The Effect of Compaction Properties on Swelling and Erosion Characteristics of HPMC and PEO Compacts

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Abstract

Hydrophilic polymers are frequently employed to develop matrices for controlled release applications. The physicochemical properties of these polymeric materials can have an impact on their compaction behaviour. Hence, the degree and extent of deformation and consolidation of these polymers can influence the compaction pressure dependant attributes that include, but are not limited to, porosity, surface roughness, compact internal microstructure and interparticulate bonding and packing. It is anticipated that these aforementioned tabletting attributes could influence the performance and functionality of hydrophilic matrices, although limited studies have been conducted in this regard. Therefore, two polymers hydroxypropyl methylcellulose (HPMC K4M), polyethylene oxide (PEO WSR N60K) and their mixture (1:1 w/w) were selected. These polymers have appreciable different compression properties but comparable molecular size and this study was carried out to understand the role of tabletting attributes on swelling and erosion characteristics. It is evident from the findings that the changes in compression pressure affect the tensile strength, porosity, bulk and apparent density, microstructural properties, bonding strength and surface roughness of all types of matrix tablets. Increase in compression pressure has monotonically enhanced the swelling rate and degree of erosion of the matrix tablets, however, in the case of HPMC K4M and HPMC K4M: PEO WSR N60K (1:1 w/w) based matrices the swelling and erosion rate become steady after 150 MPa compression pressure. All the tabletting attributes such as swelling and erosion rate, average pore diameter, surface roughness and interparticulate bonding capacity are inter-linked (mostly R^2 lies in the range of 0.74 - 0.99) and greatly affect each other. It can be concluded from the findings that a careful comprehension of tableting attributes associated with compressed matrix tablets might be valuable in developing successful hydrophilic matrices for control drug release applications.

Dedication

This thesis is dedicated to my family, particularly to my father, without their encouragement, love and obviously financial support; this would not have been possible.

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I would like to express my deepest gratitude and sincere appreciation to my research supervisors, Prof Barbara Conway and Dr Muhammad Usman Ghori for their support, supervision, guidance and enlightening me with their vast wealth of knowledge. I appreciate their moral support and warm encouragement throughout my research project. They were constant source of knowledge and inspiration, which I will remember forever.

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To my parents, I thank you for everything they taught me growing up, and the belief that hard work pays off plus their tremendous effort within their resources.

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Finally, I would like to thank my brothers and sisters for their tremendous encouragement as always.

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List of Abbreviations

API	Active pharmaceutical ingredient
Cp	Centipoise
D_a	Pore diameter
HPMC	Hydroxypropyl methylcellulose
K_E	Erosion rate
KN	Kilonewtons
K_W	Swelling rate
MC	Methyl cellulose
PEO	Polyethylene oxide
RH	Relative humidity
S	Swelling
SEM	Scanning electron microscopy
S_q	Surface roughness

1. Introduction

1- Introduction

The oral route is undoubtedly the most prevalent drug administration route among patients and physicians. The oral drug delivery market represents 52% of the overall drug delivery market with an approximate value of $49 billion in 2012 and $90 billion in 2016 worldwide (MP-Advisors, 2014). This rapid growth is primarily driven by the development and introduction of new controlled release formulations (De Robertis et al., 2015) including osmotic controlled pumps, reservoir devices and monolithic matrix systems. Monolithic systems are polymeric matrices in which active pharmaceutical ingredient (API) can be present in dispersed or dissolved form. These systems can be developed using hydrophilic or hydrophobic polymers.

1.1- Hydrophilic matrix system

A hydrophilic matrix is a monolithic system in which hydrophilic polymers are employed as drug release retardants. It is one of the most attractive controlled drug delivery systems (Alderman et al., 1984; Maderuelo et al., 2011; Ghori and Conway, 2015) with advantages including simple technology, cost effectiveness, reliability and flexibility (Li et al., 2005; Maderuelo et al., 2011). In addition, formulations are easy to manufacture and most importantly the drug can be released continuously over a prolonged period of time and steady drug plasma levels can be achieved. Hydrophilic matrix systems can further lead to a decrease in a patient to patient bioavailability variation during drug administration. Moreover, this system can reduce the total number of doses as well as possible side effects related to high drug plasma levels (De Robertis et al., 2015).

It is a mixture of drug molecules in which one or several other pharmaceutical adjuvants are embedded with hydrophilic polymer. Examples of pharmaceutically relevant hydrophilic polymers include cellulose ethers, xanthan gum, polyethylene oxide, sodium alginates and Carbopol®. Amongst these, cellulose ether derivatives, particularly methyl cellulose (MC),

HPMC K4M (hydroxypropyl methylcellulose HPMC K4M) and hydroxypropylcellulose (HPC) have been of particular interest (Li et al., 2005; Maderuelo et al., 2011; Ghori and Conway, 2015). Also, polyethylene oxide (PEO WSR N60K), particularly high molecular weight, has been successfully employed in the formulation of hydrophilic matrices over the past decade. For all the polymers above, their broad spectrum of acceptance can be attributed to their non-toxic nature, availability in different grades and good regulatory acceptance (Ma et al., 2014). Generally hydrophilic matrices are manufactured using compression, hence, the term matrix tablets is widely used in literature (Ghori 2014). Most of the aforementioned hydrophilic polymers have fairly good compression properties, therefore, these matrices can often be prepared by direct compression (Wen et al., 2010). The fundamental operations involved in the preparation of these compressed hydrophilic matrices are not different from the ones involved in the manufacturing of conventional tablets, such as mixing and compression of ingredients

1.2- Mechanism of swelling, erosion and drug release

Polymer swelling, diffusion, drug dissolution, front movement and erosion of matrices all contribute towards the release of drug at molecular or microscopic level. When these hydrophilic matrices are exposed to biological fluids, a steep fluid concentration gradient is formed between the outermost surface of matrix tablet and fluid (Caraballo 2010). Hence, fluid is imbibed into the polymer matrix network. The fluid acts as a plasticiser and the glass transition temperature [(*Tg*) a transition of a material from a hard and relatively brittle glassy state to a rubbery state] reduces to 37 °C and the polymer chains start to relax and eventually disentangle increasing the molecular surface area (Colombo et al., 1999; Colombo et al., 2000; Maderuelo et al., 2011). This phenomenon of polymer chain relaxation is termed ‘swelling’ and the continuous inward ingression of liquid breaks the hydrogen bonds formed during tablet

compaction and can lead to the development of new hydrogen bonds accommodating water molecules. Therefore, the reduction in *Tg* and formation of new hydrogen bonds results in the swelling of polymer chains. Hence, a thick gelatinous layer appears on the surface of matrix tablets, as hydrophilic polymer passes from the amorphous glassy state to the rubbery state. Over a period of time, additional water enters the system and consequently the thickness of the gel layer increases (Ghori and Conway, 2015). The formation of the gel layer and penetration (diffusion) of the medium into the matrix is accompanied by the development of a series of various regions on the surface of matrix tablet. Four distinguishable regions are the erosion front, dissolution front, penetration front and swelling front as illustrated in Figure 1.1, (Ghori 2014).

The whole process of drug release is complicated and involves various steps: first of all entry of the aqueous medium into the matrix; secondly swelling of the matrix and dissolution of the drug in the medium; thirdly diffusion of the drug through the gel layer and finally erosion of the swollen matrix. Most of the time both diffusion and erosion occur simultaneously. Four various types of release mechanisms have been categorised which depend on the aforementioned processes (Maderuelo et al., 2011).

- **Fickian diffusion**: The process which controls the release of APIs.
- **Polymer swelling:** Swelling of the polymer determines drug release.
- **Polymer swelling and polymer and drug dissolution:** API release depends simultaneously on swelling of the matrix and phenomena of diffusion.
- **Polymer erosion:** A complete hydrated layer at the surface within the dissolution medium which continues to erode.

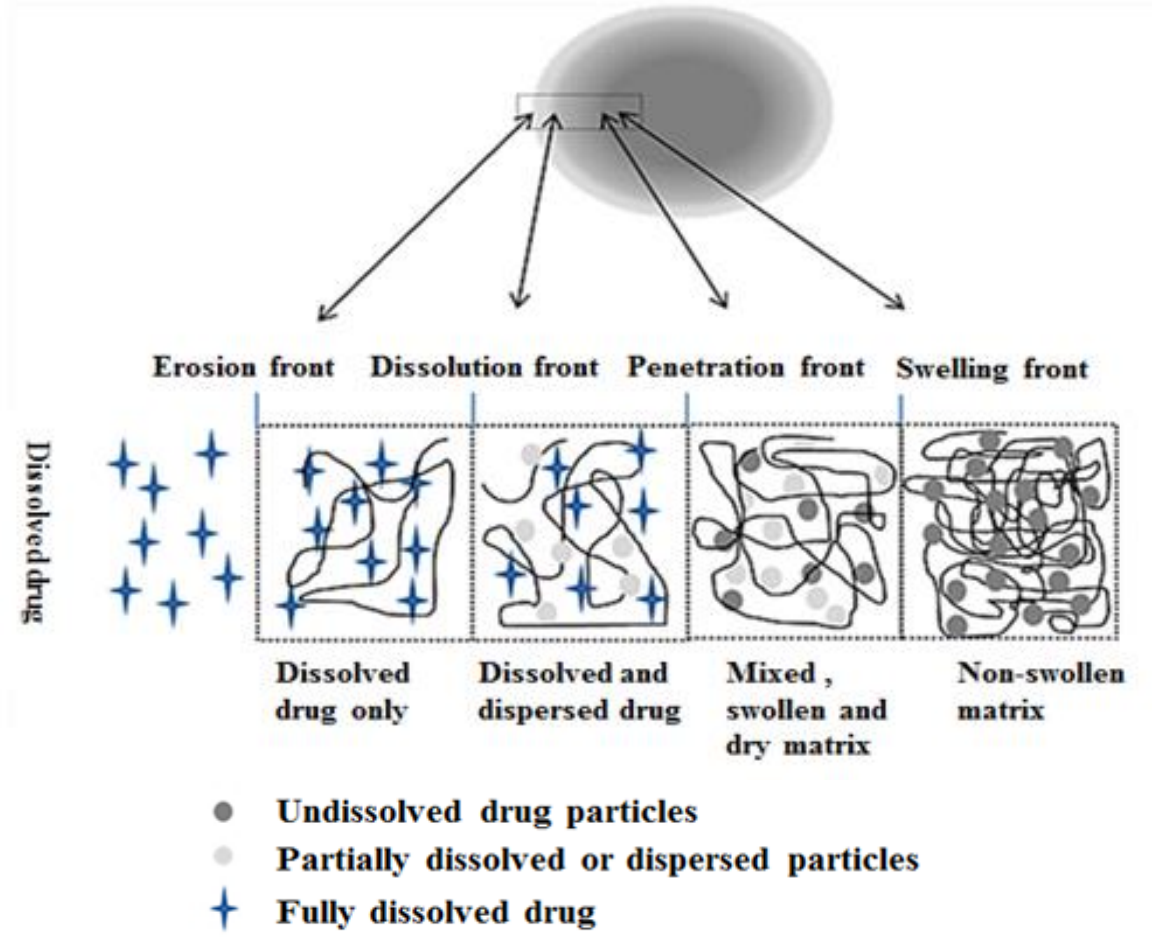

Figure 1.1: Hydrated hydrophilic matrix tablet representing various zones.(adapted from Ghori et al., 2014).

1.3- Hydrophilic polymers

1.3.1- Hydroxypropyl methylcellulose (HPMC)

Hydroxypropyl methylcellulose (HPMC) is a semisynthetic, viscoelastic inert polymer available in several grades that differ in viscosity and extent of substitution (Rowe et al., 2012). Figure 1.2 shows the chemical structure of HPMC.

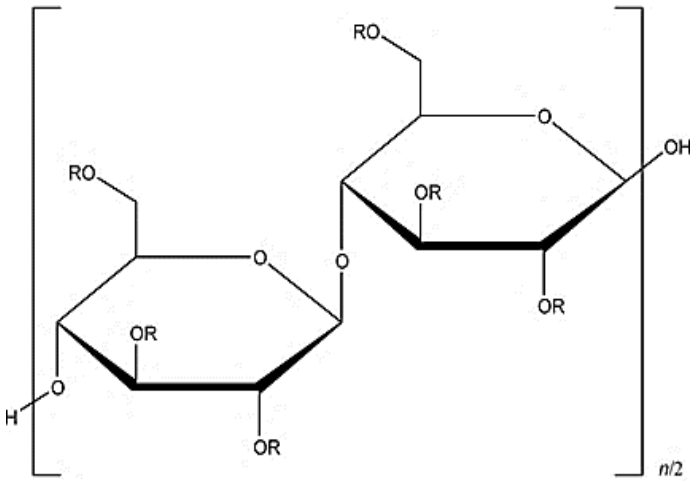

Figure 1.2: Chemical structure of HPMC, where R is H, CH_3 or CH_2 CH(OH)CH_3 (Rowe et al., 2006).

It is widely used in the formulation of pharmaceutical products as an excipient and an important component of controlled delivery in oral formulations (Wertz et al., 2010). HPMC comprises cellulose ethers which are soluble in cold water and form a viscous colloidal solution. HPMC K4M is practically insoluble in chloroform, ether, ethanol (95%) and hot water, however, it is soluble in mixtures of methanol and dichloromethane, mixtures of ethanol and dichloromethane and mixtures of water and alcohol. It is a white or creamy white fibril powder, which is odourless and tasteless.

HPMC polymers for hydrophilic matrix systems are available in different viscosity grades ranging from 4000 – 100,000 cps. A wide range of viscosity grades available is commercially and one of most commonly used grades is Methocel K4M; this has an apparent viscosity of 4000 cps at 20°C for a 2% w/v polymer solution (Rowe et al., 2006). Molecular weights available for HPMC generally range from 10 000 – 1 500 000 Da (Dow 2002).

1.3.2- Pharmaceutical applications of HPMC

Hydroxypropyl methylcellulose (HPMC) is used in the pharmaceutical industry for multiple purposes, some of these are described below and summarised in Table 1.1.

Table 1.1: Summary of pharmaceutical applications of HPMC.

Application	Effect	Reference
Tablet binders	HPMC bind the excipients and drug during wet and dry granulation process.	(Chowhan et al., 1996; Itiola, 1991)
Coating agent	Frequently used in solid dosage forms to mask the taste and to protect the sensitive drugs.	Banker et al., 1981; Wen et al., 2010
Compressibility Enhancer	Excellent properties of compaction flow during granulation, particularly during direct compression.	Shokri et al., 2013; Ghori et al., 2014
Extended release excipient	Good compression properties at different concentration to control or extend the drug release rate.	Maderuelo et al., 2011 Li et al., 2005
Ophthalmic preparations	Used as a stabilizer and thickening agent plus decrease surface tension.	Liu et al., 2008;

a) Applications as tablet binders

HPMC exhibits good binding properties for the formation of tablets and capsules (Itiola, 1991; Chowhan et al., 1996). The ability to bind the excipients and drug in moist and dry conditions throughout compression is one of the fundamental uses of HPMC in the pharmaceutical industry (Rowe et al., 2006).

b) Applications as a coating agent

Solid dosage forms such as tablets, granules, pellets and microcapsules are frequently coated for different reasons, for example to mask the taste, to protect sensitive drugs from certain environmental circumstances and humidity or to control drug release over a specific period of

time (Wen et al., 2010). HPMC has excellent film-forming properties and widely used for coating solid dosage forms (Banker et al., 1981).

c) Applications as compressibility enhancers

The majority of pharmaceutical products are administered in tablet form. Tablets can be manufactured in different ways but direct compression is a simple, convenient, and efficient tablet compression method. Usually this technique is used for tableting when the drug concentration is less than 30% w/w of the formulation for medium to high potency of drugs (Shokri et al., 2013). Unfortunately, one of the common problems during dry granulation is poor powder flow of drugs, particularly when the drug content is more than 30% w/w. To overcome this issue cellulose ether like HPMC K4M can be employed as they can significantly increase the compressibility of poorly compactable powder mixtures (Ghori et al., 2014b).

d) Ophthalmic applications

HPMC is used as a stabiliser and thickening agent for ophthalmic preparations, mainly solutions (eye drops and contact lenses) and ointments. HPMC's role is to decrease surface tension which in turn improves wetting and enhances the spreading capacity of the solution over the surface of the eye (Liu et al., 2008).

e) Applications as extended release solid dosage form excipients

Matrices, more precisely hydrophilic matrices, are simple and efficient systems for controlling drug release over extended periods of time from dosage forms. Cellulose ethers, particularly HPMC K4M are frequently used to form extended release hydrophilic matrices because of fairly good compression properties. Different concentrations of HPMC can be used to control or extend the release rate of drugs with a range of solubilities. However, the solubility of the drug can affect release profiles (Maderuelo et al., 2011).

1.3.3- Polyethylene oxide (PEO)

Polyethylene oxide (PEO) or Polyox® is a non-ionic, synthetic, hydrophilic, linear, homopolymer of ethylene oxide. The monomer is denoted using a formula (CH_2CH_2O) and the polymer might contain up to 3% silicon dioxide. PEO is prepared by the polymerization of ethylene oxide with a suitable catalyst (Figure 1.3). Polyox is available commercially in different grades, for example Polyox 301, Polyox 303 and Polyox coagulant are 4,000,000, 7,000,000 and 5,000,000 respectively (Rowe et al., 2006).

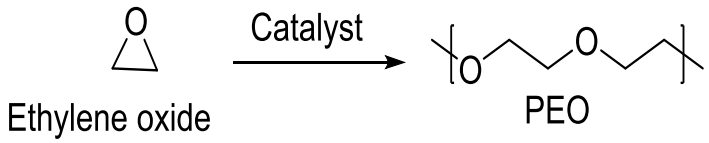

Figure 1.3: Represents synthesis of polyethylene oxide using catalyst.

Commercial PEO is a white, dry and free-flowing powder. It is soluble in water and in a number of organic solvents such as chloroform, acetonitrile, toluene and methyl chloride. It can be dissolved in both hot and cold water but the polymers will precipitate once the temperature of solution is close to the boiling point of water, generally referred to as the cloud point. The cloud point depends on the molecular weight, concentration of PEO, concentration of salt and the pH value. The glass transition temperature (*Tg*) of PEO is -67 °C whereas its melting point ranges from 65 °C to 70 °C (Rowe et al., 2006).

1.3.4- Pharmaceutical applications of polyethylene oxide (PEO)

Polyethylene oxide has numerous applications in the pharmaceutical industry for a wide range of purposes as described below and summarised in Table 1.2.

Table 1.2: Summary of pharmaceutical applications of PEO.

Application	Effect	Reference
Bioadhesive material	Long linear chain structure allows PEO to form strong interpenetrating network, which results to maintain drug release rate.	Cappello et al., 2006; Ma et al., 2014 Wu et al., 2004
Tablet binder	Binding characteristics of PEO ease the process of compaction during manufacturing.	Mahalingam et al., 2009
Coating agent	Successfully employed to protect drugs from moisture, and for taste masking	Ma et al., 2014 Maggi et al., 2000
Viscosity enhancer	Acts as suspending agent because of its viscosity increasing characteristics.	
Controlled release excipient	High molecular weight PEO at various concentrations has been used successfully to control the drug release profile. It can be used for hydrophilic and hydrophobic drugs.	Maggi et al., 2000

a) Applications as bio-adhesive in hydrophilic matrices

PEO has a long linear chain structure which enables it to form a strong interpenetrating network with mucus leading to potential retention at the site (Ma et al., 2014). Cappello et al., (2006) studied the incorporation of PEO into hydroxypropyl-β-cyclodextrin for transmucosal delivery of poorly soluble drug carvedilol. The permeation of carvedilol from this system was higher and it was concluded that the combination of PEO and cyclodextrins can be employed as a

suitable strategy to deliver poorly soluble drugs while maintaining the good mucoadhesion properties.

b) Applications as tablet binder

PEO can acts as binder in direct compression systems. The good flow and lubrication properties of PEO can ease the compression and potentially assist tableting operations (Jones 2004; Rowe 2006).

c) Applications in pharmaceutical coating

Various PEO grades have potential to utilise in as a coating material for pharmaceutical manufacturing to overcome the friability and taste issues (Mahalingam et al., 2009).

d) Viscosity increasing agent

PEO can be used as a suspending agent because of it has the potential to modify the viscosity of the liquid. During successful suspension formulation development, maintaining the product viscosity at optimum levels is key factor as a high concentration of polymer can cause gelling and physical instability (Ma et al., 2014).

e) Applications as controlled release solid dosage form excipient

PEO can be used in various dosage forms, particularly in controlled release tablet systems, for instance bioadhesive delivery systems and controlled matrix tablets. Matrices are simple and efficient systems for controlling drug release from various dosage forms. PEO, in particular high molecular weight PEO, have been suggested by various authors and successfully used in pharmaceutical industry over the past decade in controlled release dosage forms. Different concentrations can be used to control the drug release profile over the specific period of time (Maggi et al., 2000).

1.4. Factors affecting swelling/ drug release

The process of developing compressed hydrophilic matrices might be simple but it becomes very complicated and challenging when it comes to explaining the mechanism of drug release from these matrices. The physicochemical properties of the polymer and incorporated drug can substantially affect the swelling, erosion and drug release kinetics of hydrophilic matrices. Some critical factors that can affect swelling, erosion and release of drug are described below and summarised in Table 1.3.

1.4.1- Polymer particle size

The impact of the particle size of the polymer on drug release has been reported (Dabbagh et al., 1996; Viriden et al., 2009 and Caraballo, 2010). The vast majority have concluded that the particle size of the polymer does have an impact on drug release but it is complex. Generally, smaller polymer particles can initiate rapid gel layer development on the surface of matrix tablets that can slow drug release rate. Matrices formulated with polymer particle sizes larger than 200 μm can disintegrate before gel layer formation. On the other hand, matrices formulated with a particle size less than 150 μm generate the gel layer rapidly preventing disintegration of the system and leading to an extended drug release profile (Maderuelo et al., 2011).

HPMC K15M matrices, with an average particle size smaller than 113 μm release the drug through a combination of diffusion and erosion. However, when the HPMC particle size was more than 113 μm, an erosion based drug release mechanism dominates. In conclusion, smaller polymer particle sizes were most effective in the formation of a homogeneous gel layer as compared to lager size polymer (Miranda et al., 2007).

Kaialy et al., 2016 studied the effect of PEO concentration and particle size and concluded that PEO of particle size less than 180 μm develops a rapidly formed gel layer barrier, which results in slower drug release mechanism by diffusion.

Table 1.3: Comparison of HPMC and PEO properties affecting swelling/ drug release.

Factor	HPMC	PEO	HPMC	PEO
	Effect		References	
Particle size	Particle sizes < 150 μm are effective at controlling swelling	Smaller particle size reduced the drug release rate.	Dabbagh et al., 1996; Miranda et al., 2007; Kaialy et al., 2016	Miranda et al., 2007; Viriden et al., 2009; Caraballo, 2010; Maderuelo et al., 2011.
Viscosity	Higher the viscosity of HPMC, the greater the swelling index.	Swelling index increased with increased viscosity.	Daly et al., 1984; Gao et al., 1996; Hiremath et al., 2008.	Daly et al., 1984; Maggi et al., 2000; Hiremath et al., 2008.
Polymer concentration	Drug release rate decreases as the fraction of polymer increases over certain percentage.	Enhance the drug release to some extent, further increase of PEO decrease the drug release rate.	Mitchel et al., 1993; Tiwari et al. 2003**;** Ebube et al., 2004; Quinten et al. 2011.	Ebube et al., 2004; Quinten et al. 2011
Porosity	Decreased porosity in the case of HPMC showed increased swelling rate.	Higher porosity of PEO matrices decreased swelling rate.	Dabbagh et al., 1996; Lotfipour et al., 2004.	Dabbagh et al., 1996; Lotfipour et al., 2004

1.4.2- Effect of viscosity

The viscosity of the polymers is one of the basic parameters that controls drug release and determines the mechanism of release. In solution, the viscosity of a polymer depends on the chemical structure of the polymer, molecular weight, temperature and the interactions with the solvent. Commonly, polymers with high molecular weight increase the viscosity of solutions (Daly et al., 1984).

Various authors have studied the impact of viscosity of HPMC and other related cellulose ether based on drug release from hydrophilic matrices. It was concluded that the greater the viscosity of a polymer, the faster the swelling and, over time, a physically stable gel layer is formed which eventually decreases the drug release (Maderuelo et al., 2011; Ghori and Conway, 2015).

Likewise, viscosity of PEO can affect drug release, particularly for matrices containing high molecular weight polymer as they have the ability of rapid swelling which leads to the development of turbid gel layers which resist erosion and therefore potentially lead to slower drug release (Maggi et al., 2000).

The swelling and erosion behaviours of HPMC and PEO depend upon the viscosity of the polymer; the higher the viscosity of HPMC and PEO lead to higher swelling while the percentage of erosion decreases with increasing viscosity of a polymer. This can be attributed to the fact that the ability of higher viscosity polymer to absorb water is greater, which results in a rapid swelling (Gao et al., 1996; Hiremath et al., 2008).

1.4.3- Effect of polymer concentration

Generally, drug release rate decreases with an increase in the ratio of polymer in the matrix tablet. High polymer loads lead to lower porosity of the matrix tablet, which results in lower drug release rates (Tiwari et al., 2003; Maderuelo et al., 2011; Ghori and Conway et al., 2015).

For example, Ebube et al., (2004) found that an increase in the percentage of cellulose ether polymer (3.5% to 19.2%) in the matrix tablet corresponded to a decrease in the drug release rate. Similarly, Mitchell et al., (1993) found an increase in the ratio of HPMC and related polymers corresponds to a higher degree of polymer chains entanglement. Thus, in turn, viscosity decreases and as a result tortuosity of the release pathway increases which causes a slower drug release.

Conversely, there is a difference of opinions as some authors argue that release of highly water soluble drugs is not affected by polymer concentration above the critical polymer concentration (the minimum concentration require to develop a gel-layer on the surface of the tablet) as release rate did not decrease (Ghori 2014). Hydrophilic matrices containing tramadol HCl, a highly water soluble drug, were investigated by Tiwari et al., (2003). There were no significant changes in release rate with changes in the polymer concentration. Therefore, it was reported that at HPMC concentrations above 20% there is no significant impact on the drug release rate (Maderuelo et al., 2011).

In some cases, PEO has added to formulations to increase the drug release rate. Release of metoprolol from ethylcellulose tablets was increased on the addition of PEO (Quinten et al., 2011) up to a ratio of 70%.

1.4.4- Effect of porosity

Porosity will influence the swelling kinetics of hydrophilic matrices thus affecting drug release rate. Inclusion of diluents and other materials within the matrix decreases the percentage of retardant polymer causing a decrease in the release that is due to higher tortuosity of the gel through which the drug diffuses (Lotfipour et al., 2004).

In hydrophilic matrices, distribution of pores or channels affects the drug release profile. Dabbagh et al., (1996) prepared matrices with different compression forces. All matrices prepared at 78.7 mN m^{-2} or higher had similar porosities and similar dissolution profiles. On the other hand, matrices prepared at compression pressures below 78.7 mN m^{-2} had higher porosity and faster release rate. On the basis of these observations authors concluded that porosity affects release rate

The phenomenon of pore formation in the matrices of hydrophilic drugs is known, while in the case of water- insoluble drugs pore formation is impeded. During release, drug particles close to the surface can dissolve rapidly and form pores through which other drug molecules can diffuse which ultimately increase the drug release rate. If needing to negate this, the percentage of polymer may be increased to enhance physical cross-linking and reduce pore generation, however, it some cases the pore formation might be helpful in drug liberation from the hydrophilic matrix device (Reza et al., 2003).

The effect of porosity on release rate was studied for HPMC and PEO matrices. In the case of HPMC based matrices decreased porosity produced a higher swelling rate which might be attributed to higher osmotic stress (a sudden change in the solute concentration around a matrix tablet, which causes a rapid change in the movement of water across) within the compact (Maderuelo et al., 2011; Ma et al., 2014; Ghori and Conway, 2015).

1.4.5- Effect of compression pressure

Compression pressure during tablet manufacturing could be closely related to change in the porosity of tablets (Ford et al., 1985; Dahl et al., 1990; Nokhodchi et al., 1996). Apparently, an increase in compression pressure had translated into a higher degree of compactness and hence a higher apparent density of the matrix, that results in reduced porosity (Hiremath et al., 2004). Kabanda et al., 1994 found tablets with different crushing strength had differences in initial

release rates but once the polymer had swollen, the dissolution profiles were similar (Velasco et al., 1999). In case of PEO, compression pressure has a noticeable influence leading to pressure dependant reduction in tablet porosity. Other important factors affecting PEO matrices include compression speed, desired shape, size, and physicochemical characteristics of various PEO grades. PEO tablets showed initial burst effect due to variation in compression forces but once fully hydrated, the release of drugs became steady (Hiremath et al., 2008).

1.5- Tabletting and compaction properties of hydrophilic matrices

Compaction can be defined as the consolidation and compression of powder particles on application of pressure. It involves the reduction of bulk volume as the entrapped air during die filling leaks out reducing the gaseous phase. It is a mechanical phenomenon under which the state of material is changed from powder to a compact having a desired porosity (Ghori & Conway 2016). Compressed hydrophilic matrices are material composites which can be fabricated using hydrophilic polymers or their mixtures in the presence of API, moreover, other pharmaceutical ingredients such as filler, binder and glidant can also be incorporated to aid the compaction process (Ghori & Conway 2015). The physicochemical properties of these materials can influence the compaction behaviour. Hence, the degree and extent of deformation and consolidation of these polymers can influence the compaction pressure attributes that include, but are not limited to, porosity, surface roughness, compact internal microstructure and interparticulate bonding and packing (Narayan & Hancock 2003). HPMC possesses good compaction properties attributed to a relatively high propensity for plastic deformation and anti-static behaviour during powder mixing (Ghori et al., 2014b; Ghori et al., 2015; Timmins et al., 2014) which assists large surfaces to be in close proximity to each other and a large number of bonds, mainly intermolecular forces, to be established between the particles (Karehill et al., 1990; Nyström et al., 1993). Additionally, mechanical interlocking may also

contribute to the overall strength of these matrix tablets (Karehill et al., 1990). On the other hand, PEO is a synthetic hydrophilic polymer is also widely employed for the development of hydrophilic matrices also deforms plastically. However, the PEO based matrices have a propensity of higher elastic recovery during decompression and ejection. It can readily deform even at low pressures and develop soft tablets in relation to HPMC (Yang et al., 1996; Ghori et al., 2017a).

1.6- Rationale, aims and objectives of current research project

The designing, development and fabrication of successful controlled/sustained release formulations require an understanding of polymer chemistry and physicochemical principles of pharmaceutics. Factors controlling drug release mechanisms from hydrophilic polymer matrices are influenced by the physicochemical properties of polymers. PEO consolidates at low pressures and has a tendency to produce soft tablets and that can affect controlled release performance (Yang et al., 1996). In contrast, HPMC has a tendency to deform plastically and have fairly good compaction properties (Ghori et al., 2017). Mechanistically, both the polymers have a tendency to behave differently under compression pressure. Therefore, this research project was designed to investigate the swelling, erosion, intra-particulate bonding strength, compaction, microstructural and surface roughness properties of PEO WSR N60K and HPMC K4M in their native compacted form using a range of compression pressures (50-250 MPa). Additionally, 1:1 w/w (HPMC K4M: PEO WSR N60K) mixed polymer matrices will also be developed to understand how the polymer hybrid system can have an impact on the aforementioned functional properties. Moreover, the interrelationship between the various previously mentioned properties has also studied, as depicted in Figure 1.4.

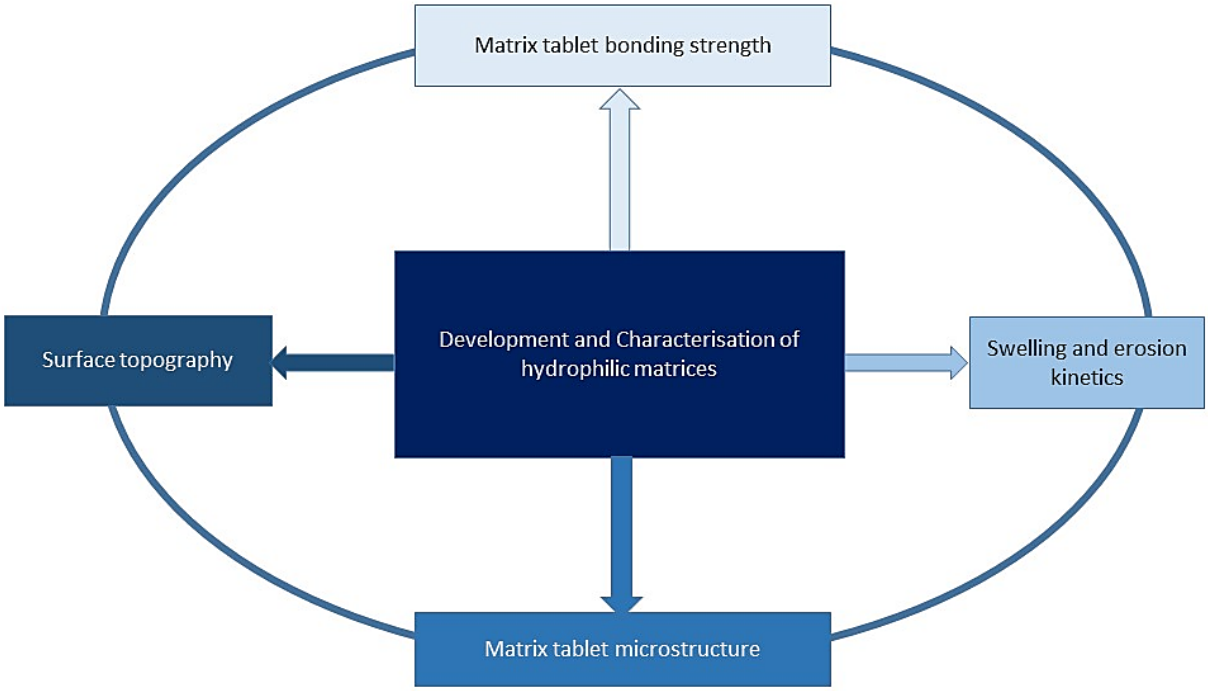

Figure 1.4: Schematic illustration of aims and objectives of research project.

2-Materials and Methods

2. Materials and Methods

2.1- Materials

Hydroxypropyl methylcellulose (HPMC K4M) (Methocel K4M) and Polyethylene oxide (Polyox WSR N60K) were kindly provided by Colorcon Ltd. (Dartford, UK) and their specifications are listed in Table 2.1.

Table 2.1: Specifications of HPMC K4M and PEO WSR N60K used in the study.

Material	**Methoxy (MeO) (% w/w) [a]**	**Hydroxypropyl (HPO) (% w/w) [a]**	**Viscosity (cps) [a]**
K4M	22.3	8.5	4351
WSR N60K	-	-	4131

[a] Data obtained from the manufacturer (Dow Chemical Co. USA)

2.2- Methods

2.2.1- Particle size fractionation

Mechanical sieving (Endecotts Ltd. London, United Kingdom) was used to obtained particle size fractions of both polymers (75- 125 µm). Briefly, sieves with openings of 125 µm and 75 µm were employed at the top and middle of the mechanical sieving assembly. The receiver pan was attached at the base and it was placed on a sieve shaker (Endecotts Ltd. London, United Kingdom). The powder was poured on the top sieve and shaken for 15 mins and the powder particles retained on the middle sieve were collected. The same powder was cycled five times (n=5) to accurately control the particle size. All powders were stored at ambient temperature (22-24°C) and humidity (RH 38-40 %).

2.2.2- Preparation of polymer powder mixtures

HPMC K4M and PEO WSR N60K were mixed at 1: 1 *w/w*. Both polymers were blended and mixed for 15 minutes to get a homogeneous mixture using a Turbula shaker-mixer (Glen Mills Inc. Clifton, NJ, USA) at 50 rpm. This mixture of polymers was stored in glass containers at ambient temperature (22-24°C) and humidity (RH 38-40 %) during the powder mixing experiment.

2.2.3- Particle surface morphology

The surface morphology of the polymer powders and respective powder mixtures (1:1 w/w) of these two polymers was observed using scanning electron microscopy (SEM). Dry powder samples were mounted onto stubs using double-sided adhesive tape and were sputter-coated with gold/palladium (80:20) for 60 seconds using a Quorum SC7620 Sputter Coater (Quorum Technologies, Laughton, UK). Samples were placed separately on the specimen holder of the SEM (Jeol JSM-6060CV, Jeol Inc. Peabody, MA, USA) under vacuum and picture formed was observed directly on the computer attached to the system and recorded photographically.

2.2.4- Determination of true density of powders

The true density of solid powders is an intrinsic property and defined as mass per unit volume (g cm^{-3}). The true density of both polymers (HPMC K4M, PEO WSR N60K) and their powder mixture (1:1 w/w) was determined using AccuPyc 1340 II Pycnometer (Micromeritic UK Ltd. Hertfordshire, UK) employing helium as an inert gas. All experiments were performed (n = 10) to determine the true density.

2.2.5- Preparation of matrix tablets

Both polymers and their mixture (50 % w/w) were compressed using a Testometric M500 – 50 CT (Testometric Company Ltd., Rochdale UK) materials testing machine equipped with a 13.00 mm Atlas Evacuable Tablet Die (Specac® Limited, UK), Figure 2.1. An analytical balance was used to accurately weigh (500 ± 2.5 mg) powder of polymers and their mixture and then manually poured into the die. During tablet preparation, two flat- faced punches were used on the upper punch and lower punch. The upper punch moved at a speed of 2 mm/min during loading and unloading. In this study, five different compression forces (7 kN, 13 kN, 20 kN, 26 kN and 33 kN) were applied to produce tablets. After ejection, the diameter and thickness of all ejected tablets were measured using a digital Vernier calliper. After this, all the tablets were stored over silica gel for 24 hours to allow for elastic recovery before any further testing was conducted. Temperature and relative humidity during whole compression process were in the range of (20-25 °C) and (RH 28-48 %) respectively (Ghori, 2014).

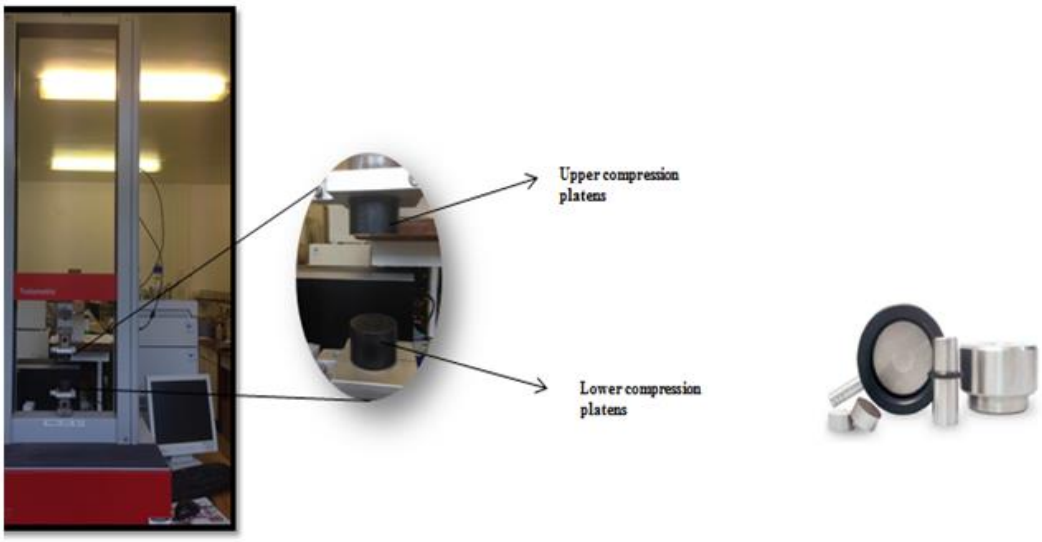

Figure 2.1: Testometric material testing machine with 13.00 mm die set. (Image was adapted from Ghori 2014).

2.2.6- Characterisation of matrix tablets

2.2.6.1- Compact internal micro-texture studies

The internal micro-texture of compacted matrices was studied using mercury intrusion porosimetry (AutoPore IV 9500, Micromeritics, USA). The porosity and its descriptive parameters (total intrusion volume, true density, bulk density, absolute density, total pore area and average pore diameter) were determined as detailed below.

The pore diameter (D) was determined using the Washburn equation, Eq. 2.1 (Washburn et al., 1921).

$$D = \frac{-4\,\gamma \cos\theta}{\mathrm{P}} \qquad \text{Eq. 2.1}$$

Where,
D = pore diameter (µm)
γ = surface tension of mercury (485 dyn cm^{-1})
θ = contact angle of mercury (130°)
P = pressure (psia)

Total pore area (A) was determined using Eq. (2.2).

$$A = \frac{1}{\gamma \cos\theta} \int_{0}^{Vtot} P.dV$$

Eq. 2.2

Where,
P = pressure (psia)
V = intrusion volume (mL g^{-1}).
V_{tot} = total intrusion volume (mL g^{-1})

Average pore diameter (D_A) was calculated using Eq. 2.3.

$$D_A = \frac{4\,V_{tot}}{A_{tot}} \qquad \text{Eq. 2.3}$$

V_{tot} = total intrusion volume (mL g^{-1})
A_{tot} = total pore area (mL g^{-1})

Bulk density (ρ_b) of tablet was calculated using Eq. 2.4.

$$\rho_b = \frac{W_s}{Vp - Vm} \qquad \text{Eq. 2.4}$$

Ws = weight of tablet sample (g)
Vp = volume of empty penetrometer (mL)
Vm = volume of mercury (mL)

Apparent density (ρ_a) of tablet was calculated using Eq. 2.5.

$$\rho_a = \frac{W_s}{Vs - V_{tot}} \qquad \text{Eq. 2.5}$$

Where,

Ws = weight of tablet sample (g)
V_{tot} = total intrusion volume (mL g^{-1})
Vs = the volume of penetrometer excluding the mercury volume (mL)

The porosity (ε, %) was determined using Eq. 2.6.

$$\varepsilon\,(\%) = \left(1 - \frac{\rho_b}{\rho_a}\right) \times 100 \qquad \text{Eq. 2.6}$$

Where,

ρ_b = true density
ρ_a = apparent density

2.2.6.2- Tensile and internal bonding strength analysis of matrices

After compaction, matrix tablets were left for 24 hours before measuring diameter (D) and thickness/height (H). Matrix tablets were broken using a Testometric M500 – 50 CT / Hardness

Tester (Pharma Test PTB 311E), maximum breaking force (F) was determined, and the tensile strength (σ_X) was calculated using equation Eq. 2.7 (Fell & Newton., 1970).

$$\sigma_X = \frac{2F}{\pi DH} \qquad \text{Eq. 2.7}$$

Where;
σ_X = tensile strength
F = tablet breaking force
D = tablet diameter
H = thickness/height

A Ryshkewitch-Duckworth relationship between the global porosity ($\varepsilon, \%$) and tensile strength was determined for every matrix tablet (Duckworth 1953) using Eq. 2.8

$$ln\left(\frac{\sigma_X}{\sigma_y}\right) = -\mathrm{k} \times \varepsilon \qquad \text{Eq. 2.8}$$

Where;
σ_X = Tensile strength
σ_y = Tensile strength at zero porosity
k = Constant referred to as bonding capacity
ε = Porosity

2.2.6.3- Surface roughness studies

The surface roughness studies of all the compacted matrices was studied using atomic force microscopy (AFM, Dimension Icon by Bruker, UK). The images were collected using contact mode and a standard optical lever method with a small offset of force. The three-dimensional root mean square roughness (Sq) (Eq. 2.9) (Blunt & Jiang, 2003; Farris, Introzzi, Biagioni, Holz, Schiraldi, & Piergiovanni, 2011; Ghori et al., 2017b) was also determined using SURFSTAND® software (University of Huddersfield) (Blunt & Jiang, 2003). The scan area was 5 × 5 μm^2 and each measurement was carried out in triplicate (n=3).

$$Sq = \sqrt{\frac{1}{MN}\sum_{j=1}^{N}\sum_{i=1}^{M} n^2\,(x_i, y_i)} \qquad \text{Eq. 2.9}$$

Where,

x = horizontal ordinate of line-scan profile at point i

y = vertical ordinate of line-scan profile at point i

M = Median of line-scan profile heights

N = samples size

2.2.6.4- Swelling studies

The swelling studies were carried out for all the tablets using USP apparatus 1 (Pharmatest PTWS D610, Pharmatest Ltd. Hainburg, Germany) at 50 rpm at 37 °C. Tablets were placed in pre-weighed baskets made of stainless steel wires and the combined weight determined. Pre-weighed matrix tablets were then immersed in the dissolution vessel containing 900 mL deionised water (swelling medium). After 15 minutes the previously weighed baskets, containing hydrated tablets were removed from the vessels, lightly blotted with 125 mm filter paper (Whatman®, UK) to remove excess liquid and then re- weighed (*Ws*). Tablets were rapidly replaced back into the medium and the process repeated at 30, 60, 120, 240, 360 and 720 minutes. The mean weight was determined for each tablet and degree of swelling (*S*) was determined by using Eq. 2.10.

$$S = \frac{W_s - W_i}{W_i} \times 100 \qquad \text{Eq. 2.10}$$

Where,

W_i = Initial weight of tablet

W_s = Swollen tablet weight

Where W_i initial weight and W_s is swollen matrix tablet weight at immersion time (t) in the water (swelling medium). The degree of swelling was determined from the mean of three replicates and presented as degree of swelling (*S*, %) against time (t)

2.2.6.5- Erosion studies

Erosion of matrix tablets was determined by a gravimetric technique (Ghori et al., 2014). The study was conducted using USP apparatus I (Pharmatest PTWS D610, Pharmatest Ltd. Hainburg, Germany) at 50 rpm at 37 °C. The dry tablets were accurately weighed and placed in baskets prior to immersion in erosion media (deionised water). Tablets were removed at 15, 30, 60, 120, 360 and 720 minutes and lightly blotted dry with 125 mm filter paper (Whatman® Ltd. UK) to remove excess water. They were subsequently dried in a convection oven at 50°C. After 24 hours, the tablets were cooled to ambient temperature and then weighed until a constant weight had been achieved and this was termed the dried weight. All studies were conducted in triplicate. The degree of erosion (E) was calculated using Eq. 2.11.

$$E = \frac{W_i - W_f}{W_i} \times 100 \qquad \text{Eq. 2.11}$$

Where, W_i is the initial weight of the matrix tablets and W_f is the weight of the dried matrices at specific sampling times.

2.2.6.6- Statistical analysis for interrelationship studies

Linear regression approach was adopted to model the relationship between the various parameters derived from swelling, erosion and tableting. The linearity was studied using R^2 values and R^2 >0.90, 0.80-0.89 and <0.80 were considered good, fairly good and weak, respectively.

3- Results and Discussion

3. Results and discussion

3.1- Characterisation of powders

True density is the density (weight per unit volume, g/cm^3) excluding the volume of any pores or spaces between powder particles. Density imparts significant effects on powder flow and compaction, ultimately affecting the quality of compacts. Table 3.1 lists the true density of HPMC K4M, PEO WSR N60K and 1:1 w/w mixture of HPMC K4M/PEO WSR N60K. True density values of all the powders are quite close to each other but HPMC K4M has the highest true density and PEO WSR N60K has the lowest while the density of 1:1 w/w powder mixture lies in between the highest and lowest value.

SEM was carried out to observe the surface morphology of powder particles of HPMC K4M and PEO WSR N60K. The SEM image of HPMC K4M in Table 3.1a shows that it comprises fibrous aggregates of irregular shape while Table 3.1b shows the aggregates of PEO WSR N60K powder particles (Hewlett et al. 2012) and Table 3.1c shows SEM image of 1:1 w/w mixture of HPMC K4M and PEO WSR N60K. The red arrow points towards the PEO WSR N60K powder particles while green dotted arrow points out the HPMC K4M powder particles.

Table 3.1: True density of materials (standard deviations are given in parenthesis, n=10)

Material	**HPMC K4M**	**PEO WSR N60K**	**HPMC K4M: PEO WSR N60K (1:1 w/w)**
$\boldsymbol{\rho}$ (g cm^{-3})	1.33 (0.001)	1.30 (0.01)	1.31 (0.005)

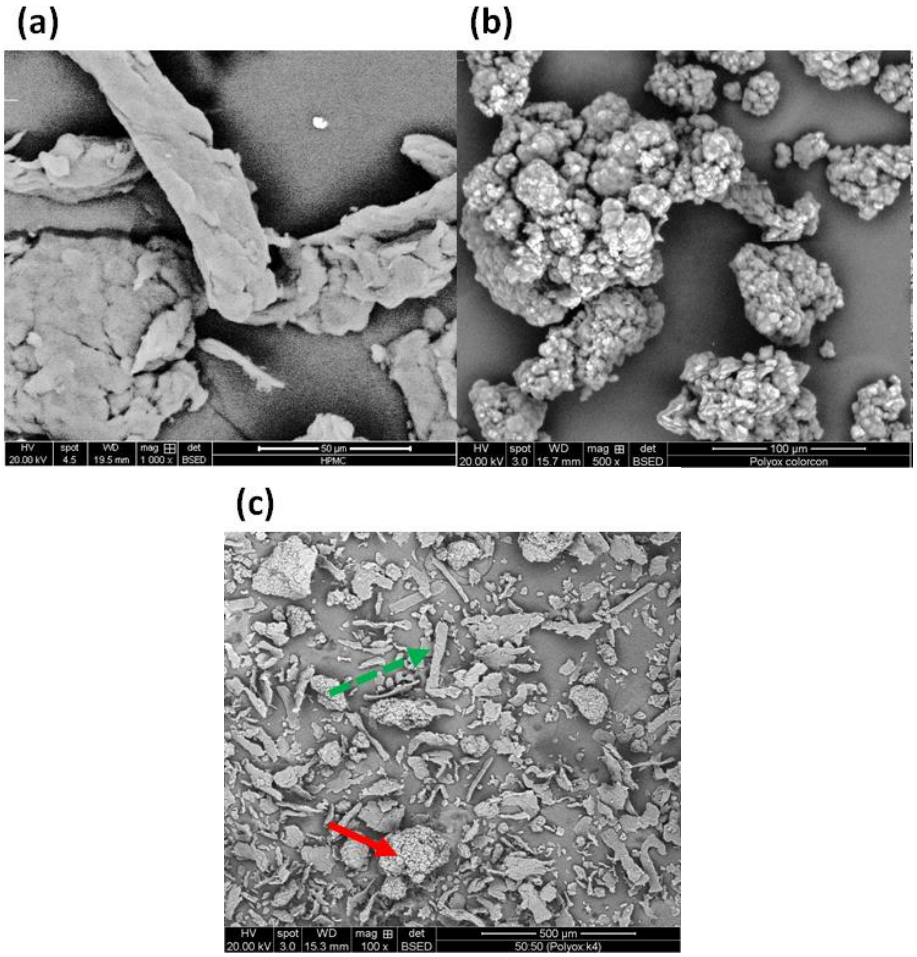

Figure 3.1: SEM micrographs of (a) HPMC K4M, (b) PEO WSR N60K and (c) 1:1 w/w powder mixture. Green and red arrows represent HPMC and PEO respectively.

3.2- Compaction, microstructural, bonding strength and surface roughness studies

Tablet compaction is a complex process and particulate materials are used to develop composites of pharmaceutical tablets. The physical and chemical properties of the particulate material affect their compaction behaviour and the final properties of the compact itself (Zhang et al., 2003). Generally, during compaction, powders undergo various transitions to form a porous solid. Powder (drug/excipient blend) is poured into a die and under a transient force profile, powder is compressed. The gradual increase in stress profile allows it to densify and

deform the powder bed into a solid compact (Ghori & Conway 2016). Hence, it is of great interest to investigate the process of compaction during the development of compressed hydrophilic matrices as the pressure exerted to compress the powder of particulate nature can be non-uniform, thus, leading to density variation affecting tensile strength, porosity and other properties and the compact will exhibit properties depending upon the interactions and bonding between particles. These density variations and bonding properties might have significant impact on the performance and functionality of the matrix tablets.

The relationship between tensile strength and compression pressure (Figure 3.2) was studied to understand the effect of compression pressure on tensile strength. In general, tensile strength has increased with increase in compression pressure. There is a gradual increase in tensile strength of HPMC K4M from 50 to 100 MPa. Beyond this pressure, there is a sharp increase in tensile strength at 150 MPa and then it again gradually increases at further increased pressures. HPMC K4M: PEO WSR N60K (1:1 w/w) also exhibits the same pattern. Overall, HPMC K4M has the highest tensile strength and PEO WSR N60K has the lowest while HPMC K4M: PEO WSR N60K (1:1 w/w) has medium tensile strength.

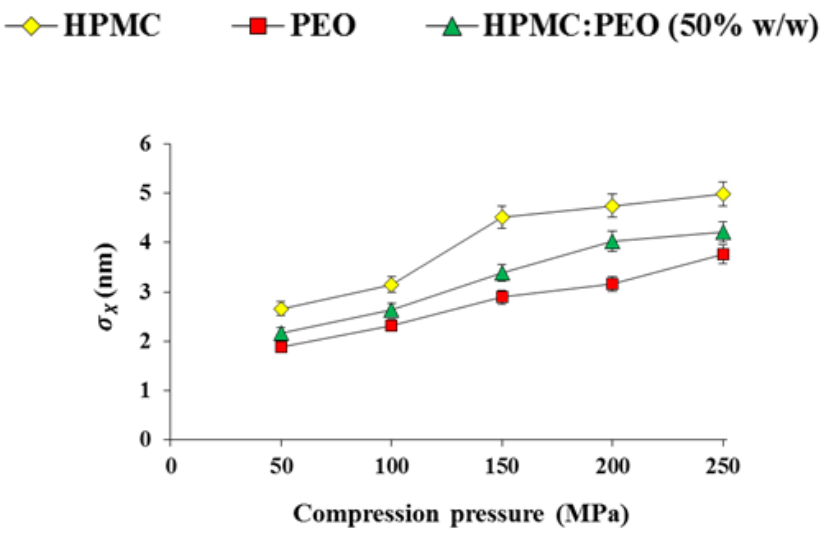

Figure 3.2: Tensile strength profile of matrix tablets with respect to compression.

Since the compaction process affects microstructural properties of the matrix tablets (Escudero et al., 2010), the effect of compression pressure on bulk and apparent density, porosity and pore size was also studied (Figure3.3). Bulk density is the ratio of mass to the bulk volume. Figure3.3 shows that, generally, the bulk density has gradually increased with an increase in pressure. The bulk densities of HPMC K4M and HPMC K4M: PEO WSR N60K (1:1 w/w) are quite close to each other especially at 100, 150 and 200 MPa. However, the bulk density of PEO WSR N60K is quite different from that of HPMC K4M and the physical mixture. HPMC K4M has the highest bulk density. Conversely, Figure3.3b shows that apparent density, ratio of mass to apparent solid volume, have decreased with increase in pressure. At some pressures, the apparent densities of HPMC K4M and PEO WSR N60K are close to each other. The apparent density of HPMC K4M and HPMC K4M: PEO WSR N60K (1:1 w/w) decreases gradually but for PEO WSR N60K initially, there was a sharp decrease from the compression pressure of 50 to 100 MPa and then decreases gradually at further increased pressures. HPMC K4M and HPMC K4M: PEO WSR N60K (1:1 w/w) has the lowest and highest apparent density, respectively.

The porosity profile of matrix tablets (Figure3.3c) shows that porosity has gradually decreased with increase in pressure. For all types of matrix tablets, porosity was highest at 50 MPa and lowest at 250 MPa. Overall, PEO WSR N60K has the highest porosity and HPMC K4M has the lowest. The porosity of HPMC K4M: PEO WSR N60K (1:1 w/w) lies in between the HPMC K4M and PEO WSR N60K.

It is quite evident from the (Figure3.3d) that average pore diameter sharply decreases when the pressure increases from 50 to 100 MPa and then decreases gradually with further increase in pressure except for the HPMC K4M where average pore diameter decreases gradually throughout the increase in pressure. The average pore diameter of HPMC K4M is the lowest

and is highest for PEO WSR N60K while HPMC K4M: PEO WSR N60K (1:1 w/w) based matrix tablets has medium sized pores.

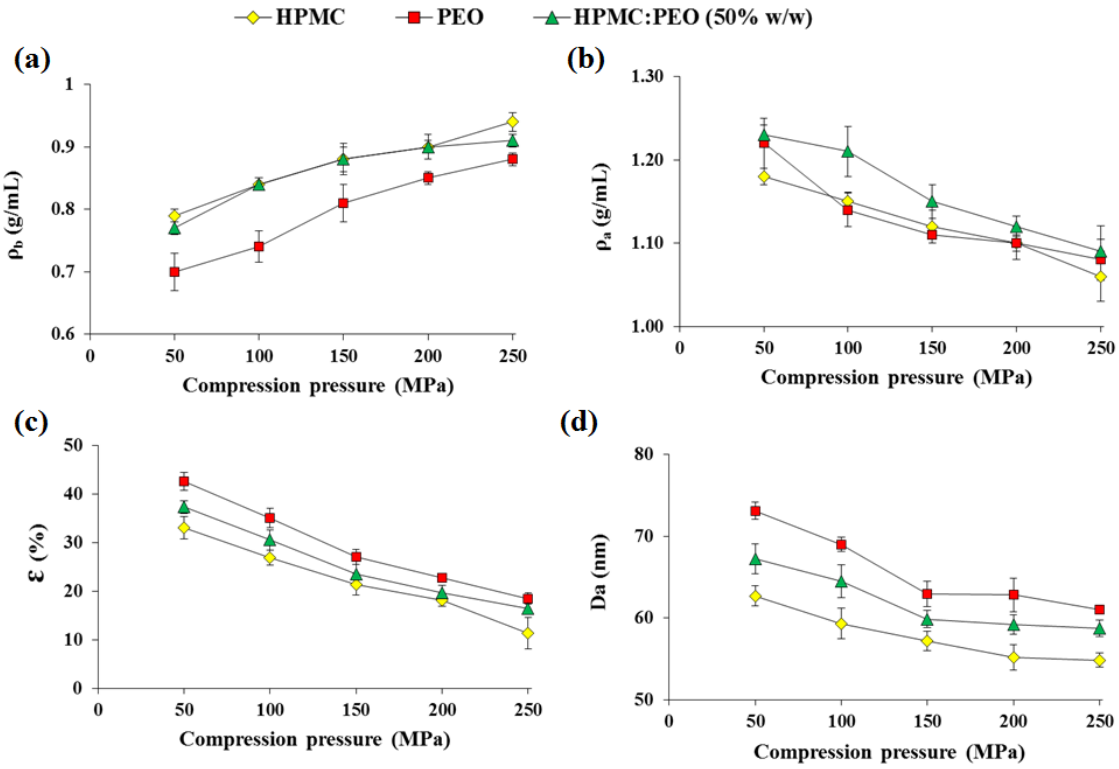

Figure 3.3: Matrix tablet microstructural profile with respect to compression pressure (a) bulk density (b) apparent density (c) porosity (d) average pore diameter.

Moreover, porosity and tensile strength are related to each other as tensile strength affects the porosity (Sebhatu et al., 1999; Tye et al., 2005). A graphical representation of porosity versus tensile strength is given in Figure 3.4a. Generally, the tensile strength decreased with an increase in porosity except for the HPMC K4M that shows quite a different pattern from the rest. It is evident from the Figure 3.4a that initially, tensile strength of HPMC K4M increases with increase in porosity but starts to decrease when the porosity increases further while Figure 3.4 b-c show that tensile strength of PEO WSR N60K and HPMC K4M: PEO WSR N60K (1:1 w/w) decreases gradually with an increase in porosity.

The Ryshkewitch-Duckworth relationship (Duckworth 1953), previously described in section.2.2.6.2, was used to investigate the relationship between tensile strength and porosity. The equation fitting parameters are given in Table 3.2. It is evident that HPMC K4M has the highest (3.50) and PEO WSR N60K has the lowest (2.76) interparticulate bonding capacity (K). Whereas, the tensile strength capacity of HPMC K4M: PEO WSR N60K (1:1 w/w) lies near to the capacity of HPMC K4M.

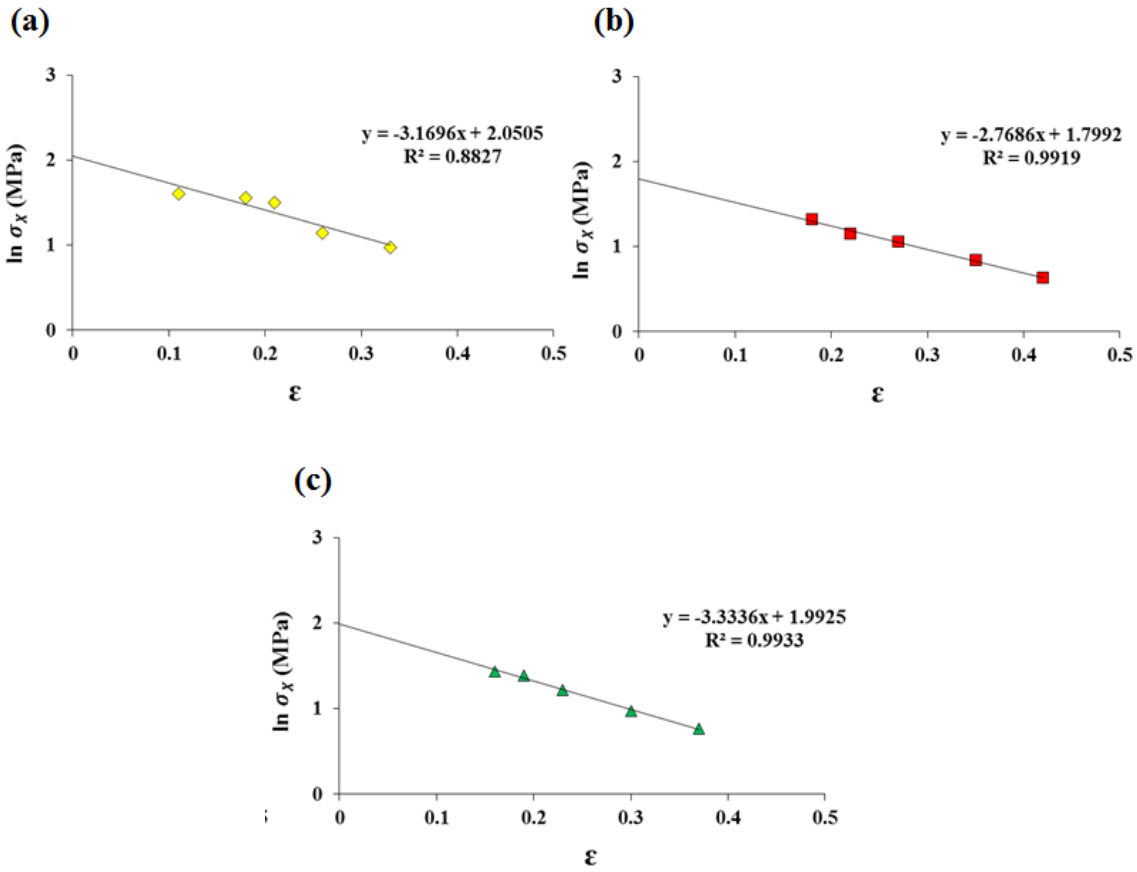

Figure 3.4: Porosity (ε) vs tensile strength relationship for (a) HPMC K4M, (b) PEO WSR N60K and (c) HPMC K4M: PEO WSR N60K (1:1 w/w).

Table 3.2: Fitting parameters from Ryshkewitch-Duckworth relationship.

Matrix tablet type	Fitting parameters		
	K	**σ_y (MPa)**	**R^2**
HPMC K4M	3.50	8.165	0.89
PEO WSR N60K	2.76	6.04	0.99
HPMC K4M:PEO WSR N60K (1:1 w/w)	3.33	7.33	0.99

To characterise the topography of matrix tablets, surface roughness can be used to determine favourable compression attributes (porosity, tensile strength, surface roughness and interparticulate bonding capacity) of hydrophilic polymers which are might be important for successful formulation development (Narayan & Hancock 2003; Ghori et al., 2017). As previously mentioned, compacts are composites of various particles that have surface roughness values which are characteristic of the configuration of their particulate components. As a result, the degree of surface roughness may influence other factors (powder particle bonding and packing) of matrix tablets (Narayan & Hancock 2005).

The values of three dimensional root mean square roughness of all types of matrix tablet were determined by using a quantitative method, atomic force microscopy (AFM). AFM allows data acquisition at very high resolution towards the molecular level. The 3D AFM images of matrix tablet surfaces can be seen in Figure 3.5 - Figure 3.7. It can be seen that increase in compression pressure has a noticeable effect on surface roughness of the matrix tablets i.e. the surface of the matrix tablets matrix has decreased or in other words, it has become smoother with increase in compression pressure. Figure 3.5 shows that the surface of HPMC K4M based matrix tablets was rough at lower pressure but with increase in pressure, the surface became smoother. The

surface of these tablets is smoother at 250 MPa as compared to the other compression pressures. PEO WSR N60K and HPMC K4M: PEO WSR N60K (1:1 w/w) also exhibited the same pattern Figure 3.6 - Figure 3.7. Overall, the surface of HPMC K4M based matrix tablets are smoother at higher compression pressures followed by HPMC K4M: PEO WSR N60K (1:1 w/w) and PEO WSR N60K.

The surface roughness profile of matrix tablets with respect to compression pressure (Figure 3.8) shows that surface roughness of all types of matrix tablets has decreased gradually with increase in compression pressure. PEO WSR N60K has the highest surface roughness and HPMC K4M has the lowest. Surface roughness of HPMC K4M: PEO WSR N60K (1:1 w/w) lies close to that of HPMC K4M at initial compression pressures but at higher compression pressures more closely resembles that of PEO WSR N60K.

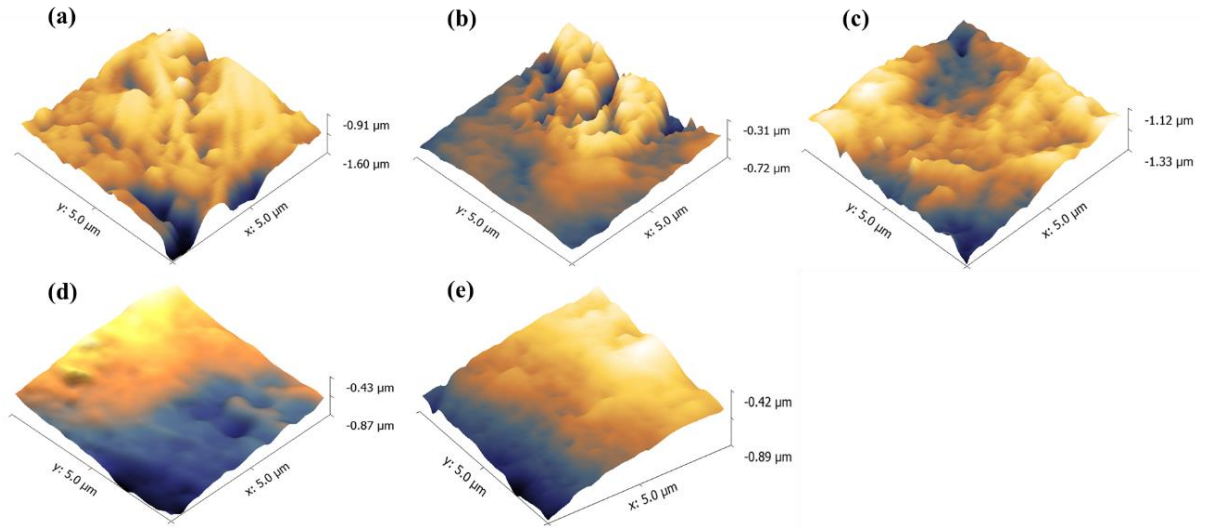

Figure 3.5: AFM surface topographical images of HPMC K4M matrix tablets (a) 50 MPa (b) 100 MPa (c) 150 MPa (d) 200 MPa and (e) 250 MPa.

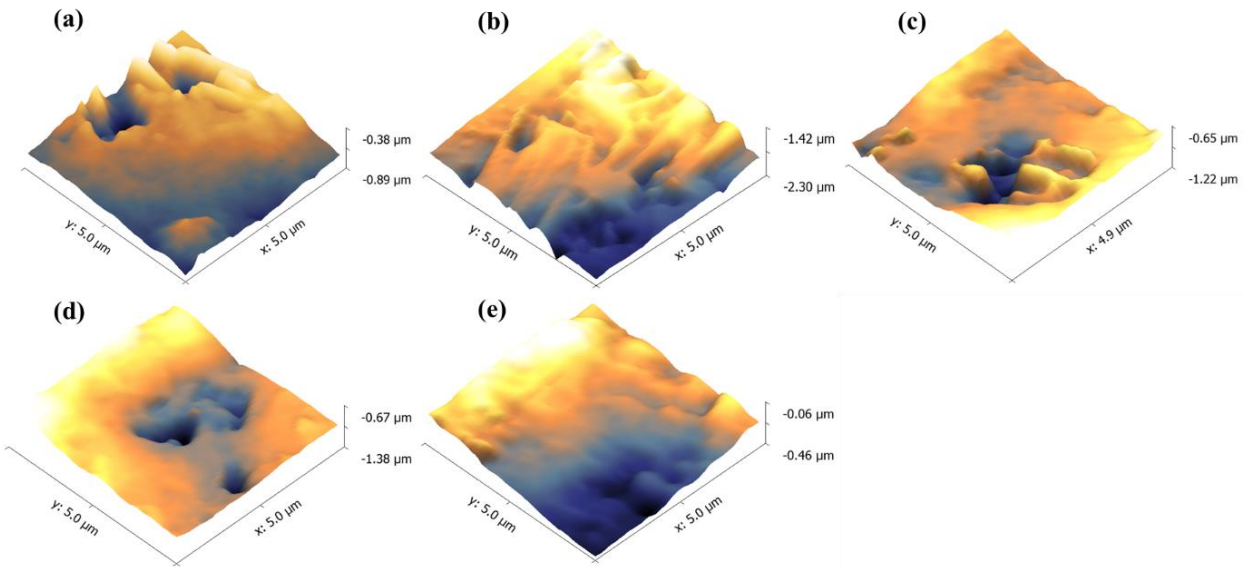

Figure 3.6: AFM surface topographical images of PEO WSR N60K matrix tablets (a) 50 MPa (b) 100 MPa (c) 150 MPa (d) 200 MPa and (e) 250 MPa.

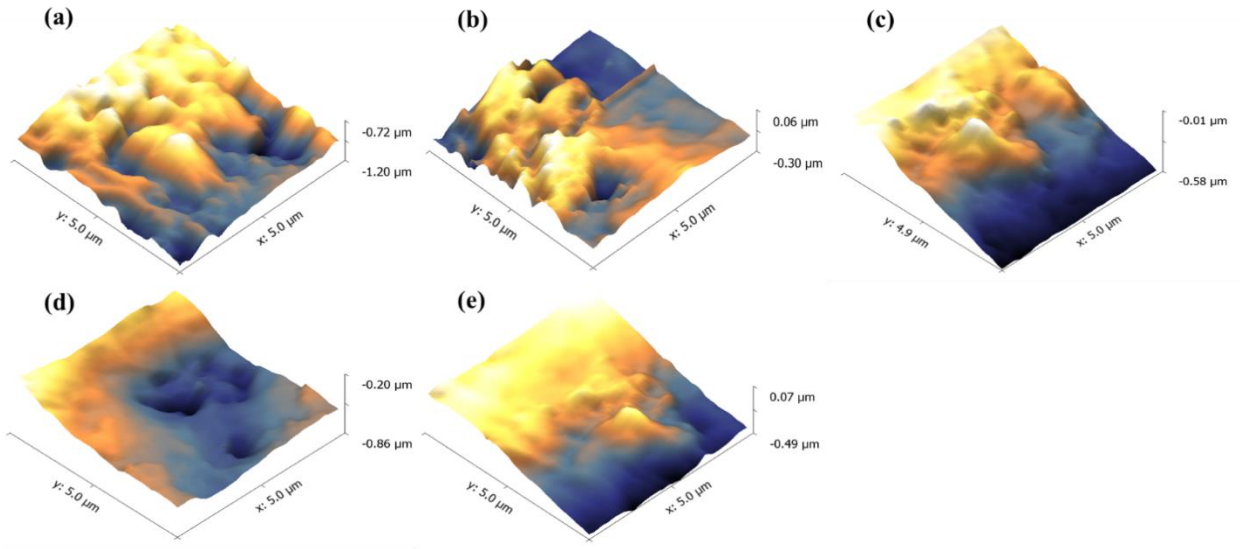

Figure 3.7: AFM surface topographical images of HPMC K4M: PEO WSR N60K (1:1 w/w) matrix tablets (a) 50 MPa (b) 100 MPa (c) 150 MPa (d) 200 MPa and (e) 250 MPa.

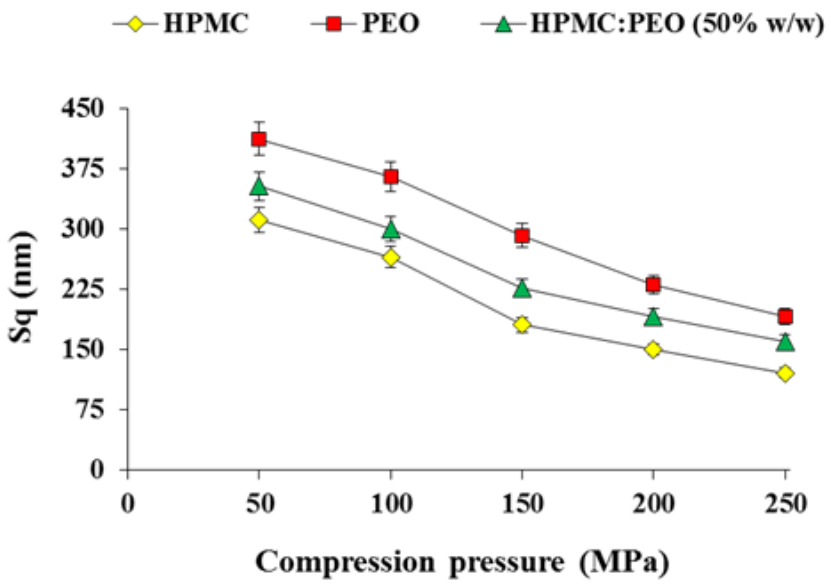

Figure 3.8: Surface roughness profiles of matrix tablets with respect to compression pressure.

3.3- Swelling and erosion studies

The rate of liquid uptake determines the extent of swelling of hydrophilic matrices. Polymer-liquid interaction was investigated using liquid uptake studies. The matrix tablets were immersed in swelling media (de-ionised water) at 37 °C and their response with respect to time is shown in Figure 3.9 a-c, in terms of weight increase (% Swelling, S) due to penetration of liquid. When the aforementioned polymeric matrices were exposed to liquid, at first, wetting occurs at the surface and then gradually progresses through the matrix network. The T_g decreases as the liquid penetrates and as it becomes equal to the temperature of the system (37 °C) it allows the polymeric chains to relax and the penetrant liquid starts acting as a plasticiser (Wan et al., 1995; Viridén et al., 2009). As a result, a viscous so-called gel layer starts to appear across the matrix tablet surface. Moreover, another phenomenon causing the matrices to swell is the osmotic stress applied on the middle region that is located between the inner dry core and the outer gel layer present around the matrix tablet.

A swelling kinetic model known as the Vergnaud (Vergnaud 1993) model was adopted to evaluate the rate and mechanism of swelling of hydrophilic matrices used in this study. This method has been used by various authors to evaluate the swelling kinetics and its equation can be expressed as Eq. 3.1.

$$M = K_w t^n \qquad \text{(Eq. 3.1)}$$

Where, M is the amount of liquid transferred, t is time, K_w is the swelling rate constant and n is the exponent indicating the mechanism of water uptake. The characteristic values of the model were calculated by putting the values in Eq. 3.1 and the results obtained are listed in Table 3.3.

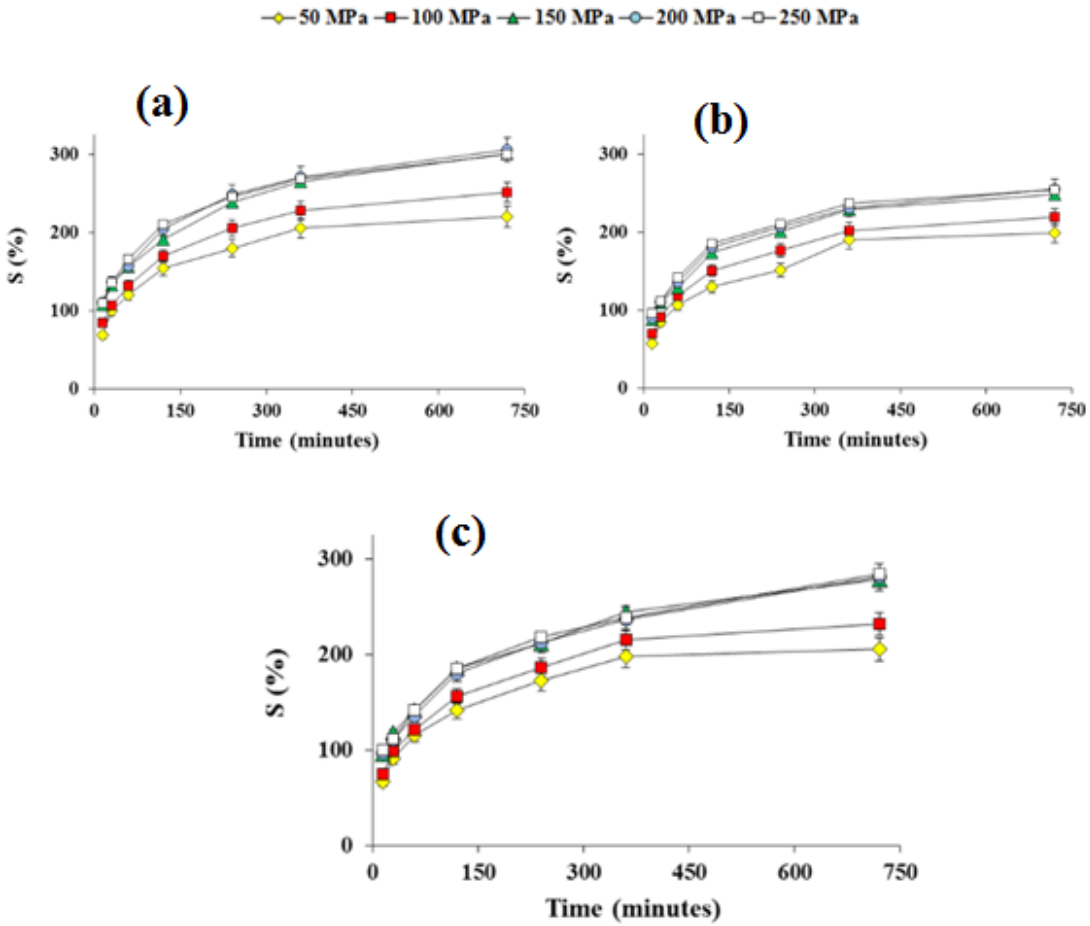

Figure 3.9: Swelling profiles of (a) HPMC K4M, (b) PEO WSR N60K and (c) 1:1 w/w (HPMC K4M: PEO WSR N60K) based matrices.

Table 3.3: Swelling and erosion kinetic parameters (n=3).

Polymer	Compression pressure (MPa)	Swelling kinetics parameters			Matrix erosion parameters	
		K_W	*n*	R^2	K_E	R^2
HPMC K4M	**50**	29.19	0.3314	0.990	0.032	0.999
	100	35.37	0.3166	0.998	0.024	0.997
	150	50.12	0.2831	0.998	0.018	0.993
	200	49.74	0.2879	0.995	0.017	0.994
	250	49.98	0.2855	0.996	0.017	0.996
PEO WSR N60K	**50**	24.37	0.3487	0.997	0.043	0.975
	100	28.51	0.3328	0.992	0.025	0.951
	150	38.49	0.3026	0.993	0.023	0.947
	200	39.13	0.3014	0.992	0.023	0.941
	250	41.54	0.3000	0.990	0.023	0.963
(1:1 w/w) HPMC K4M:PEO WSR N60K	**50**	27.83	0.3335	0.992	0.036	0.982
	100	31.19	0.3281	0.996	0.027	0.961
	150	43.74	0.2924	0.995	0.023	0.956
	200	42.93	0.294	0.990	0.022	0.966
	250	42.41	0.2932	0.989	0.021	0.957

The water uptake data exhibited a good fit to the model with the resultant R^2 values between 0.989-0.990. Ebube et al. (1997) reported that a value of $n < 0.5$ is indicative of diffusion-controlled mechanism in which the rate of diffusion is much slower than the rate of polymer hydration in a matrix tablet. However, when $n = 1$, water diffuses through the matrix at a constant velocity with an advancing liquid front marking the limit of liquid penetration into the matrix. A value of $0.45 < n < 1$ indicates anomalous behaviour in which diffusion of liquid and polymer hydration are of similar magnitude. As the swelling exponent (*n*) values for all the

types of matrices were lower than 0.5 it can be assumed that the kinetics of swelling or water uptake by the matrices follow a diffusion-controlled mechanism.

In hydrophilic polymeric systems, the outer viscous gel layer, formed by the polymeric carrier present on the surface of the matrix tablet, subsequently undergoes erosion over time (Ghori et al., 2014a). The outer gel layer controls the overall erosion rate. This gel layer potentially acts as a barrier that minimises the swelling and subsequently increases polymer dissolution (Ghori et al., 2017). Erosion studies were also carried out on the aforementioned matrix tablets. These matrix tablets were accurately weighed before immersing in swelling media (de-ionised water) at 37 °C. Tablets were removed from swelling media at specific intervals of time to place in the oven and after being dried these tablets were re-weighed. A graph was plotted to show the degree of matrix erosion (% erosion as a function of time) and a simple linear regression model was applied representing slope as an erosion rate (K_E, % min^{-1}). All the erosion kinetics parameters are summarised in Table 3.3 (Ghori et al., 2014a).

It is evident from the swelling profiles (Figure 3.9) that the compression pressure can potentially affect the extent of swelling. The trend was quite similar, which is that increases in overall swelling is noticeable with increasing pressure up to 150 MPa. It is quite evident from the Figure 3.9 that the swelling of HPMC K4M based matrices was lowest at 50 MPa but started to increase as the pressure increased to 100 and 150 MPa. However, beyond this compression pressure, any further increase in pressure had a negligible effect on swelling. Additionally, it can be seen that the HPMC K4M based matrices has the highest while the PEO WSR N60K matrices had lowest swelling and the trend of the swelling in current study was PEO WSR N60K < HPMC K4M:PEO WSR N60K (1:1 w/w) < HPMC K4M. Further, it can be inferred from the swelling kinetic data given in Table 3.3 that the order of swelling rate was PEO WSR N60K < HPMC K4M: PEO WSR N60K (1:1 w/w) < HPMC K4M. PEO WSR N60K based

matrix tablets had the lowest swelling rates and the tablets containing HPMC K4M had highest swelling rates, with the mix having rates between these extremes. The swelling exponent (*n*) values for all types of matrix tablets was less than 0.5 which revealed that swelling or water uptake by matrix tablets follows a diffusion-controlled mechanism.

From these findings, it could be suggested that in the case of HPMC K4M and HPMC K4M: PEO WSR N60K (1:1 w/w) based matrices the increase in the compression pressure up to a certain limit (150 MPa) increased the swelling to its maximum but after that limit further increase in pressure could not maximise the swelling any further. However, in the case of PEO WSR N60K the swelling rate increases with increasing compression pressure over the range studied. Erosion profiles of all matrix tablets Figure 3.10 showed that compression pressure has affected the erosion in the same way as it has affected the swelling but in the opposite pattern, which is, the degree of erosion decreases with increase in pressure to a certain limit that is again similar 150 MPa. The degree of erosion for all types of matrices was highest at 50 MPa but started to decrease as the pressure increased to 100 and 150 MPa. However, beyond this compression pressure, further increase in pressure had negligible effect on degree of erosion irrespective of polymer type used in this research project. Erosion kinetic parameters given in Table 3.3 shows that resultant R^2 values range from 0.941-0.999 and K_E of all types of matrix tablets was highest at 50 MPa but started to decrease with increase in pressure up to 150 MPa. At higher compression pressure of 200 and 250 MPa, further decrease in erosion rate was not observed and in case of HPMC K4M and PEO WSR N60K, it was constant at higher pressures of 200 and 250 MPa. Overall, HPMC K4M has the lowest erosion rate followed by HPMC K4M: PEO WSR N60K (1:1 w/w) and PEO WSR N60K and the trend of erosion in this study was HPMC K4M < HPMC K4M: PEO WSR N60K (1:1 w/w) < PEO WSR N60K.

It could be suggested that increase in compression pressure up to a certain limit (150 MPa) decreases the erosion rate to its minimum but after that limit further increase in pressure could not minimise the erosion any further.

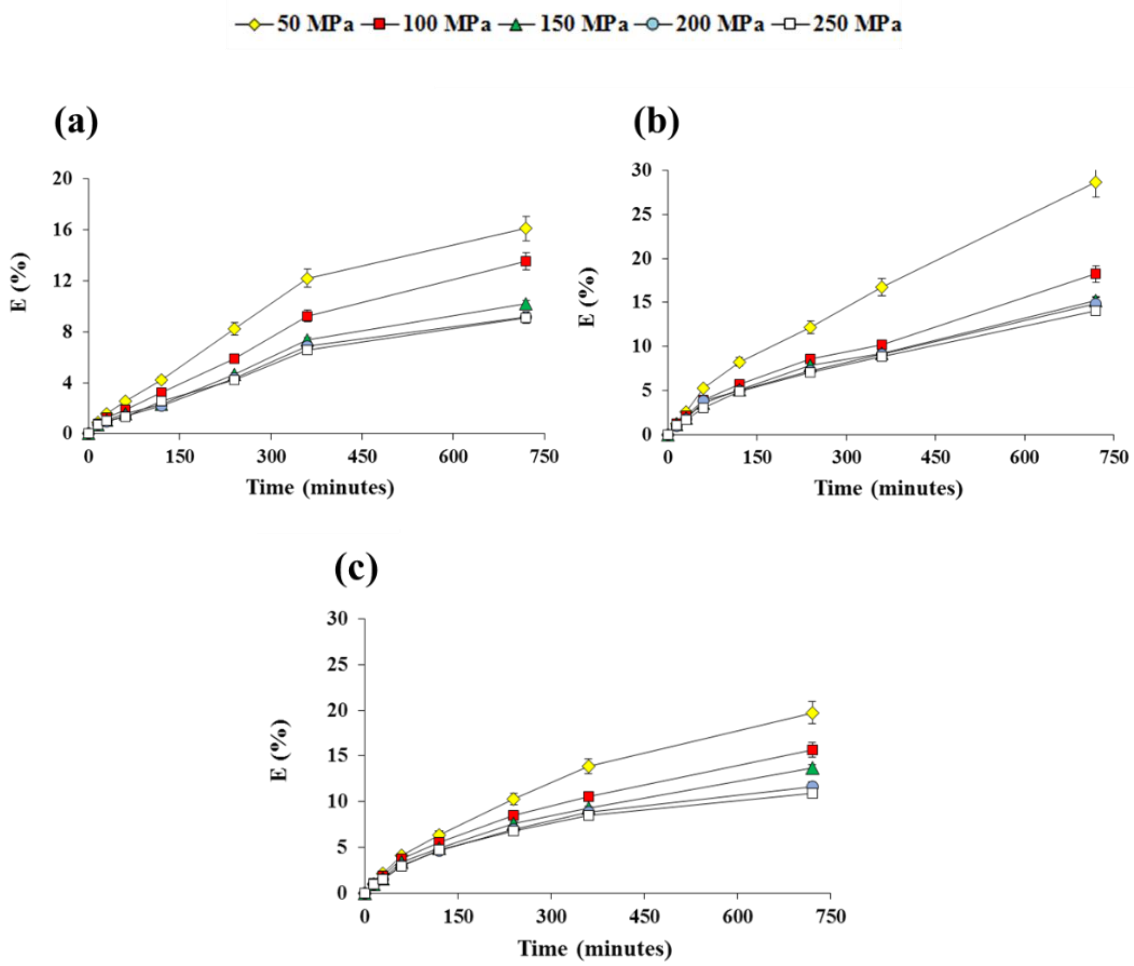

Figure 3.10: Erosion profiles of (a) HPMC K4M, (b) PEO WSR N60K and (c) 1:1 w/w (HPMC K4M: PEO WSR N60K) based matrices.

3.4- Inter-relationship studies

3.4-1. K_E vs K_W

Inter-relationship of swelling and erosion rate of (a) HPMC K4M (b) PEO WSR N60K and (c) 1:1 w/w (HPMC K4M: PEO WSR N60K) based matrices at different compression pressures is shown in Figure 3.11. It is evident that the erosion rate has decreased with an increase in swelling rate. At initial compression pressures, there was a sharp decrease in the erosion rate but at higher pressures, there was a gradual decrease. The R^2 values of this linear relationship, for all types of matrix tablets are given in Table 3.4. The R^2 value of HPMC K4M and HPMC K4M: PEO WSR N60K (1:1 w/w) shows a fairly good relationship between swelling and erosion rate. However, the R^2 value of PEO WSR N60K shows a weak relationship.

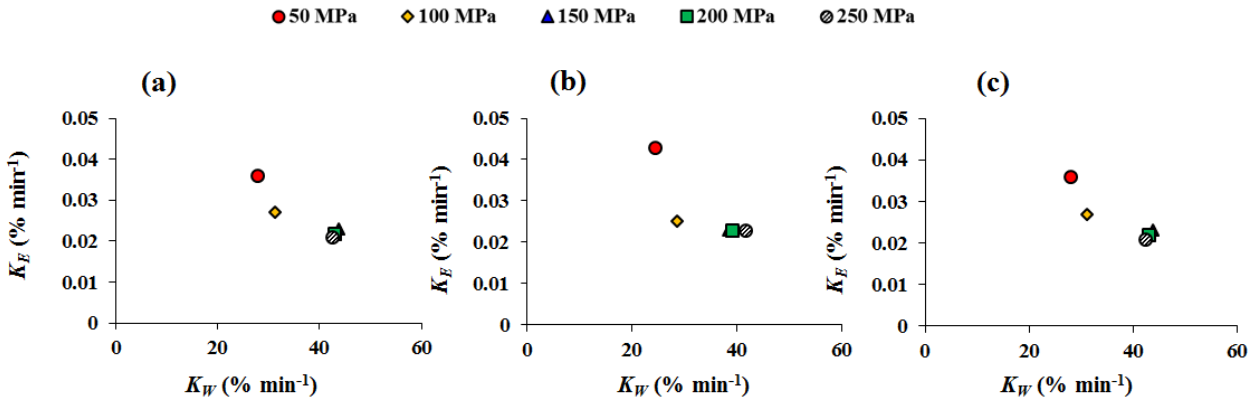

Figure 3.11: Inter-relationship of swelling and erosion rate of (a) HPMC K4M (b) PEO WSR N60K and (c) 1:1 w/w (HPMC K4M: PEO WSR N60K) based matrices at different compression pressures.

Table 3.4: Resultant correlation co-efficient (R^2) values of inter-relationship studies.

Relationship type	R^2		
	HPMC K4M	**PEO WSR N60K**	**HPMC K4M : PEO WSR N60K (1:1 w/w)**
K_E *vs* K_W	0.85	0.65	0.83
K_E *vs* S_q	0.90	0.57	0.89
K_E *vs* D_a	0.95	0.74	0.92
K_W *vs* S_q	0.83	0.93	0.87
K_W *vs* D_a	0.85	0.99	0.96
S_q *vs* D_a	0.96	0.91	0.96

3.4-2. K_E vs S_q

It is evident from Figure 3.12 that erosion rate increases initially with increase in surface roughness but at higher compression pressures a sharp and sudden increase can be noticed. The resultant values Table 3.4 of HPMC K4M shows a good relationship; and for HPMC K4M: PEO WSR N60K (1:1 w/w) it shows a fair relationship while the R^2 value of PEO WSR N60K shows there is a weak relationship between erosion and surface roughness.

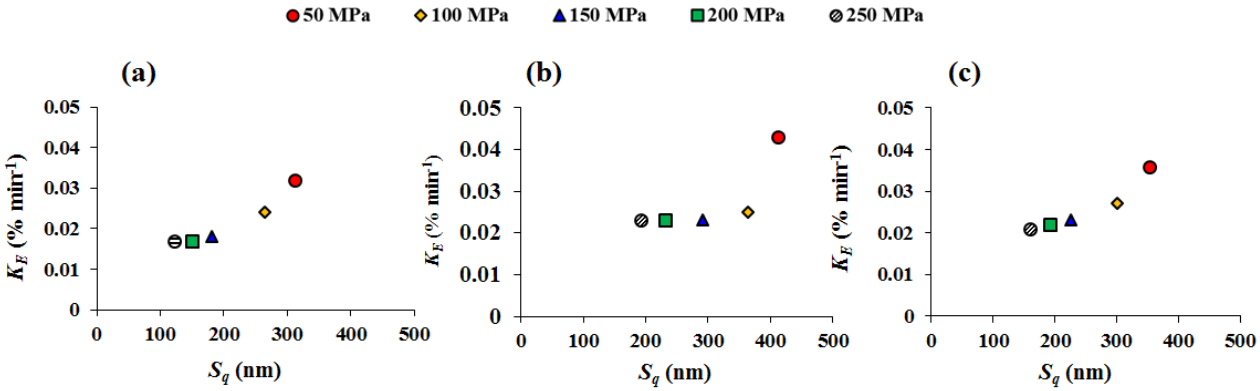

Figure 3.12: Inter-relationship of surface roughness and erosion rate of (a) HPMC K4M (b) PEO WSR N60K and (c) 1:1 w/w (HPMC K4M: PEO WSR N60K) based matrices at different compression pressures.

3.4-3. K_E vs D_a

The relationship graph between erosion rate and average diameter (Figure 3.13) shows erosion rate and pore diameter are directly related to each other i.e. erosion rate decreases with decrease in pore diameter. R^2 value Table 3.4 of HPMC K4M and HPMC K4M: PEO WSR N60K (1:1 w/w) shows a good relationship while R^2 value of PEO WSR N60K shows a weak relationship between erosion rate and pore diameter.

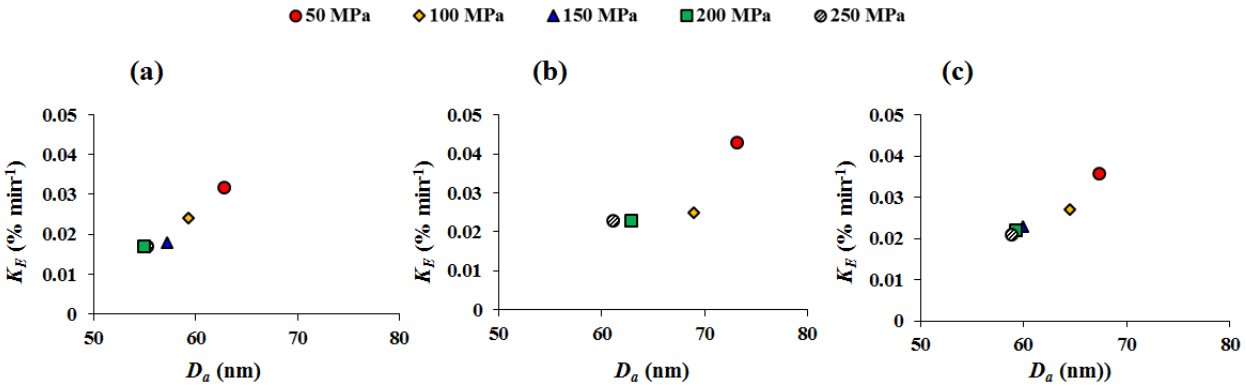

Figure 3.13: Inter-relationship of average pore diameter and erosion rate of (a) HPMC K4M (b) PEO WSR N60K and (c) 1:1 w/w (HPMC K4M:PEO WSR N60K) based matrices at different compression pressures.

3.4-4. K_w vs S_q

Figure 3.14 shows that surface roughness of the tablet has decreased with increase in swelling rate, which indicates an inverse relationship between these two parameters. The resultant value (Table 3.4) of PEO WSR N60K shows a good relationship and for that of HPMC K4M and HPMC K4M: PEO WSR N60K (1:1 w/w) the R^2 value shows a fairly good relationship between swelling rate and surface roughness.

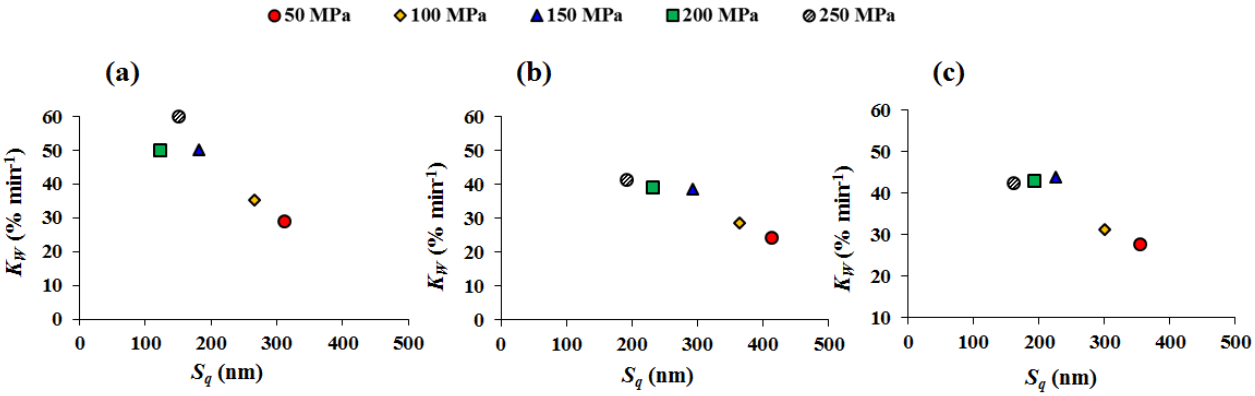

Figure 3.14: Inter-relationship of surface roughness and swelling rate of (a) HPMC K4M (b) PEO WSR N60K and (c) 1:1 w/w (HPMC K4M:PEO WSR N60K) based matrices at different compression pressures.

3.4-5. K_w vs D_a

Average pore diameter decreased with increase in swelling rate indicating an inverse relationship between these two parameters (Figure 3.15). The resultant values given in (Table 3.4) shows that PEO WSR N60K and HPMC K4M: PEO WSR N60K (1:1 w/w) has a good relationship while HPMC K4M has a fairly good relationship.

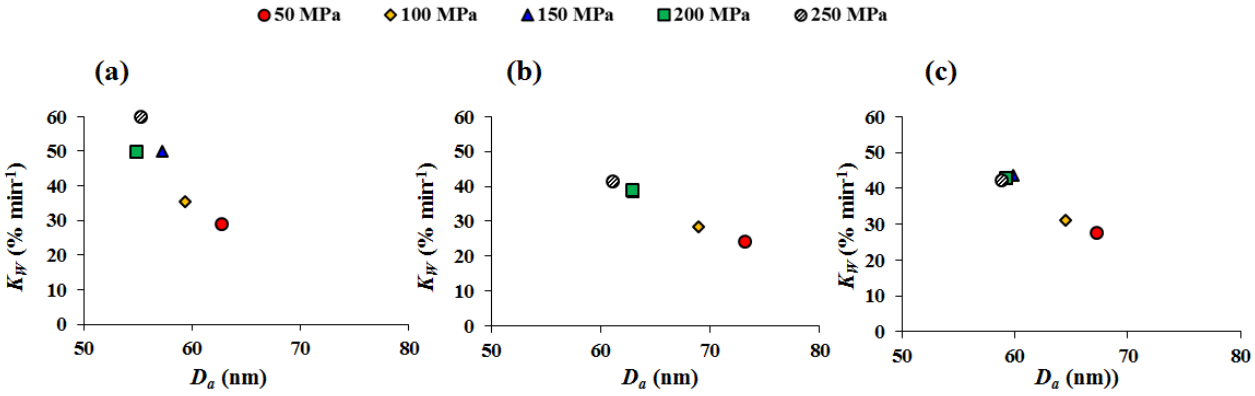

Figure 3.15: Inter-relationship of average pore diameter and swelling rate of (a) HPMC K4M (b) PEO WSR N60K and (c) 1:1 w/w (HPMC K4M:PEO WSR N60K) based matrices at different compression pressures.

3.4-6. S_q vs D_a

There is a direct relationship between surface roughness and average pore diameter, i.e., surface roughness decreases as pore diameter decreases (Figure 3.16). The resultant values (Table 3.4) show that all types of matrix tablets show a good relationship between surface roughness and average pore diameter.

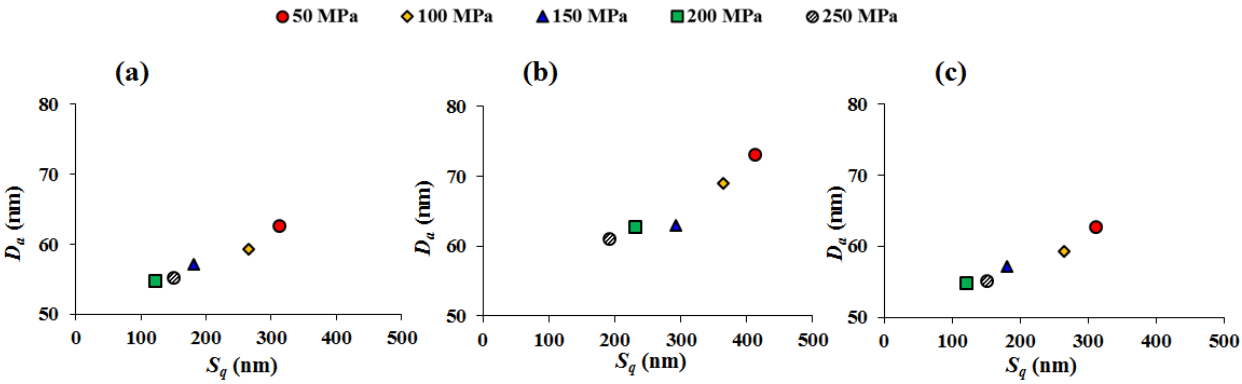

Figure 3.16: Inter-relationship of average pore diameter and surface roughness of (a) HPMC K4M (b) PEO WSR N60K and (c) 1:1 w/w (HPMC K4M:PEO WSR N60K) based matrices at different compression pressures.

4- Conclusions

4. Conclusions

The results show that compression pressure significantly affects the tensile strength, bulk and apparent density, porosity and pore size of all types of matrix tablets. The physical and chemical properties of the particulate material affect their compaction behaviour and the final properties of the compact itself. The pressure during compaction was non-uniform resulting in density variation affecting tensile strength, porosity and other properties and the compact exhibited properties depending upon the interactions and bonding between particles. It is quite evident from the results that these density variations and bonding properties have significant impact on the swelling and erosion properties of matrix tablets.

HPMC K4M: PEO WSR N60K (1:1 w/w) has medium tensile strength and pore size. The porosity of HPMC K4M: PEO WSR N60K (1:1 w/w) lies in between that of compacts of HPMC K4M and PEO WSR N60K. The interparticulate bonding capacity of HPMC K4M: PEO WSR N60K (1:1 w/w) lies near to the capacity of HPMC K4M. It is concluded from the findings presenting in this thesis that porosity and tensile strength are related to each other as tensile strength affects the porosity. Moreover, the results show that compression pressure does affect the swelling and degree of erosion of matrix tablets but in case of HPMC K4M and HPMC K4M: PEO WSR N60K (1:1 w/w) it is imperceptible beyond 150 MPa compression pressure. Moreover, an interrelationship of all the derived compaction attributes showed a relationship with swelling and erosion kinetic parameters. Finally, on the basis of these findings it can be concluded that the tableting attributes can potentially impact the performance and functionally of hydrophilic matrices. Moreover, the information extracted from the current study can be used in the future to develop and adopt strategies for development and further optimization of compressed hydrophilic matrices.

5- Future Works

5. Future Works

There are many areas of potential prospects to expand this work, including;

1. To study the impact of these tableting attributes on the release kinetics of drugs having different solubility characteristics.
2. To study the impact of fasted and fed conditions on the performance and functionality of these matrices.
3. To extrapolate this study to other polymers.

6- References

6. References

ALDERBORN, G., & NYSTROM, C. (1996). Pharmaceutical powder compaction technology. (p. 245). Marcel Dekker, Inc. New York, USA.

ALDERMAN, D. A. 1984. A review of cellulose ethers in hydrophilic matrices for oral controlled-release dosage forms. International Journal of Pharmaceutical Technology and Product Manufacture, 5**,** 1-9.

ARMSTRONG, N. A., & HAINES-NUTT, R. F. (1972). Elastic recovery and surface area changes in compacted powder systems. The Journal of Pharmacy and Pharmacology, 24, Suppl-135.

BANKER, G., PECK, G., JA, S., PIRAKITIKULR, P., & TAYLOR, D. (1981). Evaluation of hydroxypropyl cellulose and hydroxypropyl methyl cellulose as aqueous based film coatings. Drug Development and Industrial Pharmacy, 7(6), 693-716.

BLUNT, L., & JIANG, X. (2003). Advanced techniques for assessment surface topography: development of a basis for 3D surface texture standards "Surfstand". (p. 20). Elsevier, Amsterdam, Netherlands.

CAPPELLO, B., DE ROSA, G., GIANNINI, L., LA ROTONDA, M. I., MENSITIERI, G., MIRO, A., & RUSSO, R. (2006). Cyclodextrin-containing poly (ethyleneoxide) tablets for the delivery of poorly soluble drugs: potential as buccal delivery system. International Journal of Pharmaceutics, 319(1), 63-70.

CARABALLO, I. (2010). Factors affecting drug release from hydroxypropyl methylcellulose matrix systems in the light of classical and percolation theories. Expert Opinion on Drug Delivery, 7(11), 1291-1301.

CHAIBVA, F. A., KHAMANGA, S. M., & WALKER, R. B. (2010). Swelling, erosion and drug release characteristics of salbutamol sulfate from hydroxypropyl methylcellulose-based matrix tablets. Drug Development and Industrial Pharmacy, 36(12), 1497-1510.

CHOWHAN, Z. T. (1980). Role of binders in moisture-induced hardness increase in compressed tablets and its effect on in vitro disintegration and dissolution. Journal of Pharmaceutical Sciences, 69, 1-4.

COLOMBO, P., BETTINI, R., SANTI, P., & PEPPAS, N. A. (2000). Swellable matrices for controlled drug delivery: gel-layer behaviour, mechanisms and optimal performance. Pharmaceutical Science & Technology Today, 3(6), 198-204.

COLOMBO, PAOLO, RUGGERO BETTINI, & PEPPAS, N.A., Observation of swelling process and diffusion front position during swelling in hydroxypropyl methyl cellulose (HPMC) matrices containing a soluble drug. Journal of Controlled Release 61.1 (1999): 83-91.

CONTE, U., & MAGGI, L. (1996) Modulation of the dissolution profiles from Geomatrix® multi-layer matrix tablets containing drugs of different solubility. Biomaterials 17(9): 889-896.

DABBAGH, M. A., FORD, J. L., RUBINSTEIN, M. H., & HOGAN, J. E. (1996). Effects of polymer particle size, compaction pressure and hydrophilic polymers on drug release from matrices containing ethylcellulose. International Journal of Pharmaceutics, 140(1), 85-95.

DAHL, T. C., CALDERWOOD, T., BORMETH, A., TRIMBLE, K., & PIEPMEIER, E. (1990). Influence of physico-chemical properties of hydroxypropyl methylcellulose on naproxen release from sustained release matrix tablets. Journal of Controlled Release, 14(1), 1-10.

DALY, P. B., DAVIS, S. S., & KEIMERLEY, J. W. (1984). The effect of anionic surfactants on the release of chlorpheniramine from a polymer matrix tablet. International Journal of Pharmaceutics, 18(1-2), 201-205.

DAS, N. G., & DAS, S. K. (2003). Controlled release of oral dosage forms. Pharmaceutical Technology, 15, 10-17.

DE ROBERTIS, S., BONFERONI, M. C., ELVIRI, L., SANDRI, G., CARAMELLA, C., & BETTINI, R. (2015). Advances in oral controlled drug delivery: the role of drug–polymer and interpolymer non-covalent interactions. Expert Opinion on Drug Delivery, 12(3), 441-453.

DENNY, P. J. (2002) Compaction equations: a comparison of the Heckel and Kawakita equations. Powder Technology 127.2: 162-172.

DOW (2002). Methocel cellulose ethers technical handbook. The Dow Chemical Company, Midland, Michigan, USA. Retrieved on 10th November 2017 from; http://msdssearch.dow.com/PublishedLiteratureDOWCOM/dh_096d/0901b8038096d9ff.pdf

DUCKWORTH, W. (1953). Discussion of Ryshkewitch paper by Winston Duckworth. Journal of American Ceramic Society., 36, 68-69.

EBUBE, N. K., HIKAL, A. H., WYANDT, C. M., BEER, D. C., MILLER, L. G., & JONES, A. B. (1997). Sustained release of acetaminophen from heterogeneous matrix tablets: influence of polymer ratio, polymer loading, and co-active on drug release. Pharmaceutical Development and Technology, 2(2), 161-170.

EBUBE, NKERE K., & JONES, A.B., (2004)Sustained release of acetaminophen from a heterogeneous mixture of two hydrophilic non-ionic cellulose ether polymers. International Journal of Pharmaceutics 272 (1): 19-27.

ENTWISTLE, C. A., & ROWE, R.C., (1979) Plasticization of cellulose ethers used in the film coating of tablets. Journal of Pharmacy and Pharmacology 31(1): 269-272.

ESCUDERO, J. J., FERRERO, C., & JIMÉNEZ-CASTELLANOS, M. R. (2010). Compaction properties, drug release kinetics and fronts movement studies from matrices combining mixtures of swellable and inert polymers. II. Effect of HPMC with different degrees of methoxy/hydroxypropyl substitution. International Journal of Pharmaceutics, 387(1), 56-64.

FARRIS, S., INTROZZI, L., BIAGIONI, P., HOLZ, T., SCHIRALDI, A., & PIERGIOVANNI, L. (2011). Wetting of biopolymer coatings: contact angle kinetics and image analysis investigation. Langmuir, 27(12), 7563-7574.

FELL, J. T., & NEWTON, J.M., (1970) Determination of tablet strength by the diametral-compression test. Journal of Pharmaceutical Sciences 59(5): 688-691.

FERRERO, C., MASSUELLE, D., & DOELKER, E. (2010). Towards elucidation of the drug release mechanism from compressed hydrophilic matrices made of cellulose ethers. II. Evaluation of a possible swelling-controlled drug release mechanism using dimensionless analysis. Journal of Controlled Release, 141(2), 223-233.

FORD, J. L., RUBINSTEIN, M. H., & HOGAN, J. E. (1985). Formulation of sustained release promethazine hydrochloride tablets using hydroxypropyl-methylcellulose matrices. International Journal of Pharmaceutics, 24(2-3), 327-338.

GHORI, M. U. (2014). Release kinetics, compaction and electrostatic properties of hydrophilic matrices (p. 100). Doctoral dissertation, University of Huddersfield Respository. Retrieved on 15th November 2017 from; http://eprints.hud.ac.uk/id/eprint/24269/

GHORI, M. U., GINTING, G., SMITH, A. M., & CONWAY, B. R. (2014a). Simultaneous quantification of drug release and erosion from HPMC hydrophilic matrices. International Journal of Pharmaceutics, 465(1), 405-412.

GHORI, M. U., ŠUPUK, E., & CONWAY, B. R. (2014b). Tribo-electric charging and adhesion of cellulose ethers and their mixtures with flurbiprofen. European Journal of Pharmaceutical Sciences, 65, 1-8.

GHORI, M. U., & CONWAY, B. R. (2015). Hydrophilic Matrices for Oral Control Drug Delivery. American Journal of Pharmacological Sciences, 3(5), 103-109.

GHORI, M. U., & CONWAY, B. R. (2016). Powder Compaction: Compression Properties of Cellulose Ethers. British Journal of Pharmacy, 1(1).

GHORI, M. U., GROVER, L. M., ASARE-ADDO, K., SMITH, A. M., & CONWAY, B. R. (2017a). Evaluating the swelling, erosion, and compaction properties of cellulose ethers. Pharmaceutical Development and Technology, 1-15.

GHORI, M. U., MOHAMMAD, M. A., RUDRANGI, S. R. S., FLEMING, L. T., MERCHANT, H. A., SMITH, A. M., & CONWAY, B. R. (2017b). Impact of purification on physicochemical, surface and functional properties of okra biopolymer. Food Hydrocolloids. 71, 311-320. 6

GOVEDARICA, B., INJAC, R., & SRCIC, S. (2009). Formulation and evaluation of immediate release tablets with different types of paracetamol powders prepared by direct compression. African Journal of Pharmacy and Pharmacology, 5(1), 31-41.

HECKEL, R. W. (1961). An analysis of powder compaction phenomena. Transaction of the Metallurgical Society of AIME, 221, 1001-1008.

HEWLETT, K. O., L'HOTE-GASTON, J., RADLER, M., & SHULL, K. R. (2012). Direct measurement of the time-dependent mechanical response of HPMC and PEO compacts during swelling. International Journal of Pharmaceutics, 434(1), 494-501.

HIREMATH, P. S., & SAHA, R. N. (2008). Oral controlled release formulations of rifampicin. Part II: effect of formulation variables and process parameters on in vitro release. Drug Delivery, 15(3), 159-168.

HIREMATH, S. P., & SAHA, R. N. (2004). Design and study of rifampicin oral controlled release formulations. Drug Delivery, 11(5), 311-317.

HU, A., CHEN, C., MANTLE, M. D., WOLF, B., GLADDEN, L. F., RAJABI-SIAHBOOMI, A., & MELIA, C. D. (2017). The properties of HPMC: PEO extended release hydrophilic matrices and their response to ionic environments. Pharmaceutical Research, 34(5), 941-956.

ITIOLA, O. A. (1991). Formulation effects on the mechanical properties of metronidazole tablets. Journal of Pharmacy and Pharmacology, 43, 145.

JAMZAD, S., TUTUNJI, L., & FASSIHI, R. (2005). Analysis of macromolecular changes and drug release from hydrophilic matrix systems. International Journal of Pharmaceutics, 292(1), 75-85.

KABANDA, L., LEFEBVRE, R. A., VAN BREE, H. J., & REMON, J. P. (1994). In vitro and in vivo evaluation in dogs and pigs of a hydrophilic matrix containing propylthiouracil. Pharmaceutical Research, 11(11), 1663-1668.

KAIALY, W., & BELLO, H. (2016). Effect of polyethylene oxide concentration and particle size on modulating the release of diltiazem HCl from liquisolid tablet matrices. In-proceddings of 1st International Electronic Conference on Oral Drug Delivery, 15-29 November 2016, UK.

KAREHILL, P. G., GLAZER, M., & NYSTRÖM, C. (1990). Studies on direct compression of tablets. XXIII. The importance of surface roughness for the compactability of some directly compressible materials with different bonding and volume reduction properties. International Journal of Pharmaceutics, 64(1), 35-43.

KAVANAGH, N., & CORRIGAN, O. I. (2004). Swelling and erosion properties of hydroxypropylmethylcellulose (HPMC) matrices—influence of agitation rate and dissolution medium composition. International Journal of Pharmaceutics, 279(1), 141-152.

KAWAKITA, K., & LÜDDE, K. H. (1971). Some considerations on powder compression equations. Powder Technology, 4(2), 61-68.

LI, C. L., MARTINI, L. G., FORD, J. L., & ROBERTS, M. (2005). The use of HPMC in oral drug delivery. Journal of Pharmacy and Pharmacology, 57(5), 533-546.

LOTFIPOUR, F., NOKHODCHI, A., SAEEDI, M., NOROUZI-SANI, S., SHARBAFI, J., & SIAHI-SHADBAD, M. R. (2004). The effect of hydrophilic and lipophilic polymers and fillers on the release rate of atenolol from HPMC matrices. II Farmaco, 59(10), 819-825.

MA, L., DENG, L., & CHEN, J. (2014). Applications of poly (ethylene oxide) in controlled release tablet systems: a review. Drug Development and Industrial Pharmacy, 40(7), 845-851.

MADERUELO, C., ZARZUELO, A., & LANAO, J. M. (2011). Critical factors in the release of drugs from sustained release hydrophilic matrices. Journal of Controlled Release, 154(1), 2-19.

MAGGI, L., BRUNI, R., & CONTE, U. (2000). High molecular weight polyethylene oxides (PEO) as an alternative to HPMC in controlled release dosage forms. International Journal of Pharmaceutics, 195(1), 229-238.

MAHALINGAM, R., JASTI, B., BIRUDARAJ, R., STEFANIDIS, D., KILLION, R., ALFREDSON, T., & LI, X. (2009). Evaluation of polyethylene oxide compacts as gastroretentive delivery systems. AAPS PharmSciTech, 10(1), 98-103.

MIRANDA, A., MILLÁN, M., & CARABALLO, I. (2007). Investigation of the influence of particle size on the excipient percolation thresholds of HPMC hydrophilic matrix tablets. Journal of Pharmaceutical Sciences, 96(10), 2746-2756.

MIRO, A., RONDINONE, A., NAPPI, A., UNGARO, F., QUAGLIA, F., & LA ROTONDA, M. I. (2009). Modulation of release rate and barrier transport of diclofenac incorporated in hydrophilic matrices: role of cyclodextrins and implications in oral drug delivery. European Journal of Pharmaceutics and Biopharmaceutics, 72(1), 76-82.

MITCHELL, K., FORD, J. L., ARMSTRONG, D. J., ELLIOTT, P. N. C., ROSTRON, C., & HOGAN, J. E. (1993). The influence of concentration on the release of drugs from gels and matrices containing Methocel®. International Journal of Pharmaceutics, 100(1-3), 155-163.

MP-ADVISORS. (2014) Innovative drug delivery systems opportunities for generic & specialty pharmaceutical companies. Retrieved on 5th November 2017 from; http://www.reportsnreports.com/reports/275193-innovative-drug-delivery-systems-opportunities-for-generic-specialty-pharmaceutical-companies.html

MRSNY, R. J. (2012). Oral drug delivery research in Europe. Journal of controlled release, 161(2), 247-253.

NAKANO, M., OHMORI, N., OGATA, A., SUGIMOTO, K., TOBINO, Y., IWAOKU, R., & JUNI, K. (1983). Sustained release of theophylline from hydroxypropylcellulose tablets. Journal of Pharmaceutical Sciences, 72(4), 378-380.

NARAYAN, P., & HANCOCK, B. C. (2003). The relationship between the particle properties, mechanical behavior, and surface roughness of some pharmaceutical excipient compacts. Materials Science and Engineering: A, 355(1), 24-36.

NARAYAN, P., & HANCOCK, B. C. (2005). The influence of particle size on the surface roughness of pharmaceutical excipient compacts. Materials Science and Engineering: A, 407(1), 226-233.

NOKHODCHI, A., FORD, J. L., ROWE, P. H., & RUBINSTEIN, M. H. (1996). The effects of compression rate and force on the compaction properties of different viscosity grades of hydroxypropylmethylcellulose 2208. International Journal of Pharmaceutics, 129(1-2), 21-31.

NYSTRÖM, C., ALDERBORN, G., DUBERG, M., & KAREHILL, P. G. (1993). Bonding surface area and bonding mechanism-two important factors fir the understanding of powder comparability. Drug Development and Industrial Pharmacy, 19(17-18), 2143-2196.

OMIDIAN H. & PARK K. (2011). Hydrogels. In SIEPMANN, J., SIEGEL, R. A., & RATHBONE, M. J. (Eds.) Fundamentals and applications of controlled release drug delivery (pp. 103-107). Springer Science & Business Media.al of Pharmacological Sciences, Berlin, Germany.

ORLU, M., CEVHER, E., & ARAMAN, A. (2006). Design and evaluation of colon specific drug delivery system containing flurbiprofen microsponges. International Journal of Pharmaceutics, 318(1), 103-117.

QUINTEN, T., DE BEER, T., ALMEIDA, A., VLASSENBROECK, J., VAN HOOREBEKE, L., REMON, J. P., & VERVAET, C. (2011). Development and evaluation of injection-molded sustained-release tablets containing ethylcellulose and polyethylene oxide. Drug Development and Industrial Pharmacy, 37(2), 149-159.

RAVI, P. R., GANGA, S., & SAHA, R. N. (2008). Design and in vitro evaluation of zidovudine oral controlled release tablets prepared using hydroxypropyl methylcellulose. Chemical and Pharmaceutical Bulletin, 56(4), 518-524.

REYNOLDS, T. D., MITCHELL, S. A., & BALWINSKI, K. M. (2002). Investigation of the effect of tablet surface area/volume on drug release from hydroxypropylmethylcellulose controlled-release matrix tablets. Drug Development and Industrial Pharmacy, 28(4), 457-466.

REZA, M. S., QUADIR, M. A., & HAIDER, S. S. (2003). Comparative evaluation of plastic, hydrophobic and hydrophilic polymers as matrices for controlled-release drug delivery. Journal of Pharmacy and Pharmaceutical Sciences, 6(2), 282-91.

ROWE, R. C., SHESKEY, P. J., & WELLER, P. J. (Eds.). (2006). Handbook of pharmaceutical excipients (Vol. 6). Pharmaceutical Press, London, UK. Retrieved on 9th November 2017 from; https://www.medicinescomplete.com/mc/excipients/current/1001943596.htm?q=polyethylene%20oxide&t=search&ss=text&tot=31&p=1#_hit

SEBHATU, T., & ALDERBORN, G. (1999). Relationships between the effective interparticulate contact area and the tensile strength of tablets of amorphous and crystalline lactose of varying particle size. European Journal of Pharmaceutical sciences, 8(4), 235-242.

SHOKRI, J., & ADIBKIA, K. (2013). Application of cellulose and cellulose derivatives in pharmaceutical industries. In Cellulose-Medical, Pharmaceutical and Electronic Applications (pp. 48-50). InTech, Croatia.

SIMÓ, C., CIFUENTES, A., & GALLARDO, A. (2003). Drug delivery systems: polymers and drugs monitored by capillary electromigration methods. Journal of Chromatography B, 797(1), 37-49.

TALUKDAR, M. M., & KINGET, R. (1997). Comparative study on xanthan gum and hydroxypropylmethyl cellulose as matrices for controlled-release drug delivery. II. Drug diffusion in hydrated matrices. International Journal of Pharmaceutics, 151(1), 99-107.

TALUKDAR, M. M., MICHOEL, A., ROMBAUT, P., & KINGET, R. (1996). Comparative study on xanthan gum and hydroxypropylmethyl cellulose as matrices for controlled-release drug delivery I. Compaction and in vitro drug release behaviour. International Journal of Pharmaceutics, 129(1-2), 233-241.

TIWARI, S. B., MURTHY, T. K., PAI, M. R., MEHTA, P. R., & CHOWDARY, P. B. (2003). Controlled release formulation of tramadol hydrochloride using hydrophilic and hydrophobic matrix system. AAPS Pharmscitech, 4(3), 18-23.

TONG W.Q. & WEN H. (2008) Preformulation Aspects of Insoluble Compounds. In LIU, R. (Ed.). Water-insoluble drug formulation 3rd edition. (p. 70). CRC press. USA.

TYE, C. K., SUN, C. C., & AMIDON, G. E. (2005). Evaluation of the effects of tableting speed on the relationships between compaction pressure, tablet tensile strength, and tablet solid fraction. Journal of Pharmaceutical Sciences, 94(3), 465-472.

VELASCO, M. V., FORD, J. L., ROWE, P., & RAJABI-SIAHBOOMI, A. R. (1999). Influence of drug: hydroxypropylmethylcellulose ratio, drug and polymer particle size and compression force on the release of diclofenac sodium from HPMC tablets. Journal of Controlled Release, 57(1), 75-85.

VERGNAUD, J. M. (1993). Liquid transport controlled release processes in polymeric materials: applications to oral dosage forms. International Journal of Pharmaceutics, 90(2), 89-94.

VIRIDÉN, A., WITTGREN, B., & LARSSON, A. (2009). Investigation of critical polymer properties for polymer release and swelling of HPMC matrix tablets. European Journal of Pharmaceutical Sciences, 36(2), 297-309.

VIRIDÉN, A., WITTGREN, B., & LARSSON, A. (2009). Investigation of critical polymer properties for polymer release and swelling of HPMC matrix tablets. European Journal of Pharmaceutical Sciences, 36(2), 297-309.

WAN, L. S. C., HENG, P. W. S., & WONG, L. F. (1995). Matrix swelling: a simple model describing extent of swelling of HPMC matrices. International Journal of Pharmaceutics, 116(2), 159-168.

WASHBURN, E. W. (1921). Note on a method of determining the distribution of pore sizes in a porous material. Proceedings of the National Academy of Sciences, 7(4), 115-116.

WEN, X., NOKHODCHI, A., & RAJABI-SIAHBOOMI, A. (2010). Oral extended release hydrophilic matrices: formulation and design. In Oral Controlled Release Formulation Design and Drug Delivery: Theory to Practice (pp 89). John Wiley & Sons, New Jersey, United States

WERTZ, J. L., MERCIER, J. P., & BÉDUÉ, O. (2010). Cellulose science and technology (p. 148). EPFL Press, USA.

WU, N., WANG, L. S., TAN, D. C. W., MOOCHHALA, S. M., & YANG, Y. Y. (2005). Mathematical modeling and in vitro study of controlled drug release via a highly swellable and dissoluble polymer matrix: polyethylene oxide with high molecular weights. Journal of Controlled Release, 102(3), 569-581.

YANG, L., VENKATESH, G., & FASSIHI, R. (1996). Characterization of compressibility and compactibility of poly (ethylene oxide) polymers for modified release application by compaction simulator. Journal of Pharmaceutical Sciences, 85(10), 1085

ZHANG, Y., LAW, Y., & CHAKRABARTI, S. (2003). Physical properties and compact analysis of commonly used direct compression binders. AAPS PharmsciTech, 4(4), 489-499.