It has been reported that this flow could be > 90L/min (Nielsen et al., 1997). Only 4 children with asthma, 25 adults with asthma and no COPD patients inhaled > 90L/min through the Aerolizer. In contrast 73% of adults asthmatics (n=33) inhaled >100L/min and 75% (n=32) children with asthma inhaled >80L/min (Bronsky et al., 2004). This together with the Accuhaler data suggests that it could be low resistance inhalers that patients have problems with respect to efficient de-aggregation. Also when the flow is fast there will be a tendency for more oropharynegeal deposition and deposition more towards the central zones of the lungs (Newman et al, 1995; Usmani et al, 2005). When using a DPI this is counter balanced by the DPI's flow dependent dose emission especially when it is pronounced. However dose emission form an Aerolizer (Weuthen et al.,

2002) and an Accuhaler (Palander et al.,2000) is less flow dependent. Hence the low resistance of these devices together with the resultant fast inhalation flows will tend to provide low lung deposition and high oropharyngeal impaction. Reduced peripheral lung deposition has been reported when adult asthmatics and healthy volunteers inhaled salbutamol from unit dose blisters in a DPI compared to a pMDI. (Melchor et al., 1993). It has been shown that when using a Turbuhaler, that has pronounced flow dependent dose emission (Palander et al., 2000) that there is no change in the peripheral: central lung deposition ratio when using faster flows (Newman et al., 1991b; Borgstrom et al., 1994). It has been reported that high resistance DPIs do provide greater lung deposition than those with a lower resistance (Borgstrom, 2001).

The maximum pressure change (ΔP) and the acceleration rate of an inhalation (when in kPa/sec) allow a comparison between different DPIs whereas the PIF does not. PIF values are only valid when considering each DPI in isolation. The maximum inhalation flows through the Accuhaler in this study were lower than those previously reported in adults with asthma (Broeders et al, 2003; Tarsin et al, 2006). In the COPD patients these flows were also lower to previous reports (Broeders et al, 2003) but one study reported similar flows through an Accuhaler (Al-Showair et al, 2007). When using the Turbuhaler the PIF values were similar to other studies involving children (Pedersen et al, 1990; Agertoft & Pedersen, 1998) but lower than another (Stahl et al, 1996). The flows of adult asthmatics using a Turbuhaler, in this study, were faster than those attending a community pharmacy (Hawksworth et al, 2000) but lower than highly trained severe asthmatics (Tarsin et al, 2006) and untrained mild asthmatics (Broeders et al, 2003) but similar to those with an acute exacerbation of asthma (Brown et al, 1995). In COPD patients although the PIF

through the Turbuhaler in this study were lower than mild, moderate and severe COPD patients in one study (Broeders et al, 2003) overall they were similar to others (Dewar et al, 1999; Al-Showair et al, 2007; Derom et al., 2007).

In contrast to PIF values the pressure changes (hence the turbulent energy) that occurs inside each DPI during an inhalation allows a comparison to be made between different devices. The results show that the pressure changes were greater for the DPIs with a higher resistance than those with a lower flow. Figures 6.2, 6.9, 6.16 for the children with asthma, adults with asthma and the COPD data, respectively, show that when the resistance is low to medium high there is little difference between the inhalers and that for high resistance inhalers the pressure changes are much greater. This is due to the non linear relationship between this pressure change with flow and the resistance as reported by Clark and Hollingworth (1993) and later by Clark (1994). Previously these maximum pressure changes (ΔP) have not been reported.

The acceleration of the flow has been shown to be critical for de-aggregation of the formulation in a DPI (de Boer et al, 1997; Everard et al, 1997; Kamin et al, 2002). It has been shown that achieving a flow of >30L/min before the first 150ml has been inhaled through a Turbuhaler is important for the de-aggregation of the formulation in a Turbuhaler. The very strong relationships in Figures 6.22, 6.23, 6.24 show that the inhalation flow at 90% of the PIF (PIF_{90}) correlates to that of the inhalation flow when 150 ml had been inhaled. The time that this flow occurs also correlates to the time for 150 ml to be inhaled. The inhalation flow at 90% of PIF and when this occurred was therefore used to calculate the acceleration of the inhalation flow. Although there is also a strong correlation between the PIF and the inhalation flow when 150 ml occurred this was not used for calculating the acceleration flow because the individual results showed that for some the time to PIF_{90} was 0.3 seconds

whereas PIF occurred at 0.5 seconds. Use of these would result in a big difference in the acceleration rates. Nevertheless when the PIF was fast then the acceleration rates were steeper than when the PIF was slow. This agrees with information published by Broeders et al (2001). Previously only Broeders et al (2003) has reported acceleration rates when asthmatics and COPD patients inhaled through an Accuhaler and a Turbuhaler. Overall the acceleration rates of the adults with asthma were similar to those reported by Broeders et al (2003) while the COPD rates were lower. The results also show that consistent with the inhalation flow and pressure changes that occur during the inhalations the acceleration rates were lower in children with asthma than COPD patients which were both lower than the adults with asthma.

The inhaled volume has two functions. First the dose has to be emptied from the device and then the airstream delivers the particles into the airways. The inhaled volume has to be sufficient for both to occur. Some DPIs require a higher volume to empty the dose than others. It has been reported that capsule based DPI inhalers require 4L to completely empty their dose (Chrystyn, 2009; Alaboud et al., 2010), the Turbuhaler at least 1L (Kamin et al, 2002) and the Accuhaler 150ml (Kamin et al, 2002). These differences are due to the design of the device. Capsules have to be emptied. The inhalation channel in the Turbuhaler is relatively long and includes a cyclone whereas the inhalation channel of the Accuhaler is very short (Azouz and Chrystyn, 2012). Overall within the groups the inhaled volumes were similar for the different devices with a tendency for a slightly larger volume for DPIs with lower resistance. Also as expected inhaled volumes were lower in the children with asthma than the COPD patients and both these were lower than the adults with asthma. When using the Aerolizer only one child inhaled >2L and more than half <1L, 7 COPD patients inhaled >2L (one > 4L) and 5 < 1L whilst 17 adults with asthma

inhaled >2L but no one inhaled > 4L and 7 inhaled < 1L. These values highlight the ERS / ISAM Consensus statement recommendation that when using capsule DPIs the patients should make two separate inhalation for each dose (Laube et al, 2010). However the results show, in this chapter that some patients should use more than 2 separate inhalations or be prescribed a different dry powder inhaler. Nine of the children with asthma inhaled < 1L through the Turbuhaler as well as 7 of the COPD patients and 12 of the adult asthmatics which suggests that some importance should be placed on the inhaled volume. Overall in COPD (Broeders et al, 2003; Derom et al, 2007), asthma (Newman et al, 1991; Broeders et al, 2003; Tarsin et al 2006) and healthy volunteer (Farr et al, 1995) studies the volumes they reported were higher than those in this study but one study involving adult asthmatics using a Turbuhaler in a community pharmacy reported similar volumes (Hawksworth et al, 2000).

Previously, the patient's peak inhalation flow (PIF) through a DPI has been the focus of attention but the results of this study suggest that the achieved turbulent flow (ΔP), the acceleration of the flow (in kPa/sec) and the inhaled volume may be more important. The inhalation manoeuvre of these patients was not trained so these values should improve with training. The turbulent energy and the acceleration should increase when patients are trained to use a fast inhalation and that this forceful inhalation should commence immediately whilst the inhaled volume would change with the instructions of maintaining the inhalation for as long as possible and also to exhale gently before each inhalation. Whether acceleration rates, peak inhalation flows and pressure changes improve following technique training is investigated in the next Chapter.

Compendial methods recommend that dose emission and the aerodynamic characteristics of the emitted dose should be measured using a pressure change (ΔP)

of 4 kPa and an inhaled volume of 4L. The scatter plots in figures 6.7, 6.14 and 6.21 show that most patients do not achieve a pressure drop of 4kPa and an inhalation volume of 4L when they use any DPI. Furthermore no individual replicated an inhalation profile that was the same as a square wave produced by a vacuum pump. These results highlight the need to modify the compendial methodology. This could be achieved by using a computerised vacuum pump to replay an inhalation profile instead of using the traditional square inhalation profile currently provided by a vacuum pump. Further adaptations would have to be made to the method to ensure sonic flow during the dose emissions and capture of the emitted dose. Preliminary work, in this University's laboratories, has shown that this is feasible

Conclusion

The methodology has provided an insight into the inhalation manoeuvre when patients use their DPI. The results indicate that the internal turbulent energy (measured by a pressure change) and the acceleration of the patient's inhalation (measured as a pressure change over time) are greater for high resistance DPIs whereas inhalation flows are lower. These results highlight that inhalation flow should not be used to compare different DPIs but should only be used as an indicator that a patient can achieve the minimum flow required for a DPI. As expected the inhalation characteristics of children with asthma were lower than those with adults and similar to those of COPD patients. The significance of the inhalation volumes needs to be investigated.

Chapter 7: Training DPI users to improve their inhalation manoeuvre when using a Spiromax and a Turbuhaler Dry Powder Inhaler.

7.1 Introduction

All DPIs are passive devices in that a turbulent energy (measured as a pressure change) is required to de-aggregate the formulation of the dose that has been prepared for inhalation. This energy is generated by an interaction between the patient's inhalation flow and the resistance of the device (Clark and Hollingworth, 1993; Steckel and Muller, 1997b; Chrystyn, 2009). In-vitro studies have highlighted the flow dependent dose emission characteristics of DPIs (Ross and Schultz, 1996; Hill and Slater, 1998; Prime et al., 1999; Palander et al., 2000; Tarsin et al., 2004; Tarsin et al., 2006) and that this translates to higher lung deposition with faster flows (Newman et al., 1991a; Borgstrom et al., 1994; Newman et al., 2001) and altered response (Pedersen and Mortensen, 1990; Engel et al., 1992; Nielsen et al., 1997).

Training the inhalation manoeuvre of children with asthma (Agertoft & Pedersen, 1998), adults with asthma (Hawksworth et al, 2000; Broeders et al, 2003) and COPD patients (Nsour et al, 2001; Broeders et al, 2003; Al-Showair et al, 2007b) has been reported to be useful although the changes in COPD patients were small (AL-Showair et al, 2007b). The training should include information that the fast inhalation should commence immediately from the beginning of an inhalation (Laube et al, 2011) because de-aggregation and dose emission occurs in the initial phase of the inhalation manoeuvre (de Boer et al., 1997; Everard et al., 1997; Kamin et al., 2002). Everard et al (1997) showed that this occurs during the first 150 ml of the inhalation. Hence the acceleration of the flow is an important parameter. This is explained in Figure 7.1
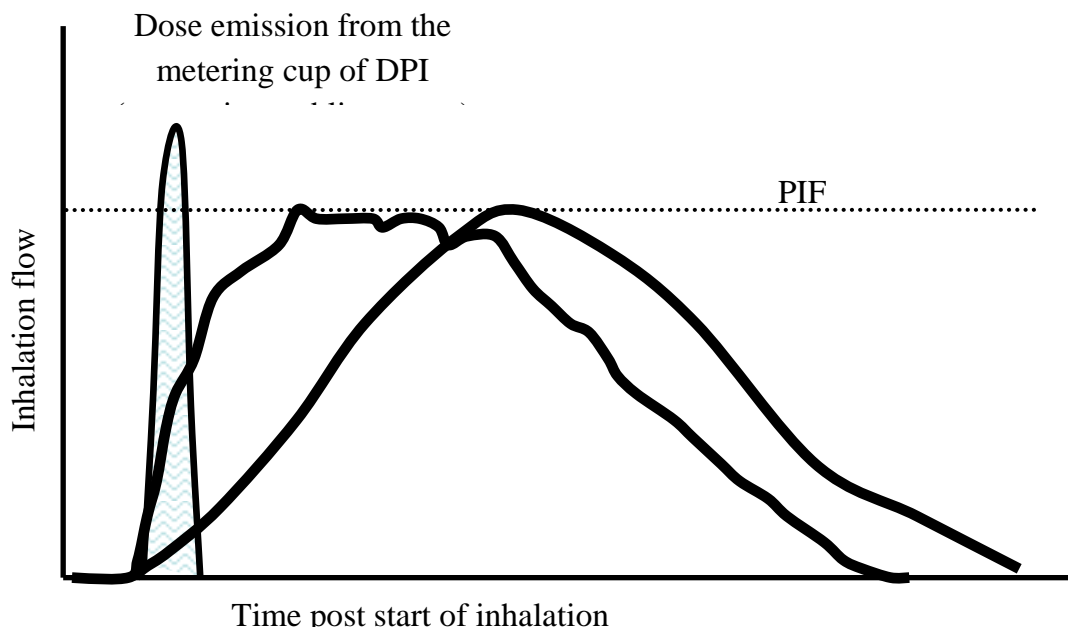
Figure 7.1. Inhalation Flow profiles of two different patients through DPIs (Chrystyn and Price, 2009).

This figure shows two different profiles with the same PIF and superimposed onto these is when the dose leaves either a multidose reservoir DPI or a multidose device which contains each dose in a separate blister. This figure shows that the acceleration of the flow while the dose leaves the DPI is much greater when the fast inhalation commences immediately compared to a gradual increase to the PIF. The acceleration of the flow can be measured with respect to volume or the turbulent energy. The latter, in kPa/sec units, is preferred because it relates to the increase in the pressure changes during the initial part of an inhalation and can be used to compare different devices.

In this current research work inhalation pressure profiles before and after training the inhalation manoeuvre when using a DPI have been measured. It was decided to use two different devices which had a similar resistance to rule out any affect caused by the appearance of the DPI.

7.2. Aim and objectives

(a) Aim

To identify if training the inhalation manoeuvre when subjects inhale through DPIs alters the inhalation parameters.

(b) Objectives

➤ Measure inhalation pressure profiles of children with asthma, adults with asthma and COPD patients as well as healthy volunteers when they inhale using a Spiromax DPI and a Turbuhaler DPI.

➤ Train patients to inhale faster through each DPI using the IN-Check Dial [ENHANCED TRAINING].

➤ Re -measure the inhalation profiles after the training

➤ Compare each inhalation parameter before and after training.

7.3 Methodology

This was a randomised, open label, cross-over study using a Spiromax DPI and a Turbuhaler DPI. Ethical approval was obtained from the NRES Committee Yorkshire and The Humber − Bradford and all subjects gave signed informed consent. Ethical committee approval for the healthy volunteers was obtained from the School of Applied Sciences Ethical Committee.

7.3.1. Study population

Stable asthmatic (adults and children) and COPD patients attending respiratory out-patient clinics and receiving regular inhaled therapy were studied. The study procedures and measurements were carried out during one visit. In addition healthy volunteers were included. These were recruited locally from the University. As far as possible these healthy volunteers were matched to those of the adult asthmatics and so these were recruited after the entire adult asthmatics had completed the study.

The study objectives and procedure were described to the patients and healthy subjects using relevant patient information sheets [APPENDIX A1, A2 , A3and A4]. Each participant kept a copy of the information sheet and was given as much time as they required to consider participating. For the patients attending the clinic they were informed that if they wanted to reflect about their decision then they were given a contact should they wish to take part. All consultations and recruitment of those < 18 years was made with them and their parent / carer. After their agreement to participate in this study, a signed informed consent form was obtained [APPENDIX A-5] (refer to the enclosed DVD).

On the basis of other studies (Bisgaard et al., 1998; Broeders et al., 2001; Burnell et al., 2001; Broeders et al.,2003; Broeders et al., 2004; Vogelberg et al., 2004; Tarsin et al., 2006) this study was designed to include 50 asthmatic children, 50 adult asthmatics, 50 COPD and 50 healthy volunteers. Hence, 50 x 4 groups of patients (total 200 subjects) were recruited into this study.

The NHS Teaching Hospitals which were involved as research sites were:

- ❖ Airedale General Hospital, Steeton, West Yorkshire, UK.

- ❖ Leeds General Infirmary, Leeds, UK

- ❖ St. James's University Hospital, Leeds, UK

- ❖ Bradford Royal Infirmary, Bradford, West Yorkshire, UK

- ❖ St. Luke's Hospital, Bradford, West Yorkshire, UK.

 (a) **Inclusion criteria:**

- ➢ Male or female, with stable asthma or COPD or healthy volunteer

- ➢ Groups:

- ❖ Children with asthma (CHILD): 4-17 years

- ❖ Adults with asthma (ADULT): 18-45 years

- ❖ COPD patients (COPD): >55 years

- ❖ Healthy adults (HEALTHY): 18-45 years.

- ➢ Prescribed inhaled medication including a DPI. Healthy adults were inhaler naive.

- ➢ Signed informed consent (including the parent/guardian in case of an asthmatic child).

(b) Exclusion criteria:

- ➢ Prescribed inhaled medication for less than 4 weeks prior to enrolment.

- ➢ Limited ability to understand/implement the study procedures and instructions.

- ➢ Other pulmonary diseases (e.g. pneumonia, TB) at study enrolment or any other severe conditions that may adversely affect the respiratory system or quality of life.

- ➢ An acute asthma or COPD exacerbation or oral prednisolone use during the 4 weeks prior to enrolment.

- ➢ Patient participating in another clinical research study at the time of or in the past 3 months prior to enrolment.

- ➢ Females who were pregnant.

7.3.2. Study Design

(a) Baseline assessments

Subjects attended a single study visit. Age, height and weight were measured and baseline lung function recorded by spirometry. For subjects with asthma their asthma status was assessed using the Asthma Control Questionnaire (ACQ) (Juniper et al. 1999; Juniper et al. 2006). The status of the subject's COPD was assessed using the total dyspnoea scale score [see section (2.2.2.2, Table 2.5)] (Fletcher 1960; Garrod et

al. 2006). Details values can be found in Appendix B 46-48 refer to the enclosed DVD)

(b) Initial training

All subjects in each group (n=50) were randomly assigned to standard training using placebo Spiromax or Turbuhaler DPI devices. This consisted of verbal instruction on correct usage according to the instructions for use contained in the patient information leaflet (PIL) supplied by the manufacturer for both the devices.

Each subject was required to perform two consecutive inhalation manoeuvres with the first DPI device. Subjects then repeated the process with the other DPI device. The DPIs were attached to an inhalation pressure profile recorder so that the maximum pressure change (Δp), peak inhalation flow (PIF), inhalation volume (IV), time to reach the PIF (Tp), the acceleration rate (ACC) and the duration of the inhalation could be recorded. For each inhalation manoeuvre through a DPI device, the profile with the highest PIF was selected for analysis.

(c)Inhalation manoeuvre training

Following the initial inhalation manoeuvres, all subjects received enhanced inhalation technique training. An inhalation airflow meter - the IN-Check Dial™ (Clement Clark International, UK), set to the resistance of the Turbuhaler, was used to improve inhalation technique (Nsour et al. 2001; Chrystyn 2003). Subjects were asked to perform inhalation manoeuvres as described above, and were then shown their PIF value displayed on the IN-Check Dial™. They were then encouraged to inhale faster during a second attempt. This was repeated until each subject had increased their PIF by >10 L/min. Following enhanced training, subjects then performed two consecutive inhalation manoeuvres through each DPI device (with the inhalation profile recorder re-attached) in the same order as before enhanced training

but using the faster inhalation technique. As before, the inhalation profile with the highest PIF was selected for analysis.

7.3.3 Inhalation profiles measurements

Each DPI was adapted so that a small tube was connected between the inhalation channel of the device and pressure sensors. The connection was airtight and did not interfere with the inhalation manoeuvres. The pressure changes with respect to time were electronically downloaded into an EXCEL spreadsheet to compute the inhalation parameters.

The resistance of the Spiromax and the Turbuhaler was 0.0313 and 0.0335 $(kPa)^{0.5}(min \ l^{-1})$, respectively.

Pre training inhalation parameters are described as Turbuhaler A [TBH-A] and Spiromax A [SPIRO-A] whilst the post training parameters are Turbuhaler B [TBH-B] and Spiromax B [SPIRO-B].

7.3.4 Statistical Data Analysis

The statistical analysis of the data was carried out using the Statistical Package for Social Sciences (SPSS for windows, version 17) software. A SPSS dataset was then set up and the analysis was performed and presented as follows:

➢ Descriptive statics: presented as mean (standard deviation)

➢ Normal distribution of the data was examined using histograms and the statistical tests for normality: Kolmogorov-Smirnov and Shapiro- Wilk tests

➢ Comparisons of measurements within the same study group were performed, using the related (paired) - sample- test for parametric data, or the Wilcoxon signed rank test for non-parametric data.

7.4 Results

7.4.1 Study population

A total of 200 patients were recruited and completed this study. A summary of their demographic, lung function (presented as FEV_1% predicted) and disease severity classification is presented in Table 7-1. Individual details of the demographic data are presented in APPENDIX B-42.B-43.B-44, B-45 together with their % predicted values respectively (refer to the enclosed DVD). A complete summary of their inhalation parameters through the Spiromax and Turbuhaler DPIs before and after training is presented in Table 7.2. The range of the individual inhalation parameters of the children with asthma, before and after training, is presented in Figures 7.2-7.7.

Table 7.1. Study participant details. All values are mean (SD) unless indicated otherwise.

Characteristics		Asthmatic Children	Asthmatic Adults	COPD	Healthy Subjects
Number (n)		50	50	50	50
Sex [M/F] (n)		28/22	21/29	22/28	21/29
Age in years		11.6 (3.6)	34.7 (7.6)	66.8(7.9)	32.6 (7.3)
Height in cm		147.7 (19.7)	168.0 (4.9)	168.7(6.9)	171.2 (7.8)
Weight in Kg		47.6(17.1)	75.4(10.4)	78.1(13.6)	73.8(14.1)
FEV_1		2.0(0.7)	2.5(0.72)	1.5(0.6)	3.6(0.75)
FEV_1 % predicted		57.1 (16.9)	69.2(16.4)	51.8(21.9)	95.7 (14.3)
PEF in L/min		251.8(115.0)	329.5(101.1)	216.5(93.3)	479.3(127.6)
PEF % predicted		55.9 (18.8)	65.9 (16.5)	46.1 (20.5)	99.7 (20.4)
FVC in Litres		2.5(1.0)	3.1(1.0)	2.3(0.9)	3.9(0.9)
Disease severity	Mild	7	18	25	N/A
	Moderate	19	20	17	N/A
	Severe	22	12	8	N/A

Table 7.2. Mean (SD) inhalation characteristics of asthmatic children, adult with asthmatic, COPD patients and healthy subjects when they inhaled through the Turbuhaler and Spiromax DPIs before and after training.

	PIF (l/min)	ΔP (kPa)	Tp (sec)	IV (L)	Ti (sec)	ACC (l/sec^2)	Acc(kPa/sec)
CHILD							
TBH-A	57.6(13.4)	3.92(1.84)	0.75(0.55)	1.451(0.72)	2.08(0.84)	3.03(1.74)	11.32(7.72)
TBH-B	71.8(14.7)	6.02(2.38)	0.47(0.20)	1.529(0.61)	1.82(0.62)	4.75(2.11)	21.73(12.47)
SPIRO-A	67.9(15.7)	4.75(2.30)	0.68(0.33)	1.711(0.80)	2.15(0.8)	3.23(1.96)	12.48(9.86)
SPIRO-B	81.0(16.4)	6.69(2.57)	0.51(0.35)	1.841(0.721)	1.95(0.71)	5.31(2.81)	24.23(16.73)
ADULT							
TBH-A	65.4(14.4)	5.14(2.55)	0.49(0.26)	2.131(1.00)	2.69(1.20)	2.69(1.21)	13.0(12.0)
TBH-B	76.7(15.0)	6.85(2.50)	0.27(0.12)	2.121(0.90)	2.31(0.85)	5.17(3.13)	25.95(20.28)
SPIRO-A	74.4(18.1)	5.74(2.56)	0.936(0.66)	2.390(1.03)	2.74(1.27)	3.55(2.79)	15.66(15.55)
SPIRO-B	85.5(14.6)	7.35(2.33)	0.292(0.17)	2.377(1.11)	2.32(1.03)	6.19(4.38)	30.02(25.29)
COPD							
TBH-A	50.1(16.2)	3.10(1.9)	0.96(0.86)	1.577(0.69)	2.94(1.36)	2.42(1.88)	8.44(9.46)
TBH-B	60.1(17.0)	4.4(2.4)	0.6(0.3)	1.665(0.71)	2.54(1.01)	3.9(2.5)	15.7(14.0)
SPIRO-A	57.5(21.0)	3.66(2.70)	0.677(0.38)	1.819(0.87)	2.71(1.0)	3.04(2.2)	11.01(12.84)
SPIRO-B	68.1(18.5)	3.94(2.1)	0.55(0.33)	1.897(0.89)	2.55(1.09)	4.67(3.1)	18.89(17.01)
Healthy							
TBH-A	78.0(11.8)	6.98(2.05.)	1.19(0.70)	2.71(0.81)	3.02(1.03)	2.58(1.67)	12.84(9.55)
TBH-B	90.36(10.9)	9.29(2.085)	0.55(0.3)	2.794(1.01)	2.71(0.8)	5.37(2.43)	30.11(14.3)
SPIRO-A	85.01(13.58)	7.25(2.2.5)	1.02(0.53)	2.984(1.01)	2.94(1.1)	3.34(2.42)	15.85(13.53)
SPIRO-B	98.68(9.15)	9.62(1.64)	0.54(0.51)	3.069(1.04)	2.67(0.82)	6.06(2.96)	32.21(17.17)

7.4.2.1 Inhalation Profiles of the children with asthma before and after training
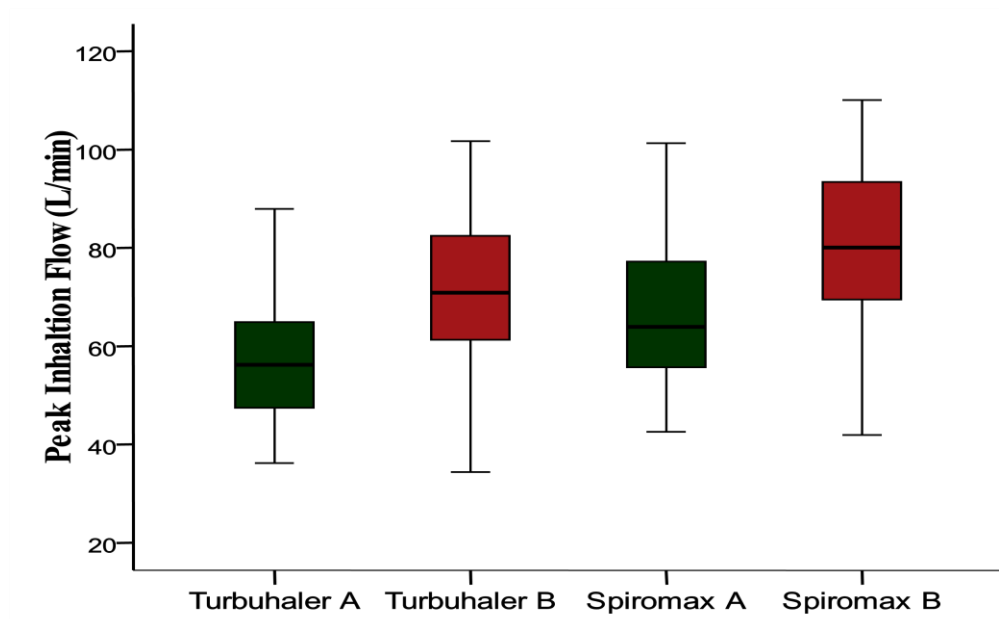
Figure 7.2. The distribution of the individual peak inhalation flows through the Turbuhaler and Spiromax, before (A) after training (B) achieved by the children with asthma.
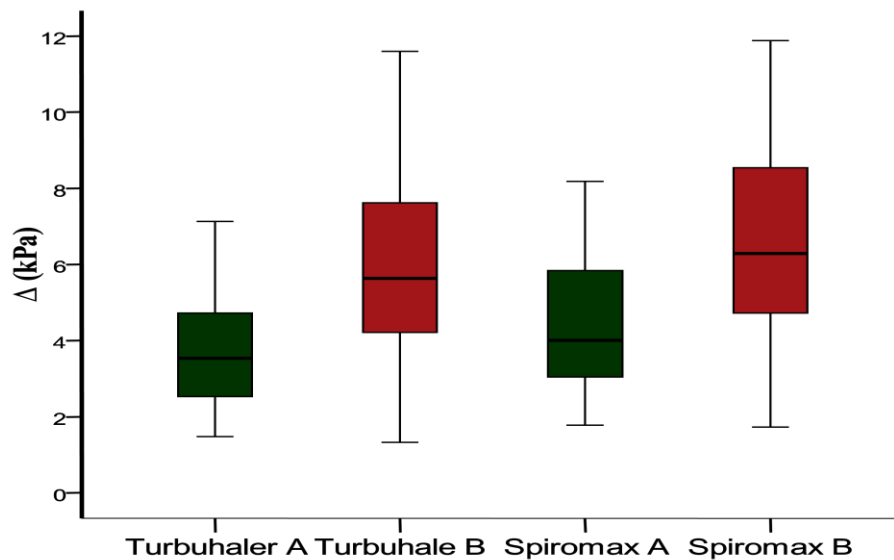
Figure 7.3. The distribution of the maximum pressure changes occurring in the Turbuhaler and Spiromax before (A), after training (B) during the inhalation of the children with asthma.
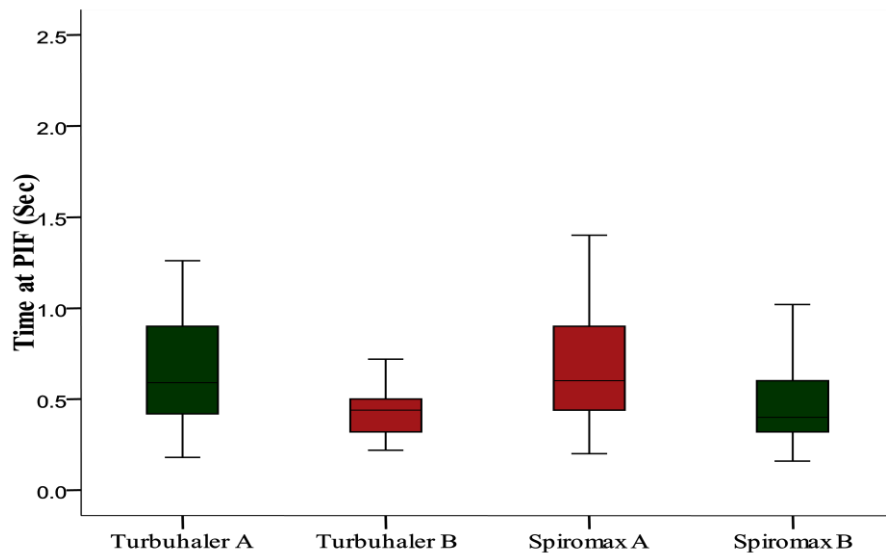
Figure 7.4. The range of the times to PIF when the children with asthma inhaled through a Turbuhaler and Spiromax before (A), after training (B).
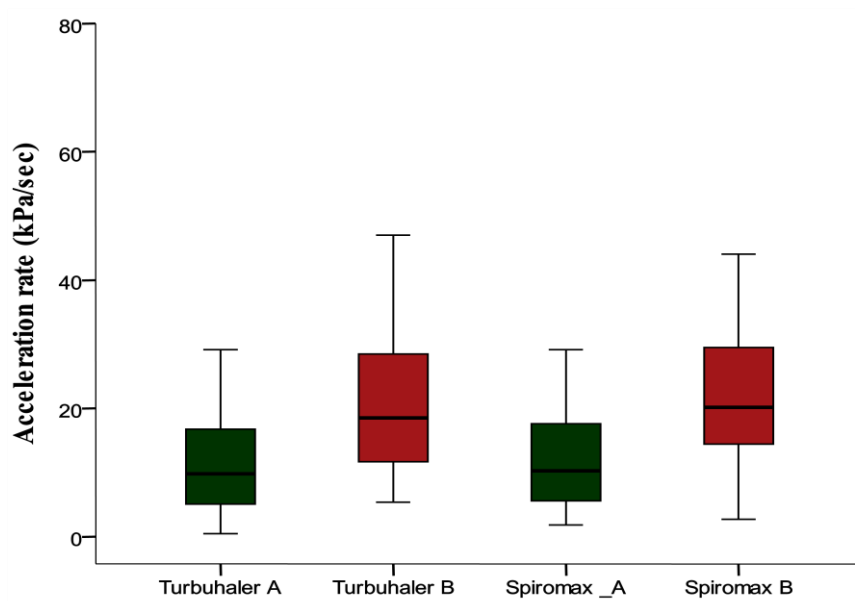
Figure 7.5. The distribution of the acceleration rates achieved by the children with asthma when they inhaled through the Turbuhaler and Spiromax before (A), after training (B).
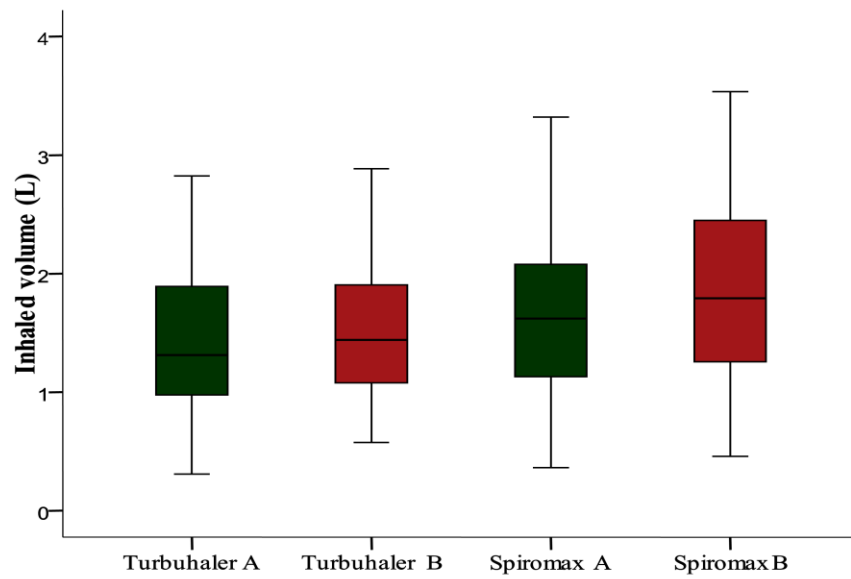
Figure 7.6. The distribution of the inhaled volume achieved by the children with asthma when they inhaled through the Turbuhaler and Spiromax before (A), after training (B).
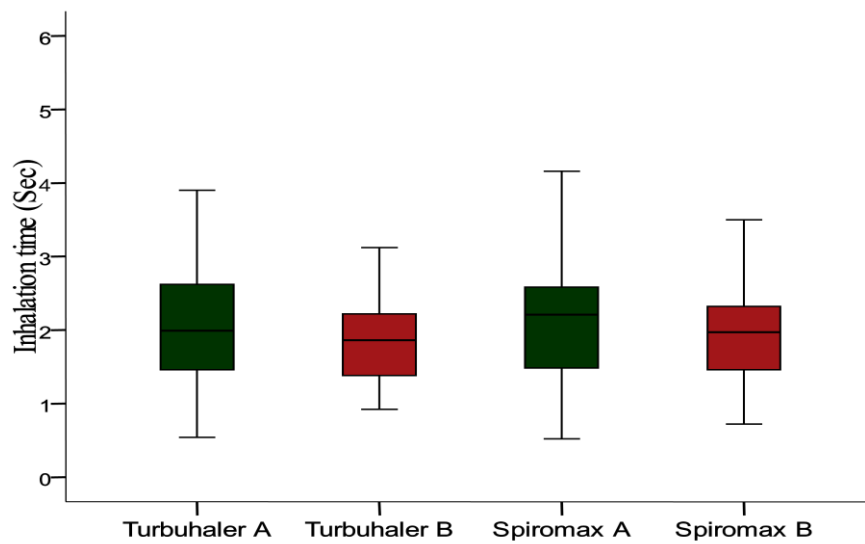
Figure 7.7. The range of the individual inhalation times when the children with asthma inhaled through the Turbuhaler and Spiromax before (A), after training (B).

7.4.2.2. Inhalation Profiles of the adults with asthma when they through the Spiromax™ and Turbuhaler DPIs before and after training.

The range of the inhalation characteristics is presented in Figures 7.8 to 7.13.
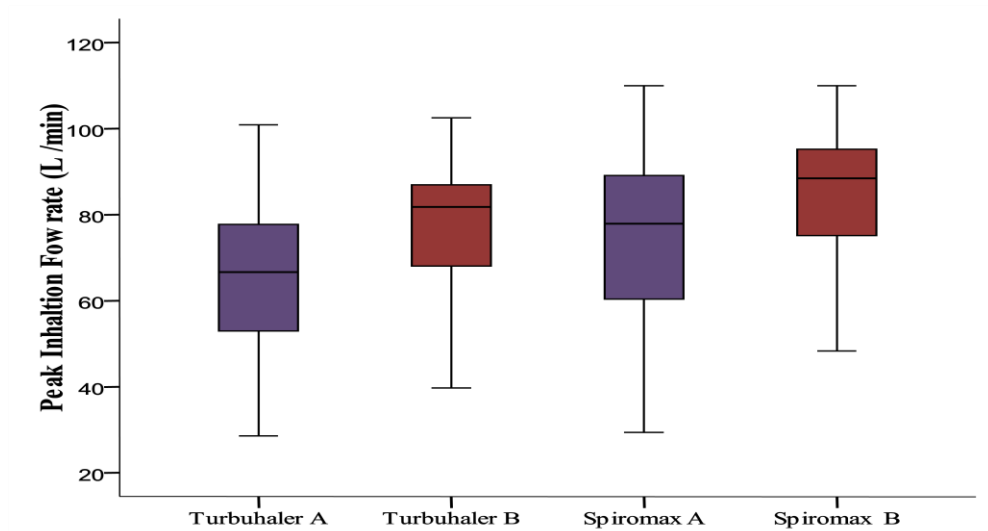
Figure 7.8. The distribution of the individual peak inhalation flows achieved by the adults with asthma through the Turbuhaler and Spiromax, before (A) and after training (B).
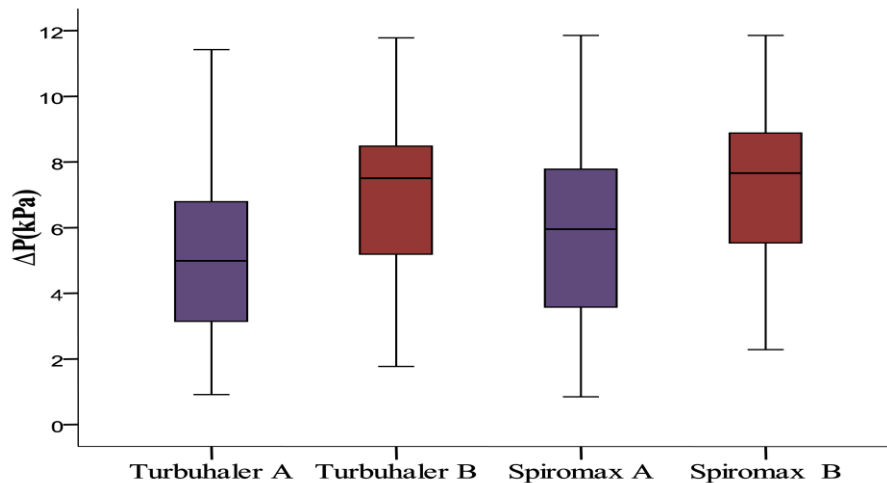
Figure 7.9. The distribution of the maximum pressure changes occurring in the Turbuhaler and Spiromax, before (A) after training (B), during the inhalations by the adults with asthma.
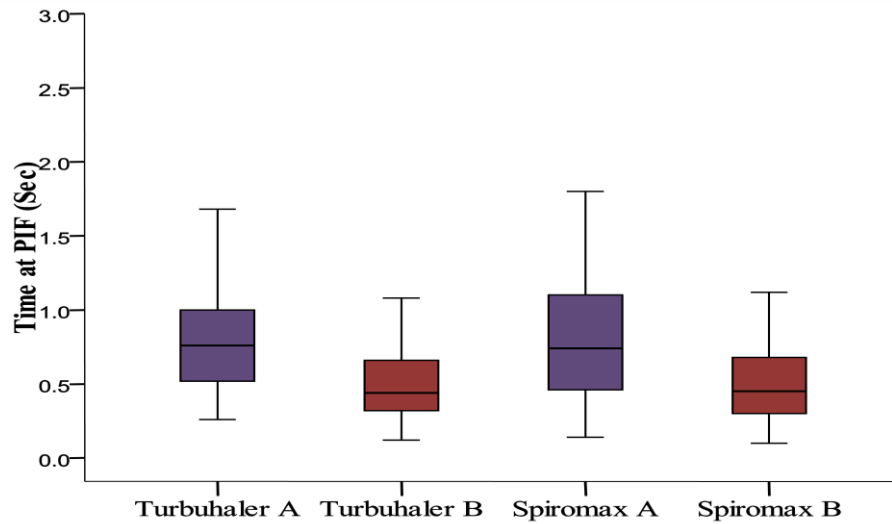
Figure 7.10. The range of the times to PIF when the adults with asthma inhaled through a Turbuhaler and Spiromax before (A) after training (B).
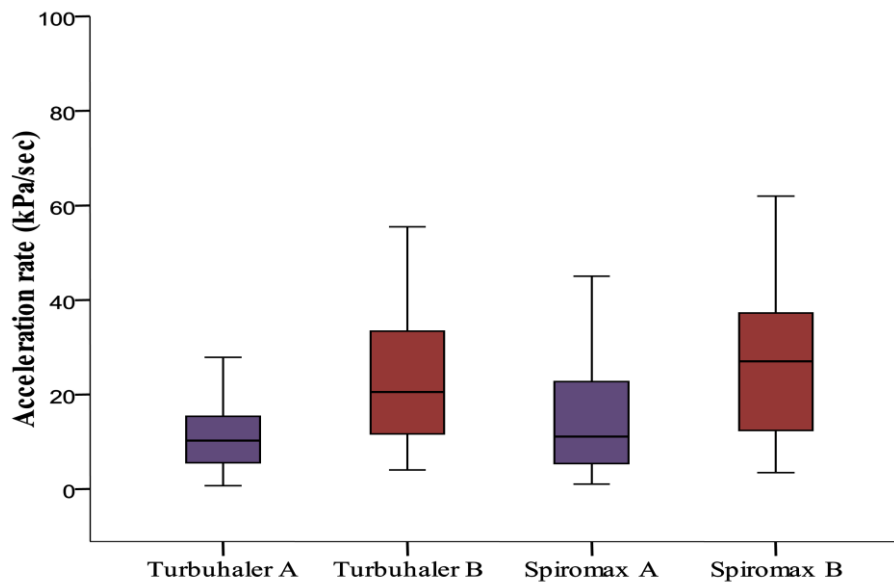
Figure 7.11. The distribution of the acceleration rates achieved by the adults with asthma when they inhaled through the Turbuhaler and Spiromax before (A) after training (B).
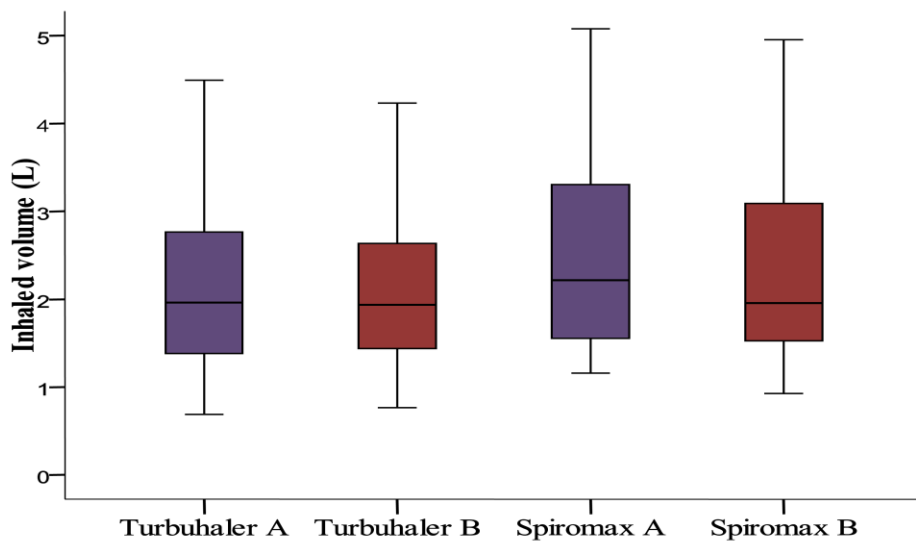
Figure 7.12. The distribution of the inhaled volume achieved by the adults with asthma when they inhaled through the Turbuhaler and Spiromax, before (A) after training (B).
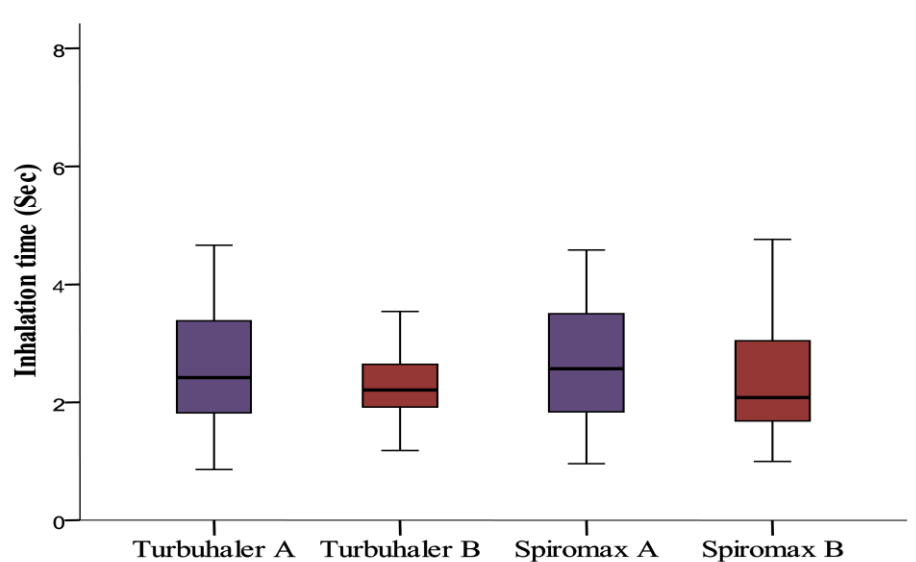
Figure 7.13. The range of the individual inhalation times when the adults with asthma inhaled through the Turbuhaler and Spiromax, before (A) after training (B).

7.4.2.3. Inhalation characterisation for COPD patients when the inhaled through the Turbuhaler and Spiromax before and after training

The range of the inhalation characteristics is presented in Figures 7.14 to 7.19.
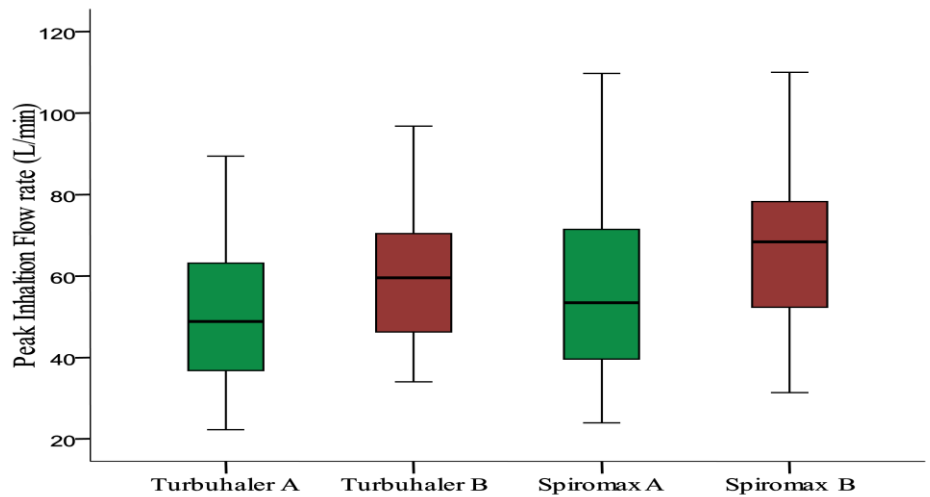
Figure 7.14. The distribution of the individual peak inhalation flows through the Turbuhaler and Spiromax, before (A) after training (B), achieved by the COPD patients
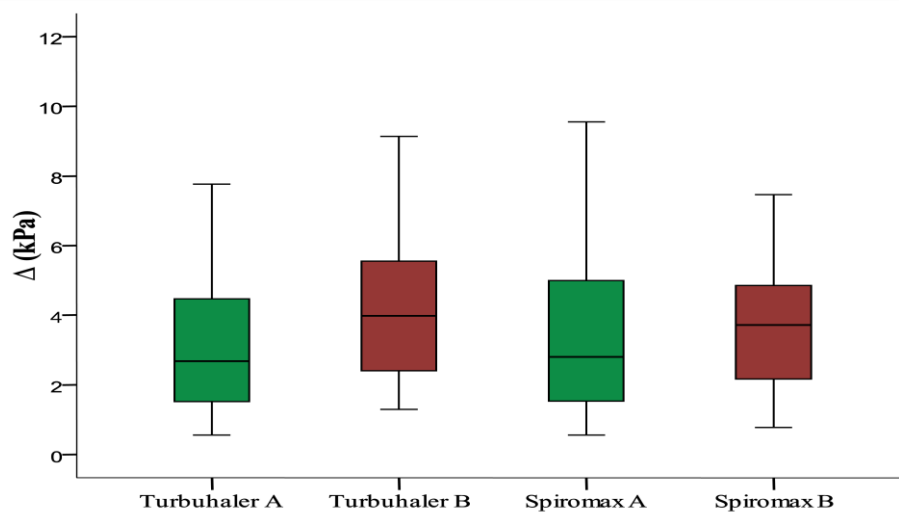
Figure 7.15. The distribution of the maximum pressure changes occurring in the Turbuhaler and Spiromax, before (A) after training (B), during the inhalations by the COPD patients
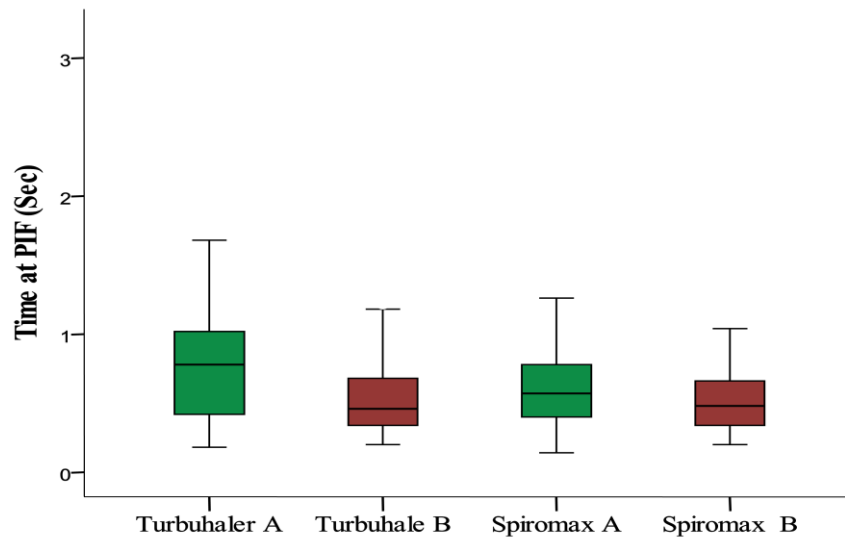
Figure 7.16. The range of the times to PIF when the COPD patients inhaled through a Turbuhaler and Spiromax before (A) after training (B)
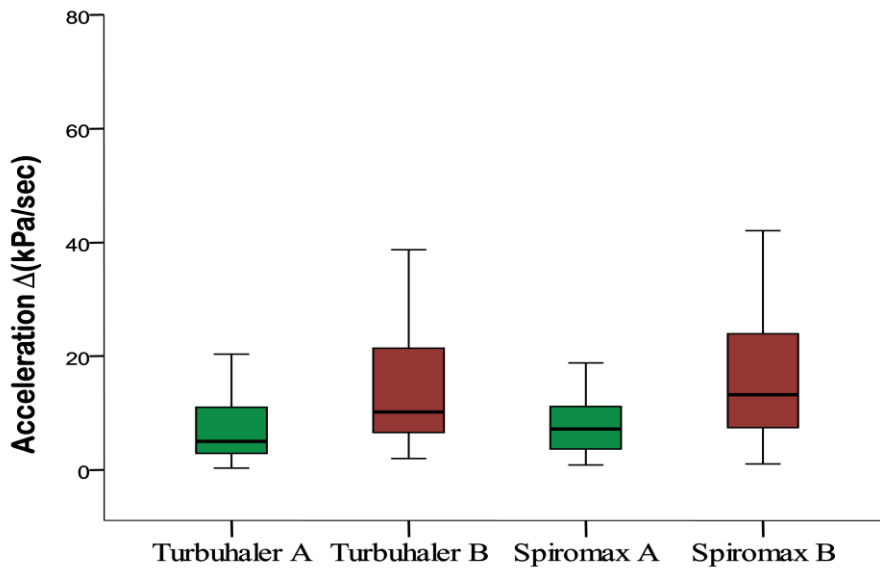
Figure 7.17. The distribution of the acceleration rates achieved by the COPD patients when they inhaled through the Turbuhaler and Spiromax before (A) after training (B)
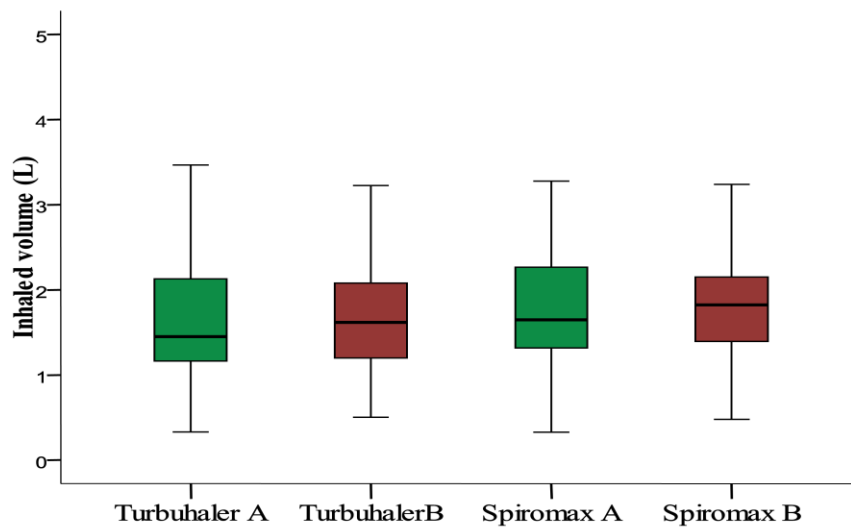
Figure 7.18. The distribution of the inhaled volumes achieved by the COPD patients when they inhaled through the Turbuhaler and Spiromax before (A) after training (B)
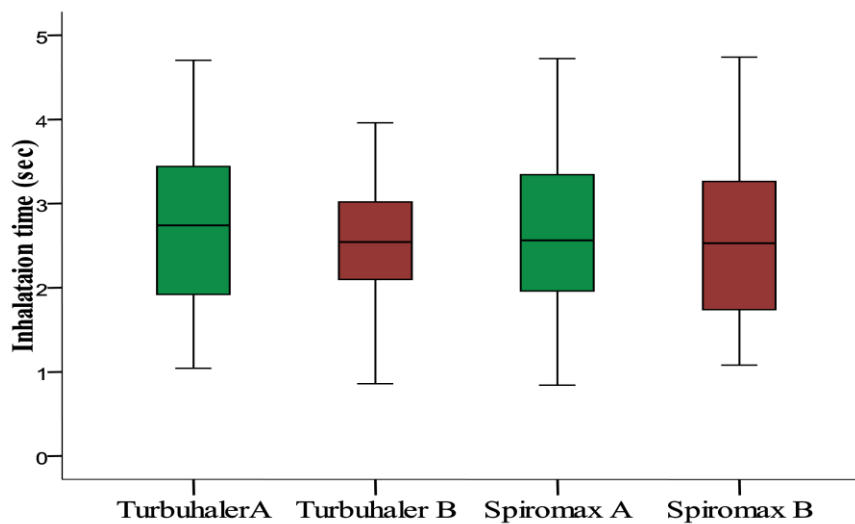
Figure 7.19. The range of the individual inhalation times when the COPD patients inhaled through the Turbuhaler and Spiromax before (A) after training (B).

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7.4.2.4. Inhalation characterisation for healthy subjects when the inhaled through the Turbuhaler and Spiromax™ DPIs before and after training

The range of the inhalation characteristics is presented in Figures 7.20 to 7.25.
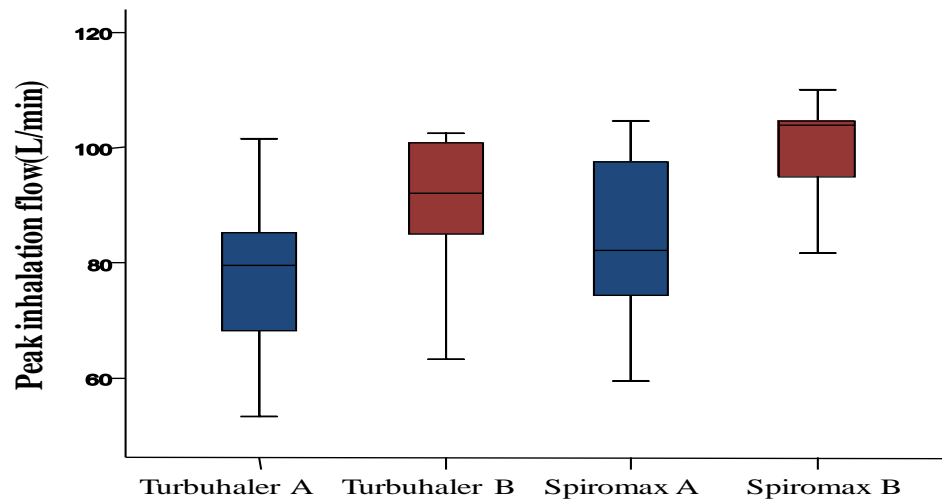
Figure 7.20. The distribution of individual peak inhalation flows achieved by the healthy volunteers through the Turbuhaler and Spiromax, before (A) after training (B).
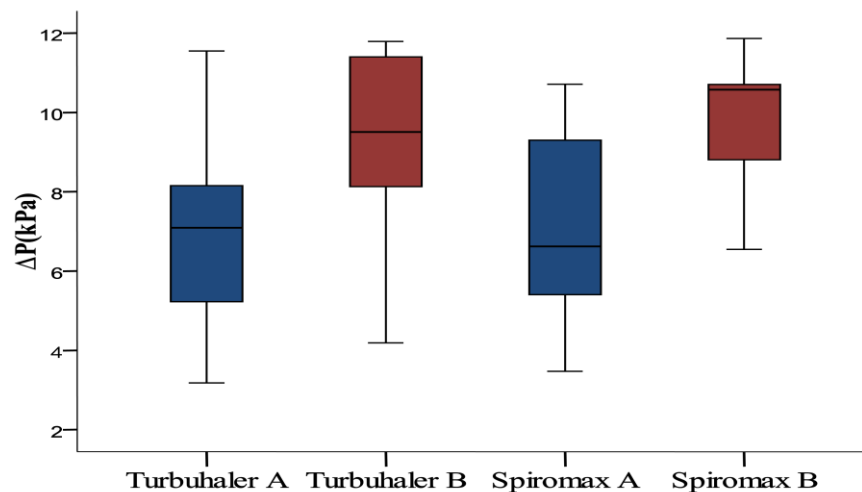
Figure 7.21. The distribution of the maximum pressure changes occurring in the Turbuhaler and Spiromax, before (A) after training (B), during the inhalation of the healthy volunteers.
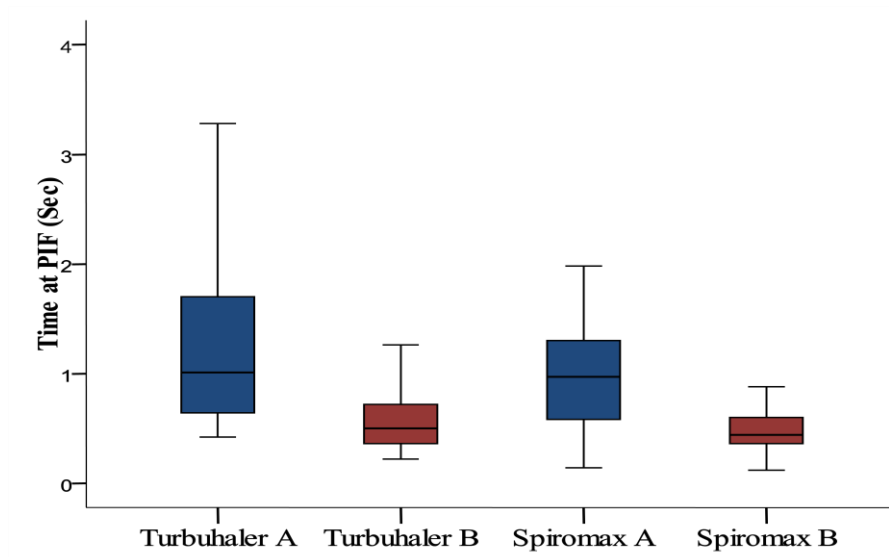
Figure 7.22. The range of the times to PIF when the healthy volunteers inhaled
through a Turbuhaler and Spiromax, before (A) after training (B).
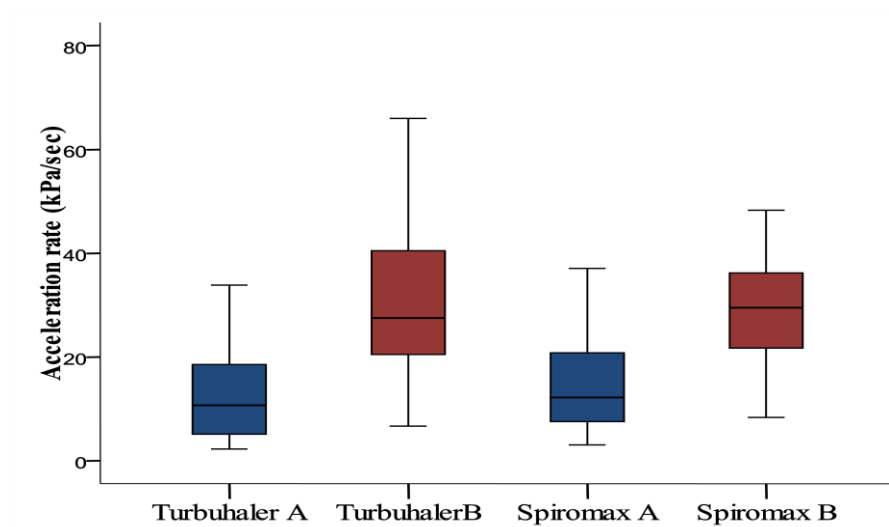
Figure 7.23. The distribution of the acceleration rates achieved by the healthy
volunteers when they inhaled through the Turbuhaler and Spiromax, before (A) after
training (B).
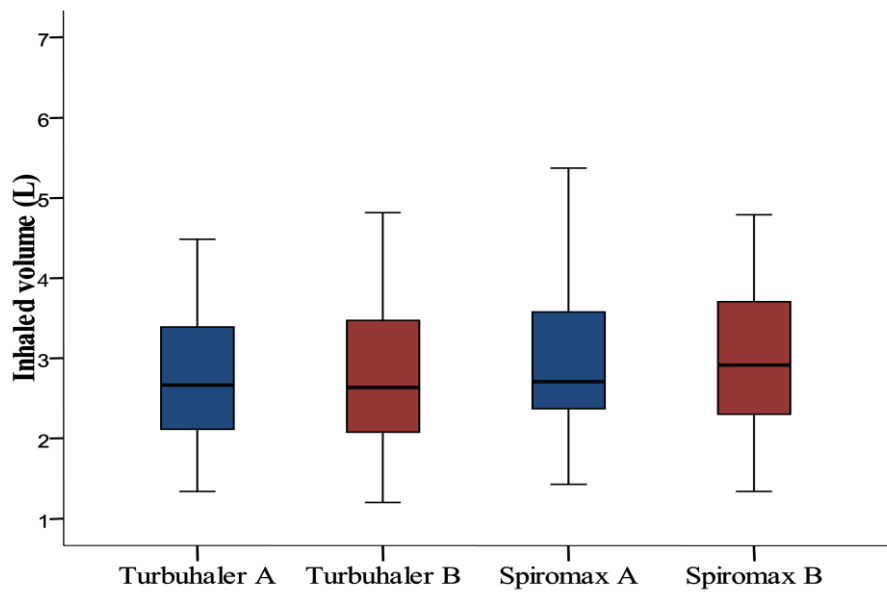
Figure 7. 24. The distribution of the inhaled volumes achieved by healthy volunteers when they inhaled through the Turbuhaler and Spiromax, before (A) after training (B).
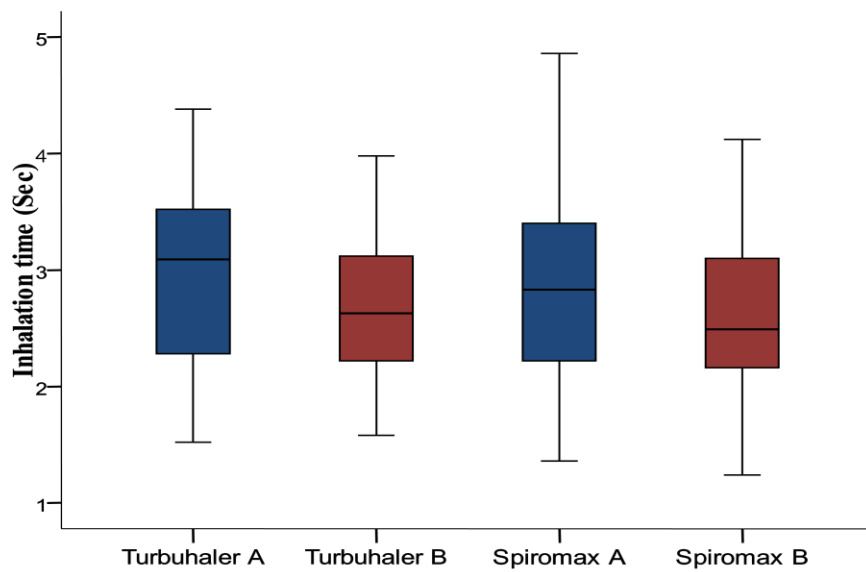
Figure 7.25. The range of the individual inhalation times when the healthy volunteers inhaled through the Turbuhaler and Spiromax, before (A) after training (B).

7.4.3. Comparison of the Inhalation Profiles through the different DPIs

Spiromax and Turbuhaler

The normality distribution tests (the Kolmogorov-Smirnov and Shapiro-Wilk tests) showed that the parameters were not normally distributed. Comparison, therefore, between the various parameters of the inhalation profiles through the different DPIs: was made using the two related-samples, nonparametric Wilcoxon signed rank test. Table 7.3 shows the comparison between the means of the different inhalation parameters

Table 7.3. Statistical analysis (*p* values are quoted).

PIF	TURB(A)v's SPIRO(A)	TURB(A)v's (B)	SPIRO A v's B	TURB B'vs SPIRO B
CHILD	0.000	0.000	0.000	0.000
ADULTs	0.000	0.000	0.000	0.000
COPD	0.000	0.000	0.000	0.000
Healthy	0.000	0.000	0.000	0.000
PkPa				
CHILD	0.000	0.000	0.000	0.000
ADULTs	0.016	0.000	0.000	0.004
COPD	0.002	0.000	0.169	0.039
Healthy	0.585	0.000	0.000	0.490
IV				
CHILD	0.000	0.045	0.004	0.000
ADULTs	0.001	0.709	0.178	0.000
COPD	0.006	0.067	0.534	0.067
Healthy	0.005	0.950	0.178	0.000
ACC				
CHILD	0.191	0.000	0.000	0.000
ADULTs	0.201	0.000	0.000	0.029
COPD	0.735	0.000	0.000	0.029
Healthy	0.057	0.000	0.000	0.585
Inhalation Time				
CHILD	0.000	0.011	0.825	0.212
ADULTs	0.521	0.007	0.010	0.712
COPD	0.735	0.124	0.126	0.836
Healthy	0.164	0.002	0.041	0.809
Time at PIF				
CHILD	0.000	0.000	0.000	0.560
ADULTs	0.732	0.000	0.000	0.444
COPD	0.018	0.000	0.014	0.000
Healthy	0.158	0.000	0.000	0.069

7.4.4 Asthma control Questionnaires (ACQ)

(a) Children with asthma

The mean (SD) ACQ scores are presented in Table.7.4. Table 7.5 presents the level of asthma control of child with asthma with respect to the ACQ. Details of each individual's ACQ are presented in APPENDIX B-4 6(refer to the enclosed DVD)

Table 7.4. Mean (SD) scores of (ACQ) for children with asthma.

	Mean(SD)Scores	Minimum	Maximum
ACQ	1.68(0.99)	0.33	4.83

Table 7.5. Level of asthma control (Child with Asthma).

	ACQ Categories	Frequencies
Asthmatic Children	≤ 0.75 (well controlled)	5(10.0%)
(n= 50)	0.75-1.50 (not well controlled	25(50.0%)
	≥ 1.50(uncontrolled)	20(40%)

(b) Adults with asthma

A summary of the ACQ is presented in Table 7.6 and Table 7.7 presents the level of asthma control with respect to the ACQ. Details of each individual's ACQ are presented in APPENDIX B-4 7(refer to the enclosed DVD)

Table 7.6. Mean (SD) scores of (ACQ) for asthmatic Adults.

	Mean(SD)Scores	Minimum	Maximum
ACQ	1.84(0.90)	0.67	4.50

Table 7.7. Level of asthma control.

	ACQ Categories	Frequencies
Asthmatic Adults	≤ 0.75 (well controlled)	2(4.0%)
(n= 50)	0.75-1.50 (not well controlled	22(44.0%)
	≥ 1.50(uncontrolled)	26(52%)

(c) COPD patients

A summary of the MRC scores for COPD is presented in Table 7.8. Details of each individual's MRC scores are presented in APPENDIX B-48 (refer to the enclosed DVD)

The MRC "Degree of Breathlessness"

Degree of breathlessness using the MRC Dyspnoea Score (reflects exercise tolerance and functional limitation). The frequencies of the COPD patients in the MRC "Degree of Breathlessness" categories for one visit study and the frequencies of COPD patients in the MRC "Degree of Breathlessness" categories are presented in Table 7.8.

Table 7.8. Dyspnoea (MRC Score) for COPD patients.

*Degree of breathless related to activities					
Grade	**1**	**2**	**3**	**4**	**5**
Total average COPD no.=50	Non	2	3	4	5
Pt. No. (%)	Non	9/50(18%)	18/50(36%)	15/50(30%)	8/50(16%)
M/F	Non	6/3	4/14	9/6	2/6

*Degree of breathlessness using the MRC Dyspnoea Score 4 (reflects exercise tolerance and functional limitation)

7.5 Discussion

Although DPIs are breath actuated many patients have problems preparing a dose for inhalation and with using the recommended inhalation manoeuvre (Molimard et al, 2003, Chrystyn & Price, 2009; Haughney et al, 2010; Melani et al, 2011). Hence the ERS / ISAM Consensus Statement recommends that patients are made aware of the dose preparation procedures for each DPI and that the inhalation should be as forceful and long as possible and that this manoeuvre should commence immediately at the start of the inhalation (Laube et al, 2011). These inhalation manoeuvre instructions are based on the need to de-aggregate the dose and that this occurs during the initial phase of an inhalation when using a DPI (de Boer et al., 1996; de Boer et al., 1997; Everard et al., 1997; Kamin et al., 2002).

It is important therefore to train patients on how to use their DPI. These results were available during the draft stage of the ERS / ISAM Consensus Statement and were used to inform the recommendation to focus on the initial phase of the inhalation during DPI technique training.

In this study, which was a repeated measure design, all subjects received the DPI training that they would have received routinely in the clinic. This included the technique instructions recommended in the patient information leaflet. The first set of measurements represents those that would be achieved from standard DPI technique training in the clinic. The subjects then received the enhanced training with the IN-Check Dial which is not part of routine inhaler technique training. The very highly significant improvements highlight realistic changes in the peak inhalation flow and more important in the pressure change (hence turbulent energy) and the acceleration of the inhalation (with respect to the pressure changes). An alternative study design would have been to randomise the subjects after the standard training to

one group that received the enhanced training and another that received a repeat of the standard training. Although this randomised control trial design would require more subjects due to the parallel groups the results would not reflect a training effect. However the differences in this repeated design study are very significantly better after the intervention and so suggest that any training effect did not influence the results.

Studies have shown that patients with stable asthma (Hawksworth et al, 2000; Broeders et al, 2003) and COPD (Nsour et al, 2001; Broeders et al, 2003; Al-Showair et al 2007) as well as children with asthma (Agertoft & Pedersen, 1998) do improve their inhalation flows after routine training and that highly trained asthmatics (Tarsin et al, 2006) and COPD (Derom et al, 2007) patients do inhale with faster flows. The results in this chapter confirm that patients can improve their inhalation manoeuvres even further with enhanced training using the IN-Check Dial. This training tool provides objective feedback about the inhalation manoeuvre rather than the subjective response provided during standard inhalation technique training. Two different DPIs that had a similar resistance were used so that it could be identified that the changes were due to the training and not a device effect. As expected the healthy adults produced the best set of inhalation parameters followed by the adults with asthma with the children with asthma slightly higher than the COPD patients.

The pressure changes (hence the turbulent energy), the acceleration rates and the inhalation flows were greater for Spiromax than the Turbuhaler in all 4 groups although there was little difference in the resistance of the two DPIs. This is consistent with the results in Chapter 6. The faster flows would be due to the slightly lower resistance of the Spiromax. In Chapter 6 it was found that the influence of the higher resistance with respect to the pressure changes and the acceleration flows was

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not linear and there was the suggestion of a cut-off point when resistance dominates the pressure changes. It may be that the resistance of the Spiromax and the Turbuhaler is such that inhalation flow influences the pressure changes (and turbulent energy) more than the resistance of the device. Inhalation volumes were significantly greater when using the Spiromax DPI which would be due to its lower resistance.

Very highly significant improvements (p<0.001) in the maximum pressure change (equivalent to the maximum turbulent energy) were obtained after the enhanced training in all 4 groups for both DPIs except for the COPD patients when using the Spiromax. The lower values in the COPD subjects would be due to the reduced inspiratory effort of these patients. All acceleration rates, PIF values and the time to the PIF all significantly (p<0.001) improved post enhanced training. The improvements in the acceleration rate when using the Turbuhaler were much more pronounced in the asthma and COPD patients than those obtained from similar patients who received specific and additional verbal instructions using the patient information leaflet (Broeders et al, 2003). In this 2003 study the training these patients received was similar to standard training that patients would receive in the clinic and thus similar to the initial training given to the patients in this study. These differences highlight the importance of using more objective methods during technique training. The improvements also highlight the value of the IN-Check dial as a training aid (Azouz & Chrystyn, 2012).

In Chapter 6 the patients used their normal real-life technique whereas in this study they received standard and enhanced inhalation technique training. This would have contributed to the difference between the inhalation parameters measured in the two studies. Some differences in the demographics of the patients would also influence

the different parameters measured. The baseline inhalation characteristics of the children with asthma (age range 5 to 16 years) when they inhaled using the Turbuhaler in this Chapter was greater than those in Chapter 6. In addition to the training these children were older and taller than those of the study in Chapter 6. However their acceleration rates were slower than those of Chapter 6 even though they had received verbal and written instructions to inhale as fast as possible. The inhalation characteristics of the adults with asthma in this Chapter were also higher but compared to the children the difference was smaller (overall less than 10%). There was only a small difference in the FEV_1 % predicted between the adult asthmatics in the two studies. Their acceleration rates were very similar but inhalation volumes were higher which could be due to instructions to exhale before the inhalation manoeuvre. There were smaller difference between the results in this chapter and those in Chapter 6 when COPD patients inhaled using than Spiromax and the Turbuhaler.

The PIF values with the Turbuhaler after the enhanced training was similar to those of highly trained COPD (Derom et al, 2007) and asthma (Tarsin et al, 2006) patients. In patients receiving standard training the PIF values through the Turbuhaler are similar to those reported for COPD patients (Dewar et al, 1999; Al-Showair et al; 2007), adults with asthma (Meijer et al, 1996; Broeders et al, 2003) and children with asthma (Stahl et al 1996). Four COPD patients and 1 adult with asthma but no children with asthma used a PIF < 30L/min with the Turbuhaler. All these significantly improved above >30L/min post training. Improvements in inhaled volume were only small indicating that the participants always made a full inhalation. Studies have shown that volume is important when using a DPI with upto 1L required through a Turbuhaler (Kamin et al, 2002). After the enhanced training 10

children with asthma (two 5 years old, two 6 years, three 7 years and one 9, 10 and 13 year old), 4 adults with asthma (FEV_1 43, 52, 72 and 78 % predicted) and 9 COPD patients (FEV_1 21, 25, 26, 32, 35, 42, 45, 52 and 60 % predicted) did not inhale greater than 1L. Inhalation volume may be more important to consider that any other inhalation characteristic when choosing a DPI.

The inhalation characteristics shown in the scatter plots (relationships) highlight that the compendial methods for in-vitro testing using a pressure change of 4kPa with an inhaled volume of 4L are unrealistic. These relationships confirm that focus should be directed to methodologies that can use patient inhalation profiles during in-vitro testing in place of the vacuum pump that can only replicate a square wave.

The results show the value of training patients to use a faster flow rate and encouraging them that their fast inhalation should begin as soon as they start to inhale. Using the IN-Check Dial as a training aid to achieve faster inhalation flows is useful. The similar increases of the Spiromax and the Turbuhaler show that the improvements in training were due to the method and were not influenced by the different design or appearance of the devices.

Chapter 8: Summary

8.1 Summary and Conclusion

Pressurised metered dose inhalers (pMDIs) and dry powder inhalers (DPIs) are routinely used in the management of asthma and COPD. The pMDI was first introduced in 1956 followed by the single dose DPI in 1967 and multidose DPIs in 1987 (Sanders, 2007). Although some of these devices were introduced over 50 years ago patients have problems using the correct technique (Crompton et al., 2006; Laube et al., 2011; Melani et al., 2011). The correct inhalation technique by patients is crucial for maximum lung deposition and the success of therapy (Laube et al., 2011). Studies have shown that poor technique is related to poor disease control in asthma (Giraud & Roche, 2002; Al-Showair et al., 2007; Melani et al. 2011) and COPD patients (Melanie et al., 2011) and is linked with more hospitalisations (Melani et al., 2011). National and World guidelines on the management of asthma (BTS / SIGN, 2011; GINA 2011) and COPD (NICE, 2010; GOLD, 2011) all stress that before a patient's inhaled therapy is altered then their inhalation technique and their compliance should be checked first.

A pMDI should be used with good co-ordination and a slow inhalation flow whereas a DPI should be used with a fast inhalation and that this forceful inhalation should commence from the beginning (Laube et al., 2011). The inhalation phase for both inhaler types should last as long as possible so that the emitted particles have a greater chance to be deposited throughout the airways (especially the peripheral regions of the lungs).

Despite the differences in the instructions when using a pMDI and a DPI for efficient delivery of the particles from the emitted dose the inhalation flow should be similar. It has been suggested that this inhalation flow should be >30 L/min <90L/min (Pauwels et al., 1997). The pMDI is an active device because the particles are

generated by the device in that when the canister is depressed a valve opens and as the propellant evaporates the particles are emitted. There is no resistance to flow in a pMDI and so to achieve < 90L/min patients should be encouraged to inhale slowly. DPIs are passive devices in that an external source is required to emit the dose from the device and generate particles with the potential for lung deposition. This external source is the patient's inhalation flow interacting with the internal resistance of the DPI to create a turbulent force / energy (measured as a pressure change) which de-aggregates (breaks up) the formulation into particles that have the potential for lung deposition (Clark & Hollingworth , 1993).

De-aggregation takes place during the inhalation manoeuvre because when the dose of a DPI has been prepared for inhalation the formulation does not have the characteristics for its drug particles to be deposited in the lungs (Chrystyn, 2003). During manufacture and dose metering good powder flow is essential and so the particles in the formulation are attached to a large particle lactose carrier or formulated into spherical agglomerates. The resistance to airflow in each DPI means that to achieve the required inhalation flows patients need to use a forceful inhalation (Chrystyn, 2003). Also the de-aggregation and dose emission from a DPI occurs in the first part of an inhalation (de Boer et al, 1997; Everard et al, 1997; Kamin et al, 2002) and so the forceful inhalation should commence from the start of each inhalation (Laube et al, 2011). Also for each DPI there is a threshold below which the turbulent energy generated during an inhalation is not sufficient to efficiently de-aggregate the dose (Laube et al, 2011). Overall this minimum flow is assumed to be 30L/min but will be higher in those DPIs with a lower resistance and vice versa (Laube et al, 2011).

Many patients have problems using their pMDIs. These problems first surfaced in 1965 (Saunders, 1965) but it was from 1976 in the studies by Crompton (Paterson and Crompton, 1976; Crompton 1982) that the problem of poor co-ordination were realised and still remain today (Melani et al, 2011). Until recently not using a slow flow was not realised as a problem mainly because studies had used bronchodilators which would benefit from more central lung deposition (which occurs when using a fast flow) as well as high doses. It has been shown that slow flow through a pMDI improves asthma control without any changes in the spirometry (Al-Showair et al., 2007). This reflects better particle penetration of the corticosteroids into the peripheral zones of the lungs. Slow inhalation flow improves lung deposition especially in the peripheral zones of the lungs (Usmani et al, 2005). Only 8% of asthmatics use a slow flow with good co-ordination (Al-Showair et al, 2007).

Training pMDI and DPI technique can help but patients do revert back to their old technique soon after the training session when they leave the clinic (Shim and Williams, 1985). Although patients do not always use the correct inhalation technique they do receive some benefit from their inhalers but this would be improved when using a good technique. There is a need, therefore, to identify simple methods that could be used during inhaler technique training that help patients use the correct technique and that this trained technique is then used by them at home.

All the studies in this Thesis used the patients' untrained inhalation technique (there were two studies that assessed the effect of training but the starting point was their untrained technique).

In *the first study* the inhalation characteristics of 20 children with asthma, 57 adults with asthma and 32 COPD patients was measured electronically when they inhaled through a pMDI. These patients routinely used a pMDI and they received no training

in the inhalation technique that they should use. The results provide a significant contribution of data that describe the inhalation characteristics of patients when they use their pMDI. No studies have reported values on children when they use pMDIs and spacers

Previously it had been shown that an inhalation flow of < 90 L/min (Farr et al., 1995; Pauwels et al., 1997) indicated slow flow. The mean (SD) inhalation flows of these patients were 108.9(40.4), 146.0(58.8) and 107.3(50.6) L/min. Only 7 children, 10 adults and 10 COPD patients inhaled using a slow flow of < 90L/min. The mean (SD) inhalation times were 1.4 (0.27) seconds for the children with asthma, 1.5(0.3) seconds by the adults with asthma and 1.6(0.2) seconds by the COPD patients. Overall these are shorter than the 5 seconds for an adult and 2-3 seconds by a child that has been recommended by the ERS Consensus Statement on the use of inhalers (Laube et al, 2011). It is the results of this Thesis that informed the ERS Consensus statement to include the recommendation about the focus on the length of the inhalation. Inhalation volumes were a mean (SD) of 1.14 (0.6), 2.1(0.9) and 1.8(1.0) (L), respectively. The clinical significance of these values is not known. This was a preliminary study and the methodology could not measure the point when the patient actuated a dose with respect to the start of their inhalation. The methodology of the second study was designed to capture co-ordination data. In general the inhalation parameters when these patients used their pMDI were similar to those when they inhaled through a pMDI attached to a spacer. Overall all inhaled volumes were greater than the volume of an AeroChamber but some young children did not achieve an inhaled volume greater than that of the Volumatic confirming the standard practice for these patients to use tidal breathing rather than one full inhalation. The

methodology used in this study did not allow a measure of the time between pressing the canister and the start of an inhalation.

The *second study included* methodology to measure the co-ordination of dose actuation and with the start of their inhalation. Like study one this was a data capture study to describe how patients with asthma (both children and adults) and COPD patients use their inhalers. Like study one there is no such published data to describe how children with asthma and similar data on asthma patients and COPD subjects are limited. Previously it had been shown that 0.2 seconds between the start of an inhalation and the actuation of the dose was an indicator for good co-ordination (Goodman et al., 1994; Farr et al., 1995). 20 children with asthma, 130 adults with asthma and 31 COPD patients completed the study. Their mean (SD) inhalation flows were 70.5(36.4) 131.4(60.8) adults and 70.9(28.1) L/min. Overall the flows in the children with asthma and in the COPDs were the best with 15 out of 20 (75%) children and 24 out of 31 (77%) using a flow <90 L/min. It is amongst the adult asthmatics that flow was too fast. Overall 93/130 (72%) used a fast flow with 21 (16% of the total) inhaling >200 L/min. Five children, 53 of the adults and 10 of the COPD patients were good co-ordinators but of these only 3, 6 and 9 patients also used a slow flow. Their mean (SD) inhalation times were similar to those of the first study; 1.25 (0.46) seconds by children with asthma, 1.68(0.82) seconds by the adults and 1.44 (0.65) seconds for the COPD patients. The studies suggest that when patients use a pMDI their inhalation times are too short (Laube et al, 2011) so they should be trained to inhale for longer. Theoretically when the patient makes a full inhalation then the inhaled volume should not change and so their flow will decrease. There were no clinical endpoints to this study because the data was collected at one visit. However it was possible to classify the patient's disease severity and

investigate if this was related to technique. Only a small number of patients achieved a good technique and so a comparison of their disease control to those with good technique was not possible. Furthermore all the patients with good technique were clinically not well controlled. This could be due to compliance or that their asthma was so severe and affected them so much that they focussed more on their technique to ensure they obtained as much therapeutic benefit as possible. In this study good correlations were found between the inhaled volume and the forced vital capacity <u>of</u> the adult asthmatics with a ratio of around two thirds between the inhaled volume and the forced vital capacity. This could be an indicator about the full inhalation that patients are recommended to use (breathe out gently from the start and then inhale until the lungs are full of air). Electronic aids are in development to help with the training of patients by identifying the mistakes they are making (for example AIMS2 by Vitalograph, UK). Thus by entering the patient's spirometry and checking this to the inhaled volume then this ratio would indicate to the trainer if a full inhalation has been made

The two studies in these chapters confirm that not using a slow flow with a pMDI is the most common mistake made by patients (Al-Showair et al, 2007). They also show that the duration of the inhalation is short. There has never been any mention in previous literature or recommendations of inhaler technique that one major problem is that the inhalation phase is too short when patient use a pMDI. For this reason this was included in the investigations of the third pMDI study.

The previous two studies had shown that overall patients inhaled too fast and that their inhalation phase was relatively short

. _Chapter 5_ of this thesis investigated the inhalation parameters of asthmatic adults when a co-ordination aid was used and then including an instruction to length the

inhalation phase. The co-ordination aid increased the resistance of the pMDI and so it would naturally slow inhalation flows. The inhalation profiles of 71 stable asthmatic patients were measured, their mean (SD) FEV_1 was 78.31 (21.03) % predicted. The order of inhalations was the pMDI, pMDI+CAP (the cap is the co-ordination aid) and pMDI+CAP+TRAIN (the train was the instruction to prolong the inhalation phase to 5 seconds). Their mean (SD) inhalation flows were 155.6(61.5), 112.3 (48.4) and 73.8 (34.9) L/min, respectively ($p< 0.001$). Inhalation volumes did not change and the duration of the inhalations was 1.60 (0.21), 1.92 (0.80) and 2.99 (1.03) seconds ($p<0.001$). Thus the increased resistance from the co-ordination aid naturally decreased their flow and by prolonging the inhalation time with no change in the inhalation volume reduced their flows even further. Overall 70% percent of patients used the correct pMDI technique with the cap and the simple instruction for their inhalation phase to last 5 seconds. Excellent correlations were found between the inhalation volumes and the forced vital capacity. The mean inhaled volume to forced vital capacity ratio when using the pMDI on its own was 70%. This suggests that such a ratio can be used to indicate a 'full inhalation' (exhale gently as far as comfortable followed by an inhalation until the lungs are full of air).

This study was in progress when the ERS Consensus statement was in the draft stage. These results like that of the two previous studies informed the ERS consensus statement about the importance of recommending patients to use a long inhalation (upto 5 seconds) when they use a pMDI. The correlations are consistent with those identified in second study and consolidate the recommendation that the inhaled volume to forced expiratory volume ratio could incorporated into electronic inhaler training aids to indicate a full inhalation

Figure 8.1 shows why inhalation flow decreases when the inhalation volume does not change and the inhalation time is increased. Also the results suggest that when a new pMDI is designed or a new chemical entity is introduced in a pMDI, then some resistance should be included because this will naturally slow down the inhalation flow.
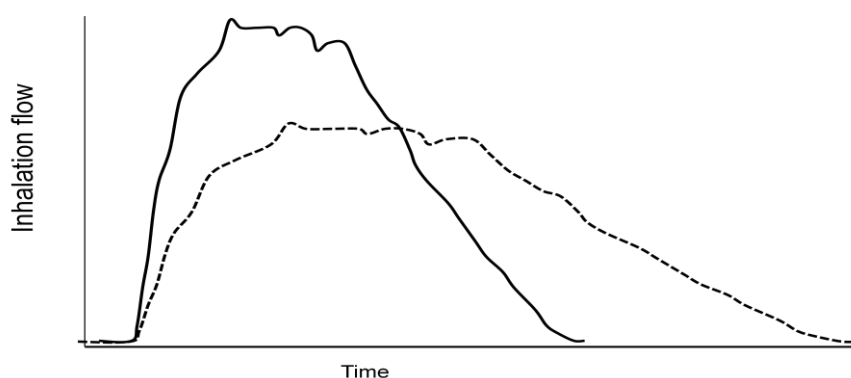
Figure 8.1. The effect of lengthening the time of the inhalation phase (dashed line)

This third pMDI study was a repeated measure design instead of a more traditional parallel trial. The benefits of this design are that it improves efficiency (since fewer subjects are required) and it eliminates variability due to individual differences in overall performance thereby allowing the outcome data to stand out. The changes in the peak inhalation flow and inhalation times are very highly significant hence they were realistic changes. However it is possible that there is an element of a training effect with the 5 second inhalation. A different approach would have been that after they inhaled through the pMDI and the pMDI cap there could have been a randomisation of the patients for one group to receiving the training to prolong the inhalation time to 5 seconds and the other group to receive to training

Two studies involving DPIs are presented in *Chapters 6 and 7*. The first study in *Chapter 6* again involved children with asthma (n=16), adults with asthma (n=53) and COPD (N=29) patients. The DPIs used ranged from low to high resistance DPIs

(Laube et al, 2011) and the main reason for the study was to provide data on the inhalation characteristics of patients when they use different DPIs.

For these measurements patients were asked to use the same inhalation manoeuvre to that when they used their own inhaler. Their peak inhalation flow was measured as well as the pressure changes (hence turbulent energy) and the acceleration of their flows. Measurement of pressure changes in kPa units and acceleration rates in kPa/sec units allows a comparison to be made between different DPIs when used by patients (Azouz and Chrystyn, 2012). Previously there has not been any emphasis on these measurements. The time to the peak inhalation flow, inhaled volume and the duration of each inhalation were also measured. Also these chapters provide substantial data on the inhalation parameters of patients when they use different DPIs The results in these studies confirm that when inhaling through the same DPI children with asthma generate lower PIF values than COPD patients and both these are lower than the rates achieved by adults with asthma. Another important issue is that for each DPI there will be minimum threshold energy for efficient de-aggregation of the dose. It is universally recognised that the flow through a DPI to exceed this minimum threshold energy is 30 L/min. Three of the 16 asthmatic children did not achieve 30L/min through the Accuhaler. These were all boys aged 5, 7 and 12 years old. The 5 and 12 year old did not achieve this flow through the Turbuhaler but there were 4 others with flows of either 31 or 32 L/min. The same 2 children failed to achieve 30L/min with the Clickhaler but only one of them (the 12 year old) with the Easyhaler. This suggests that it may be the low resistance inhalers that patients have problems with exceeding the minimum required flows rather that high resistance DPIs.

It has been suggested that a failure to achieve an inhalation flow of 30 L/min within the first 150 ml of the inhalation affects de-aggregation (Everard et al., 1997) and thus inhalation characteristics about the first 150 ml of the inhaled volume were obtained. The results show that the PIF at 90% of the inhalation flow corresponded to when 150 ml had been inhaled through a Turbuhaler and so this portion of the inhalation profile was used to calculate the acceleration rates. The acceleration rates were greater in DPIs with high resistance. This together with the pressure changes suggest that more efficient de-aggregation occurs in these DPIs and may explain why these provide higher lung deposition than low resistance DPIs (Borgstrom, 2001).

Pressure changes, acceleration rates and volumes were lower in the children and the highest values were the adults with asthma. The inhalation flows through DPIs with high resistance were lower than those with low resistance but the pressure changes were greater. The results highlight the value of including the pressure change measurements and the acceleration of the flow when examining inhalation profiles.

As expected inhaled volumes were lower in the children with asthma than the COPD patients and both these were lower than the adults with asthma. When using the Aerolizer only one child inhaled > 2 L and more than half < 1 L, 7 COPD patients inhaled >2L (one >4L) and 5 < 1 L whilst 17 adults with asthma inhaled >2L but no one inhaled >4L and 7 inhaled < 1L. These values highlight the recommendation that when using capsule DPIs then patients should make two separate inhalations for each dose (Laube et al, 2010). Also many patients (especially children and COPD patients) did not achieve an inhaled volume of >1 L through a Turbuhaler. It has been suggested that a minimum of 1L is required to be passed through a Turbuhaler to efficiently empty the dose from the device (Kamin et al, 2002).

The study highlights the misunderstanding during the routine clinical practice that focuses on the inhalation flow. As expected inhalation flows were significantly faster when the DPI had a lower resistance and vice versa for high resistance DPIs. To make a comparison of flow between inhalers is flawed because it is the turbulent energy created by the inhalation manoeuvre inside the inhalation channel of the DPI that is critical for the de-aggregation of the dose. The data in this study shows that this turbulent energy is higher for the DPIs with higher resistance. This concept is not understood during routine practice and was the reason for the review that has arisen from this thesis (Azouz & Chrystyn, 2012)

It has been recommended that patients use DPIs with a forceful and deep inhalation manoeuvre for as long as possible and that this should commence immediately at the start of the inhalation (de Boer et al, 1996; ibid, 1997; Everard et al, 1997; Kamin et al, 2002: Laube et al, 2011). It is important therefore to train patient on how to use their DPI (Laube et al, 2011). The final study, in *Chapter 7,* describes the changes in the inhalation parameters that occur when the inhaler technique training of patients is focussed on getting them to use a forceful inhalation that begins at the start of their inhalation. Two different DPIs (Spiromax and Turbuhaler) with a similar resistance were used so that changes were due to the training rather than the resistance or the device.

All subjects that entered this study received the same routine DPI training that they would have received in the clinic (usually from the nurse). This training included instructions with reference to the information contained in the Patient Information leaflet. Hence the subjects would have been trained to exhale and then use an inhalation manoeuvre that is as deep and fast as they can. After the measurements enhance training was provide by including the IN-Check Dial as a training aid.

Patients were children with asthma, adults with asthma and COPD as well as healthy volunteers. There were 50 in each group

The healthy subjects in this study produced the best set of inhalation parameters followed by the adults with asthma with the children with asthma slightly higher than the COPD patients. The acceleration rates (pressure change over time), the pressure changes (hence the turbulent energy), and the inhalation flows were greater for Spiromax than the Turbuhaler in all 4 groups. This study showed that highly significant improvements ($p<0.001$) in the maximum pressure change (equivalent to the maximum turbulent energy) were obtained after the enhanced training in all 4 groups for both DPIs except for the COPD patients when using the Spiromax. All acceleration rates, PIF values and the time to the PIF all significantly ($p<0.001$) improved post enhanced training. The improvements in the acceleration rate when using the Turbuhaler were much more pronounced in the asthma and COPD patients than those obtained from similar patients who received verbal instructions using the patient information leaflet (Broeders et al, 2003). Hence, using objective methods during inhalation technique training is useful and should be encouraged and the results show the value of using the IN-Check Dial as a training aid with a focus on the initial part of the inhalation. This enhanced training is extra to that provided in a routine clinical setting. Again the study was designed as a repeated measure approach starting with standard DPI training with the patient information leaflet followed by the enhanced training with the In-Check Dial. A different approach would have been to randomise the patients into two groups following the routine DPI training. One group would receive the enhanced training and for the other the routine clinic training would be repeated.

Figure 8.2 explains the value of using such a technique compared with a slower inhalation that starts slowly and gradually builds up. The results in Chapter 7 show why patients should be encouraged to use a fast inhalation and that this should commence from the start of each inhalation.
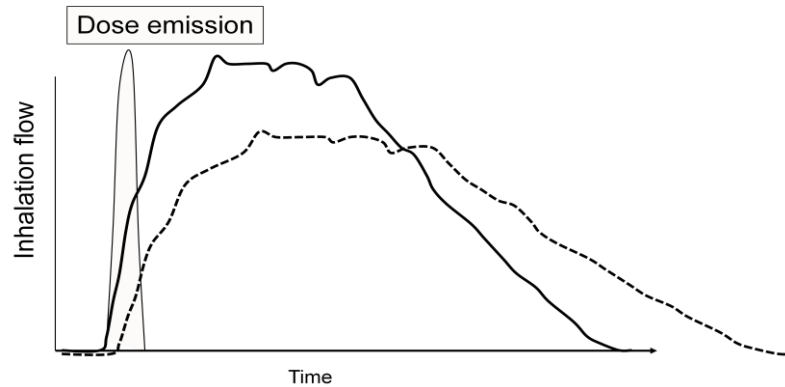
Figure 8.2. A fast (continuous line) and a slow (dashed line) inhalation flow profile through a DPI. Dose emission is superimposed onto the profiles

In conclusion when using a pMDI the focus of the training should be increasing the inhalation time towards 5 seconds (3-4 seconds in a child) and then instructing them to depress the canister, to release a dose, soon after they start to make their slow inhalation. When using a DPI patients should be encouraged to inhale as fast as they can for as long as possible and that this forceful inhalation should start from the beginning of the inhalation. To achieve this, the IN-Check dial is a useful training aid. These simple modifications to how patients are trained to use their inhalers should improve their disease control and help meet the GINA challenge (Fitzgerald et al, 2011) to reduce hospital admissions.

Chapter 9: Future Work

9.1 Future Work

The research studies in this thesis have used electronic measurements to objectively highlight the problems patients have using their pMDI and DPIs during real life use. Incorporated into the studies were a novel co-ordination aid for use with a pMDI and a novel approach to train patients how to solve the common problems with the inhalation manoeuvre. The focus of this was to concentrate on getting patients to prolong their inhalation time. For the DPI the training used was enhanced by using the IN-Check Dial as a training aid. All these studies generated inhalation profiles that have demonstrated that there is a large inter-patient variability of the inhalation manoeuvre when using all inhalers. The studies involved children with asthma, adults with asthma and patients with COPD.

All the measurements were completed at one visit so future studies need to investigate if the training methods provide lasting changes to the patients' inhalation manoeuvre and whether this improves their disease control. For asthma as well as spirometry the asthma control questionnaire (ACQ) would be used whilst for COPD the newly introduced COPD Assessment Test (CAT) would be a suitable method. Long term studies would include GP visits and hospitalisations. These would need to be randomised into trained and not trained patients (both patients would receive standard inhaler technique training in addition according to routine patient management).

The first study would be to determine the clinical outcomes that occur when patients are trained to prolong their inhalation to 5 seconds. The classical group to use would be adult asthmatics but a similar approach could be adopted for the children with asthma and the COPD subjects. The length of the study in asthma would have to be

>12 weeks so that any changes due to better anti-inflammatory control could be identified. The schematic design of such a study is presented in the figure below
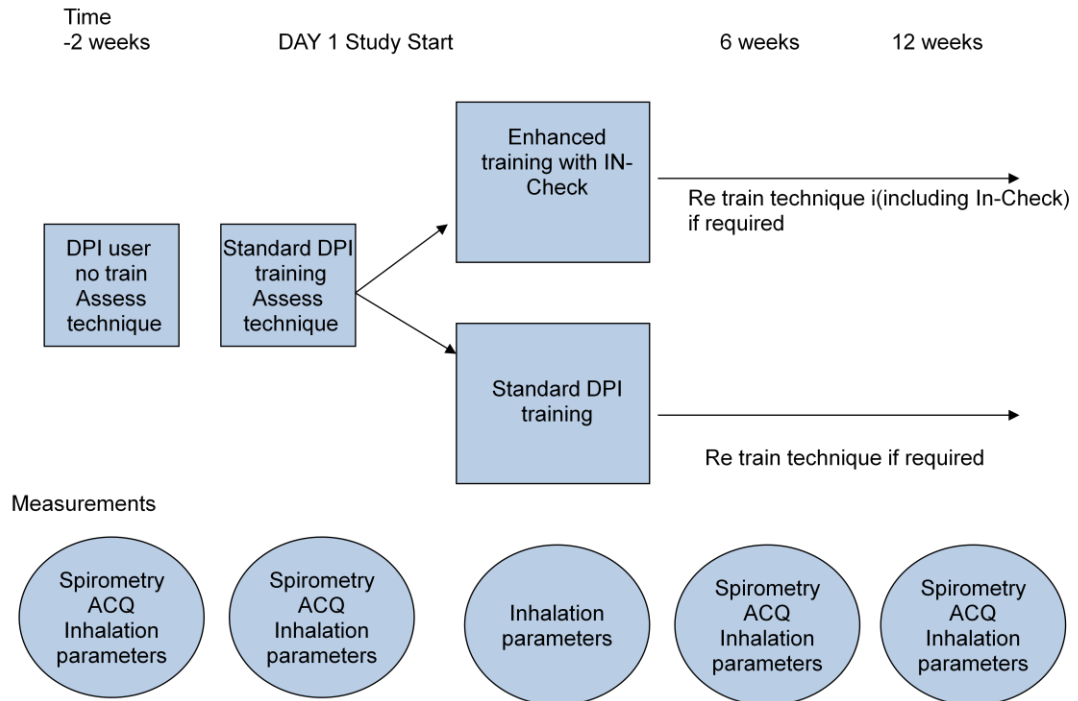
Figure 9.1.Schematic design of the study to determine the clinical outcome of the 5 second inhalation instruction

A longer study with visits at 6 months and 12 months would enable the impact of training to be evaluated and also allow the inclusion of acute exacerbations. This design could also be used in children with the same outcome measures. Similarly the study design could be used with COPD patients with CATS replacing ACQ. For COPD a 12 month study (or longer) would be desirable.

Clinical studies using the co-ordination cap are required if this aid is to be introduced. These would include an evaluation of the potential critical error that was identified during the study. It was noted that some patients do not keep the canister depressed throughout the duration of their inhalation. This causes the slits in the cap to close thereby preventing any further inhalation. This is a strong feedback

mechanism and so patients should quickly realise that the canister has to be kept depressed for the entire duration of their inhalation. Whether this is a potential critical error or not needs to be identified. Also the methodology to measure the electronic inhalation profiles needs to be adapted such that co-ordination with the co-ordination aid can be measured. This was not measured in the study because of the need to maintain an airtight seal within the inhalation system. However this problem has been overcome.

In this study the patients would be divided into standard pMDI and pMDI plus cap groups. To further investigate the effect of the 5 second inhalation then each group could then be further randomised into one half that received the extra training and the other half that did not. A schematic representation of the randomised groups is described in Figure 9.2.
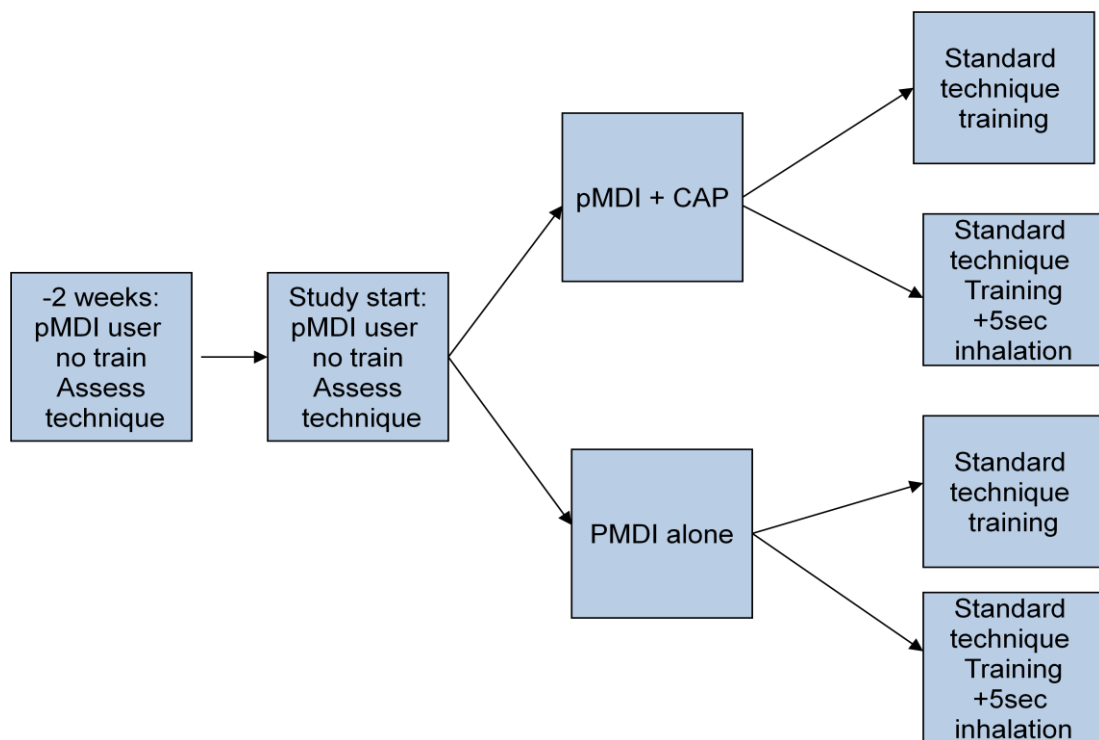
Figure 9.2. Schematic design of the randomisation process.

Like the study above the length of the study could be 12 weeks with a 2 week running period before the study start and the randomisation. Outcome measures

would be spirometry and ACQ as well as the inhalation parameters. In COPD subjects CATS would replace ACQ.

The DPI study in Chapter 7 also warrants further investigation as a clinical study. One limitation was that it was a repeated measures design and that instead of providing enhance training then one half could have had the standard training repeated. After randomisation into these two groups then clinical studies could then be extended to 12 or 52 weeks with the same endpoints as the two studies described above. A schematic representation of this study is shown in figure 9.3
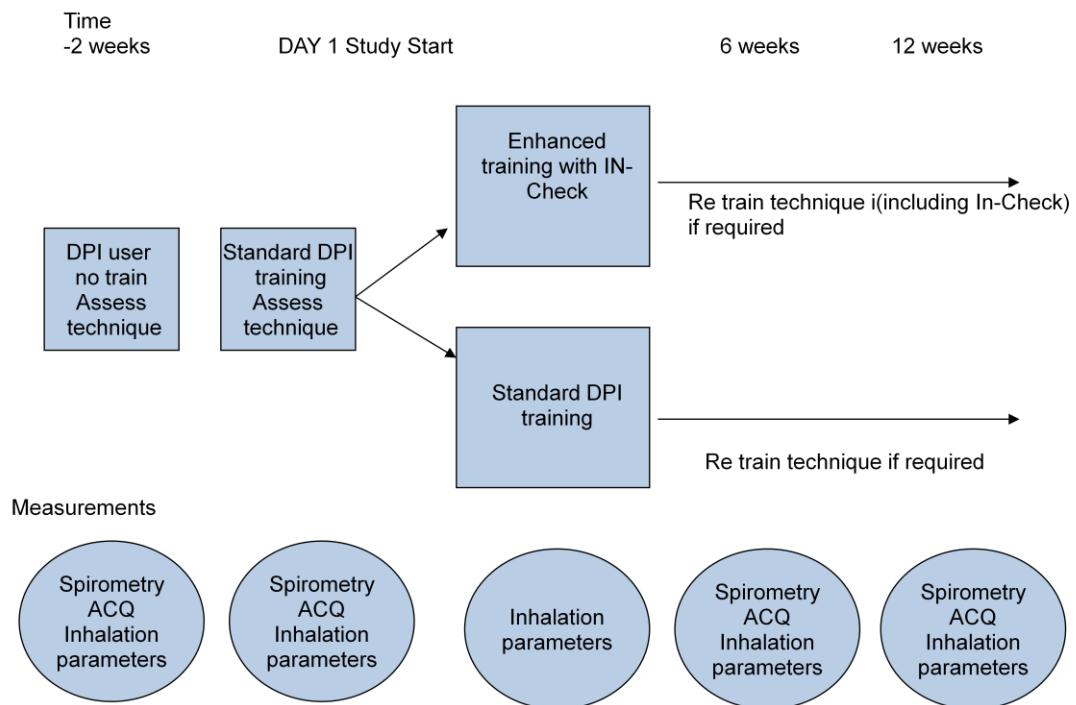
Figure 9.3. Schematic design of the DPI enhanced training study

For all the above three studies the data from the studies in this Thesis together with other clinical studies can be used to inform the number of patients to be included. It is anticipated that due to the parallel design of the studies that large numbers will be required.

Finally the different inhalation profiles and the parameters achieved by patients show that the in-vitro compendial methods to characterise the aerodynamic characteristics of the emitted dose are not realistic. The scatter plots in Chapter 6 show that this applies to all DPIs. The compendial methods use a vacuum pump that can only produce a square wave inhalation profile and are set at an inhalation volume and a pressure change (hence flow) that is not achieved by most patients. At present the results generated by these methods are quality control measures. For DPIs (and even pMDIs) it is possible to replay the inhalation flow profile using a computer controlled vacuum pump. This should replace the standard square wave and be incorporated into in-vitro compendial methodologies.

Figure 9.4 shows a schematic diagram of the in-vitro methodology that could be used. The Andersen Cascade Impactor (ACI) method described in the Pharmacopoeias is adapted so that dose emission from an inhalation profile can be determined. This is achieved by using a mixing inlet that inputs supplementary air, airflow at 60L/min, whilst the vacuum pump draws air at 60L/min through the ACI - see figure 9.4. Hence when the inhaler is in situ there is no flow through it. The inhalation profile is introduced into the supplementary which results in this profile being replayed as an inhalation through the inhaler in situ. This method is classified as an ex-vivo, technique and can be used for a selection of patient profiles to provide in-vitro dose emission data about the dose the patient would have inhaled.
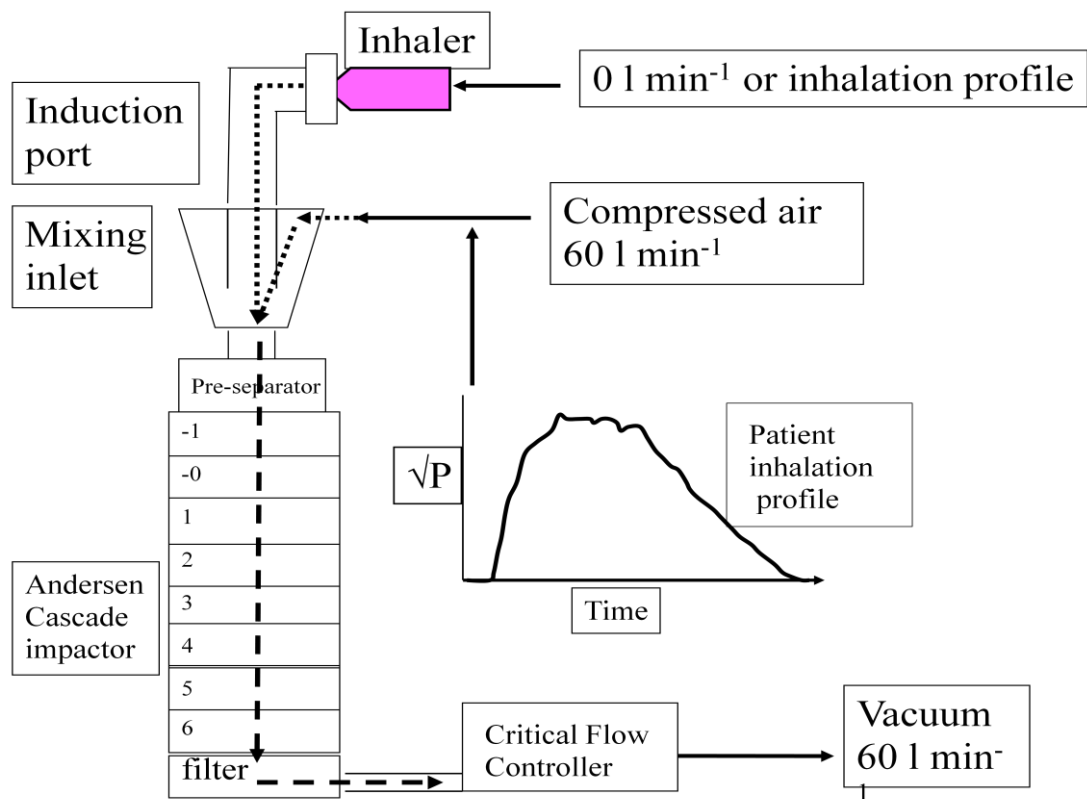
Figure 9.4 Schematic design of in-vitro methodology to incorporate inhalation profiles.

Although the work in this thesis can suggest other further studies the ones described above are those that are recommended because these will consolidate the results presented in the thesis

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