The Application of Microwave Heating Methods in Pharmaceutical Formulations

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The Application of Microwave Heating Methods in Pharmaceutical Formulations

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I certify that this work has not been accepted in substance for any degree, and is not concurrently submitted for any degree other than that of Doctor of Philosophy (PhD) of the University of Huddersfield. I also declare that this work is the result of my own investigations except where otherwise stated.

Quorum, ita texturae ceciderunt mutua contra ut cava conveniant plenis haec illius illa huiusque inter se, iunctura haec optima constat (Titus Lucretius Caro, 96-55 BC, De Rerum Natura, Liber VI).

Bodies, that interact in structural harmony to fill each other's voids, combine most perfectly (Translation by James Grant, 1896-1966, English poet).

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Many thanks go to the technical staff at the Department of Chemical and Biological Sciences at the University of Huddersfield.

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This thesis is dedicated to the memory of my father,
Robert Bedford.

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Abstract

This study investigated the potential application of formulating pharmaceutical products using microwave heating methods alongside associated analytical investigations. Firstly, the interaction between three functionally related drugs, ibuprofen, ketoprofen and flurbiprofen, with two distinct forms of cyclodextrin at three temperatures, 298, 303 and 310K was investigated using isothermal titration calorimetry (ITC). In all cases, the associated changes in Gibbs free energy, enthalpy, and entropy are presented along with the stoichiometry and binding constant. It was found that binding always occurred at a 1:1 ratio with an associated negative enthalpy and Gibbs free energy with the formation of the complex enthalpically, rather than entropically driven. The data further demonstrated a clear relationship between the thermodynamic behaviour and log*P* of the drug molecules and provides an insight into the chemistry of drug-excipient binding for the compounds under investigation in this work.

Secondly, four drugs, ibuprofen, ketoprofen, flurbiprofen and paracetamol were formulated using microwave and conventional heating, with and without the presence of water, with four excipients, namely, stearic acid (SA), β-cyclodextrin (BCD), 2-(hydroxypropyl)-β-cyclodextrin (2HPBCD) and polyvinylpyrrolidone (PVP). Three different analytical techniques were employed to determine whether the formulation method made a significant difference to the appearance and behaviour of the product. For example, the thermal behaviour of the drug and excipient, was investigated by differential scanning calorimetry (DSC). Scanning electron microscopy was utilised to determine if the formulation method illustrated any physical differences between the formulations and lastly, a thermal activity monitor was used to investigate the stability of the different formulations. Overall, it was found that the formulation method can make a significant difference to the character of the resultant formulations with a change in thermal behaviour or physical appearance observed in certain formulations but with a consistent stability seen across all products.

Lastly, each of the resultant formulations were subjected to dissolution analysis to determine if the presence of water or choice of heating method, i.e. conventional heating vs. microwave heating affected the dissolution profile obtained. It was found that in the majority of cases water increased drug dissolution, which may have occurred because of a reduction in particle size. In summary, the application of microwave heating for pharmaceutical formulations has been thoroughly investigated and found to be a potential alternative to conventional heating with several distinct benefits for industry and the patient.

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Chapter One

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Introduction

Chapter One

1:1 What are pharmaceuticals?

The pharmaceutical industry covers many subject areas, which are all associated with converting drugs into medicines in the most efficient and effective way. Therefore the definition of pharmaceuticals is the formulation of a drug, also referred to as medicine or medication, which can be loosely defined as any chemical substance intended for use in the medical diagnosis, cure, treatment, or prevention of disease. However to get the medicine to this stage many problems may be encountered that are either associated with the drug, for example stability and solubility, or the formulation method[1]. Consequently it is important to start with, and understand, any problems that may be associated with each candidate drug. A major problem is that of aqueous solubility, as low solubility may limit the bioavailability of the drug. Aqueous solubility is a crucial molecular property for successful drug development as it is a key factor governing drug access to biological membranes[1].

A scientific framework that may be used for guidance and help determining the solubility of a drug is a called the Biopharmaceutical Classification System (BCS). This classification system, along with *in vitro* dissolution of the drug product, has the following established parameters[1-2]:

1. Class one: High permeability and high solubility
2. Class two: High permeability and low solubility
3. Class three: Low permeability and high solubility
4. Class four: Low permeability and low solubility.

The fundamental basis for the BCS was established by Dr Gordon Amidon[2], and a drug substance can be considered highly soluble when the largest dose of a compound is soluble in < 250 mL of water over a pH range of 1.0 to 7.5. Drugs can be classed as highly permeable when the compound demonstrates > 90% absorption of the administered dose[2]. Once all the possible problems associated with the drug itself have been investigated, the next stage in drug development is to look at the most effective way of formulating the drug to produce a medicine[2].

1.2 How drugs are delivered

Medicines are drug delivery systems and research must be continuously undertaken to ensure that these medicines offer the most efficient, safe and convenient way of administering the drugs incorporated in them to the site of action[1].

1.2.1 The therapeutic window

The therapeutic window or zone is a way of estimating the dosage of a drug which stays within a range that is safe for the patient. In other words, it is the dosage of a medication that gives a desired effect (effective dose), is above a level where the drug is ineffective (pain zone) but below levels where adverse effects may be illustrated (Figure 1.2.1.1).

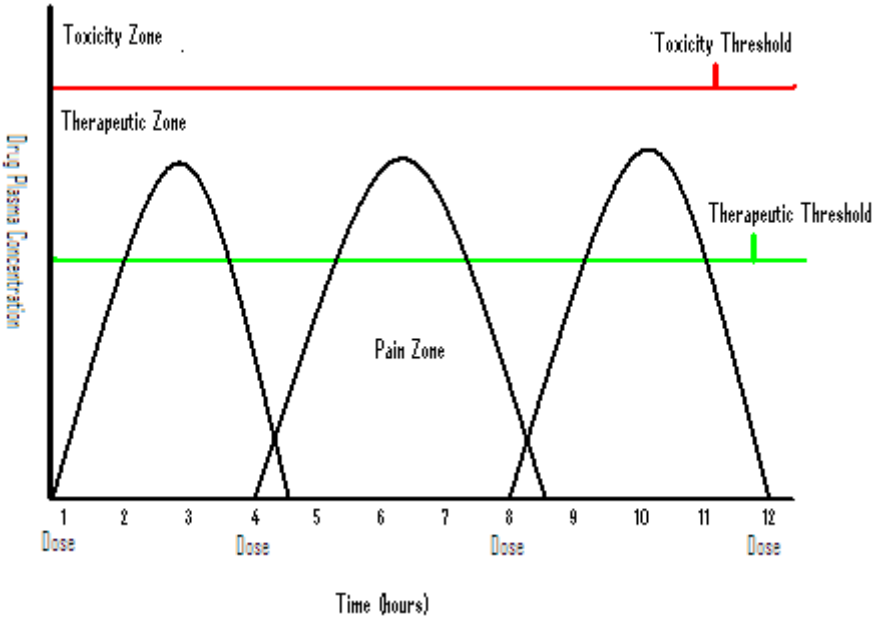


Figure 1.2.1.1: Therapeutic Drug Plasma Concentration Time Profile[3]

For any drug delivery system to be therapeutic, the drug must first be administered, once it enters the body it then enters into the blood stream where it is transported to the site of action. The drug is then metabolised, at which point it begins to work and after a set period of time it is excreted. If the bioavailability of the drug is limited then the therapeutic window may not be reached (i.e. limited benefit) as the drug concentration is

too low. If however the drug delivery system causes the drug to be released too rapidly then the concentration will exceed the upper limits of the therapeutic window and toxic effects may occur. As a result it is exceptionally important to administer the drug in the correct way to optimise the therapeutic benefits. To do this there are a number of drug delivery systems available, with different routes to deliver the correct amount of drug to the site of action.

1.2.2 Methods of drug delivery

Table 1.2.2.1 is a summary of the major drug delivery systems and the different routes of administration for each one.

Route	Example
Oral	Capsules and tablets
Rectal	Suppositories and creams
Topical	Ointments and lotions
Parenteral	Injections and implants
Respiratory	Inhalations and sprays
Nasal	Inhalations and solutions
Eye	Solutions and creams
Ear	Solutions and creams

Table 1.2.2.1: Examples of drug delivery systems[1]

The oral route is the most common form of administration, with tablets and capsules the most likely drug delivery system to be encountered. However, there are also a number of problems associated with this type of administration, for example the stability and solubility of the drug can be an issue.

1.2.3 The requirement for formulation

Each of the above delivery methods will have a number of requirements so that the drug is effective. The drug may need protection to prevent it from being metabolised before it reaches the target site[1]. The drug will have to be released at a certain rate so that the levels remain within the therapeutic zone for the optimum amount of time plus it may have to overcome problems associated with solubility, and possibly stability. As a result, depending on the drug and mode of delivery, the pharmaceutical active is rarely

used in the pure form but combined with one or more materials called excipients (inactive part of the medication)[4].

1.2.4 Excipients

Excipients are added to the formulation for a number of reasons. They may function, for example, as an antimicrobial preservative, a solubility enhancer, a stability enhancer or a taste masker, to name a few[1]. As a result the International Pharmaceutical Excipients Council (IPEC) has defined a pharmaceutical excipient as: Any substance other than the active drug which has been appropriately evaluated for safety and is included in a drug delivery system to either[4]:

1. Aid processing of the system during manufacture, or
2. Protect, support or enhance stability, bioavailability or patient acceptability, or
3. Assist in product identification, or
4. Enhance any other attribute of the overall safety and effectiveness of the drug product during storage or use.

Each additive must have clear justification for inclusion into the formulation and must perform a defined function in the presence of the active component and any other excipient present in the formulation. Each excipient must be shown to be compatible with the formulation and effectively perform its desired function in the product[4]. Above all it must not be toxic to humans after consumption and not affect the bioavailability of the drug. After the choice of drug and excipients have been established the next stage in development is a formulation method that will enable these components to interact and work together to produce the final product medicine[4].

1.3 Formulation methods

Along with the importance of choice of the excipient, the way the drug and excipient are mixed together becomes important. This is known as the formulation method, and because the type of dosage form and its method of preparation can influence drug dissolution and consequently the bioavailability of the drug, the

formulation method must not affect these key parameters. Therefore the method must be optimal and not cause any problems with the final product[4].

There are a number of different methods available and the choice is dependent on the type of dosage form that is required, for example any injected medication needs to be in solution and as a result the solubility and stability of this type of formulation is critical[4,5]. Therefore the choice of excipients and the formulation method must ensure that the active remains within solution but is also protected and stable until the site of action is reached[4,5]. The following diagram is an illustration of the different types of formulation methods that can be used to formulate tablets and capsules (Figure 1.3.1).

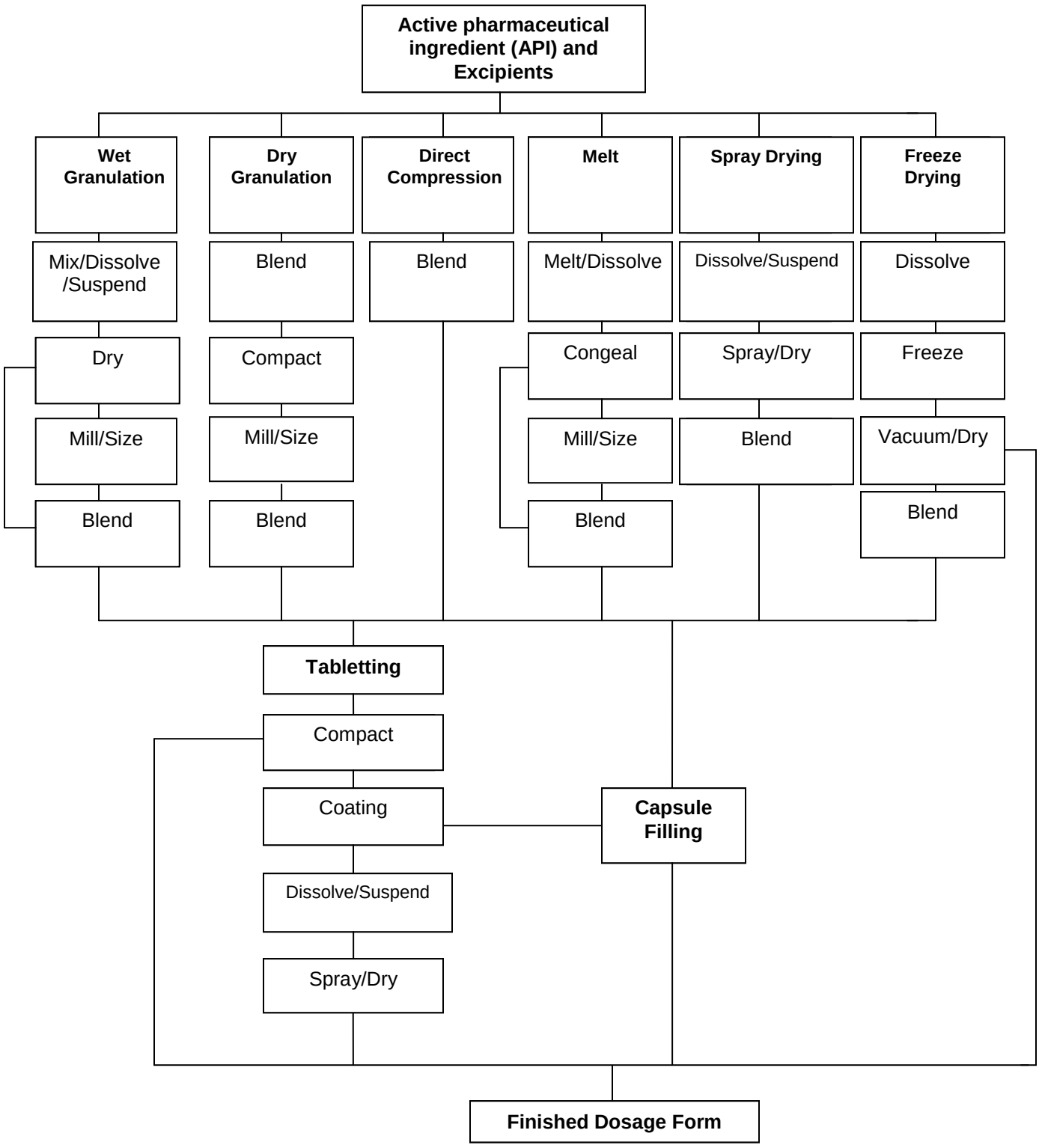


Figure 1.3.1: The major formulation methods for tablets and capsules[1].

The focus of this research specifically considers an adaptation of the melt method to formulate drugs with excipients to produce solid dispersions.

1.3.1 Solid dispersions

One way to overcome the problem of poorly aqueous soluble drugs is to mix with particular excipients producing what is now commonly known as a solid dispersion.

The first solid dispersion was developed in 1961 by Sekiguchi and Obi[6-8]. Their research found that by melting Sulfathiazole with urea and cooling the mixture in an ice bath a solid dispersion was produced that enhanced the absorption of the drug[6]. Sekiguchi then extended this work in 1964, with the fusion method used to prepare chloramphenicol and urea to improve formulations with this drug[7].

In 1966, Arthur Goldberg and his team confirmed that the drug may be molecularly dispersed in a matrix, forming a solid solution. Subsequent investigation then went into a wide range of drugs and methods to produce solid dispersions[9-14]. As a result, a solid dispersion is now defined as:

The dispersion of one or more active ingredients in an inert excipient or matrix, where the active ingredient could exist in a finely crystalline, solubilised or amorphous state[15-18].

Solid dispersions can be formulated in the following three ways[14-16]: the Fusion method, the Solvent method, and the Melt-Solvent method.

1.3.2 Fusion method

The first fusion method consisted of a physical mixture of a drug and a water soluble carrier, which were heated directly until both melted. The melted mixture was then cooled and solidified rapidly in an ice bath whilst stirred. Finally, the solid mass was then crushed, pulverised and sieved. An advantage of this method includes its simplicity and disadvantages included that the drug and/or excipients may decompose, or evaporate, at temperatures sufficient to melt either or both components[6-7,14].

1.3.3 Solvent method

For the solvent method, the physical mixture of the drug and carrier are dissolved in a common solvent followed by evaporation leaving the solid dispersion of the drug in the carrier. Advantages for this method include the thermal decomposition of drugs or carriers can be prevented because low temperatures are required for the evaporation of organic solvents. Disadvantages include the high cost of preparation, difficulty in removing solvent completely, possible adverse effects of solvent on the stability of drugs, and also difficulty in reproducing crystal forms[14,16,19].

1.3.4 Melt-Solvent method

For this method the drug is first dissolved in a suitable solvent, and then incorporated directly into a melt of a chosen excipient.

Over the past fifty years the three methods discussed, have received much interest including different ways of mixing drugs with different excipients to produce a solid dispersion[14,20-31].

Although solid dispersions have been extensively studied, their application in drug development has only become significant in the last twenty years. This is because of the discovery of more and more poorly soluble drugs that are now under development. Common strategies such as particle size reduction, salt formation, and solubilisation in organic solvents, are not always successful at achieving the desired dissolution and absorption enhancement for a drug[4].

Current issues that impede the commercial development of solid dispersions include: problems in scaling up from the laboratory to industrial manufacture, difficulty in controlling physicochemical properties, difficulty in delivering solid dispersion formulations as tablets or capsules, and physical and chemical instability of drug and/or excipients[4].

Despite these potential issues, solid dispersions still remain a viable way to improve current problems within formulation of drugs. As previously discussed there has been much research into solid dispersions, however little is known with respect to the potential of microwave heating for this method of formulation. This consequently forms the basis of the current project.

1.3.5 Microwave assisted formulation

A research paper published in 2003 by Bergese *et al*[27] reported that by heating a drug and an excipient, solid state diffusion may occur between the two components. Furthermore, this diffusion may be enhanced by the use of microwave heating but so little data has been published in this area it is hard to be certain of this statement.

1.3.6 Conventional heating

In conventional heating, thermal energy passes to the surface of the sample from an external heat source mainly through conduction[32] (Figure 1.3.6.1). The temperature of the sample is usually uneven with the outside hotter than the interior. In the case of pharmaceutical formulations prepared by melting or thermal diffusion a non-uniform product may result, which could have detrimental effects on the product. Thermal conduction mainly occurs in solids and it works because every atom in the solid is physically bonded together in some way. If heat energy is supplied to one part of the solid the atoms begin to vibrate faster, and this vibration is passed onto the adjoining atoms[32]. This eventually passes throughout the material and the temperature increases.

Conduction always occurs from regions of high temperature with the heat energy passed to regions of low temperature to equalise the temperature differences[33]. Different types of solids will transfer heat by conduction at different rates, and the rate each solid will transfer heat is calculated by the material's thermal conductivity. Materials with a large thermal conductivity will transfer large amounts of heat over time, and materials with a low thermal conductivity will transfer small amounts of heat over the same period of time[33].

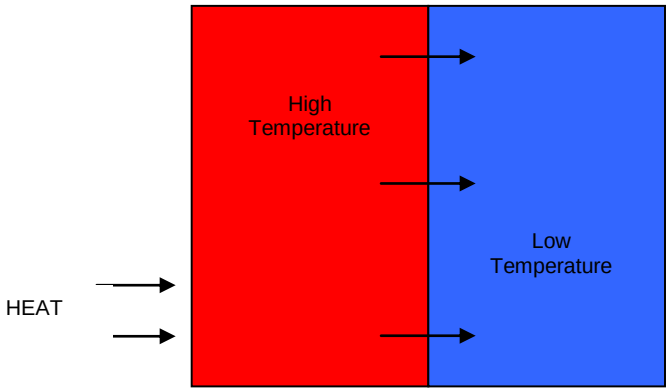


Figure 1.3.6.1 – Illustration of thermal conduction

1.3.7 Microwave heating

Microwave technology is a relatively new technique to the pharmaceutical industry, and previous work has concentrated on applying microwaves to the drying of pharmaceutical products[34-39]. However the use of microwave energy is now advancing into the formulation side of the pharmaceutical industry[27-31] with the prospect of improving drugs with water solubility issues and also controlling how a drug is released *in vitro/in vivo*.

Microwaves are part of the electromagnetic spectrum. Electromagnetic radiation is a form of energy radiated in a wave travelling at the speed of light[40]. It compromises of an electric and magnetic field that oscillates at right angles to each other and in the direction of propagation (Figure 1.3.7.1). Generally electromagnetic radiation is classified by the wavelength into radiowaves, microwaves, infrared radiation, visible light, ultraviolet radiation, X-rays, and gamma rays[40], with microwaves spanning the 300MHz to 300GHz frequency range of the spectrum[39]. The growing interest in microwave heating technology derives from the fact that it relies on direct interaction of the material with the electromagnetic radiation and less dependence on thermal conduction[41-44]. The benefit of microwave heating compared with conventional heating includes selective and faster heating which allows energy and time saving[41-42]. The depth of microwave heating depends mostly on the frequency of the microwave, the power used and the electrical and thermal conductive properties of the material[41]. This type of heating is instantaneous, uniform and penetrating throughout the material[41].

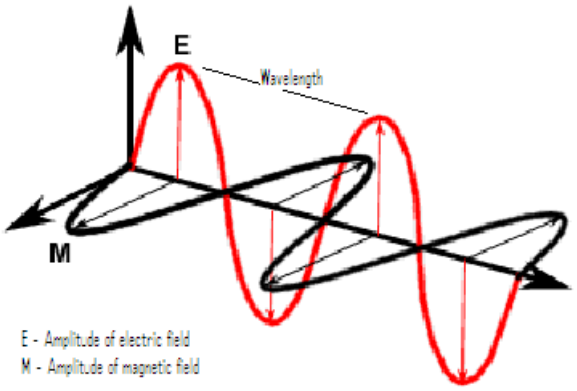
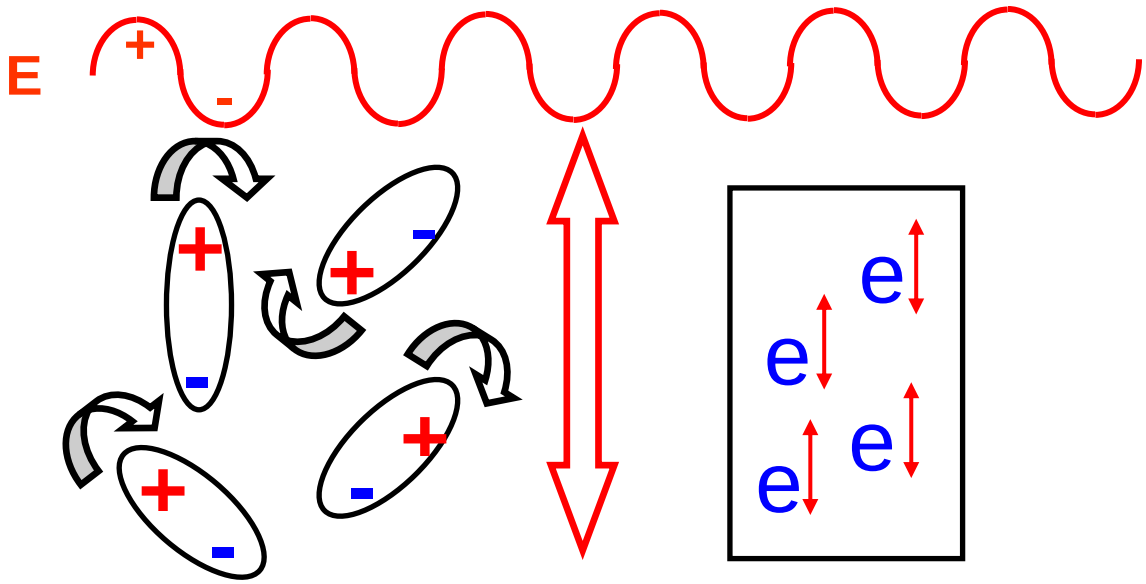


Figure 1.3.7.1: Diagram of the electromagnetic wave[45]

Not all materials are heated to the same extent when exposed to microwave radiation [41-44]. When considering how a material will behave once exposed to microwave heating, a critical factor is the material's dielectric properties. This is the ability to form a dipole when exposed to an electric field[45]. The operation of microwave heating can be explained simply in terms of two mechanisms: Ohmic and Frictional heating[45-46].

In ohmic heating (conductance), which particularly applies to solids, the alternating electric field of the microwave (E) causes movement of charged carriers, like electrons within the solid[45,47]. This movement creates a current which produces heat through any electrical resistance of the solid (dielectric properties). In frictional heating (dipolar polarisation), which practically applies to polar liquids such as water or ethanol, the permanent dipoles attempt to track the alternating electric field of the microwave[47]. At microwave frequencies, the molecules can't quite track the rapidly alternating field and the resultant 'jostling' produces heat and the liquid heats up (Figure 1.3.7.2).



Frictional (Liquids)

Polar mobile molecules (groups) rotate trying to track alternating E-field.

Ohmic (Solids)

Electrons dragged back and forth through material trying to track alternating E-field.

Figure 1.3.7.2: Illustration of Ohmic and Frictional Heating in Solids and Liquids[45]

The ability for a material to turn microwave energy into heat is sometimes called the 'loss factor'. Materials with a high loss factor will readily absorb microwave energy, for example, water and alcohol. Materials with a low loss factor are either reflecting or transparent to the microwave energy, for example quartz glass and PTFE[35,45]. The diagram below illustrates some materials and how they behave upon exposure to microwave energy (Figure 1.3.7.3).

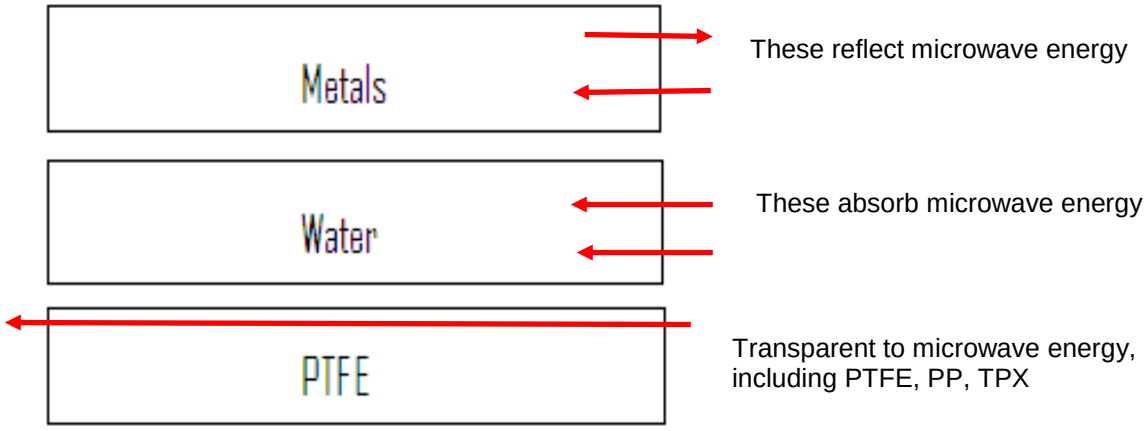


Figure 1.3.7.3 Interactions of materials with microwave energy[45]

The loss factor is temperature dependant and for some materials can rise as it gets hotter. In addition, chemical or physical changes in the material (i.e. going from solid to liquid) can cause a significant change in the loss factor[35]. These changes may contribute to the process called thermal run-away (illustrated in Figure 1.3.7.4, seen within the highlighted circle). This is where the temperature of the material rises rapidly even though the amount of microwave power is unchanged[35].

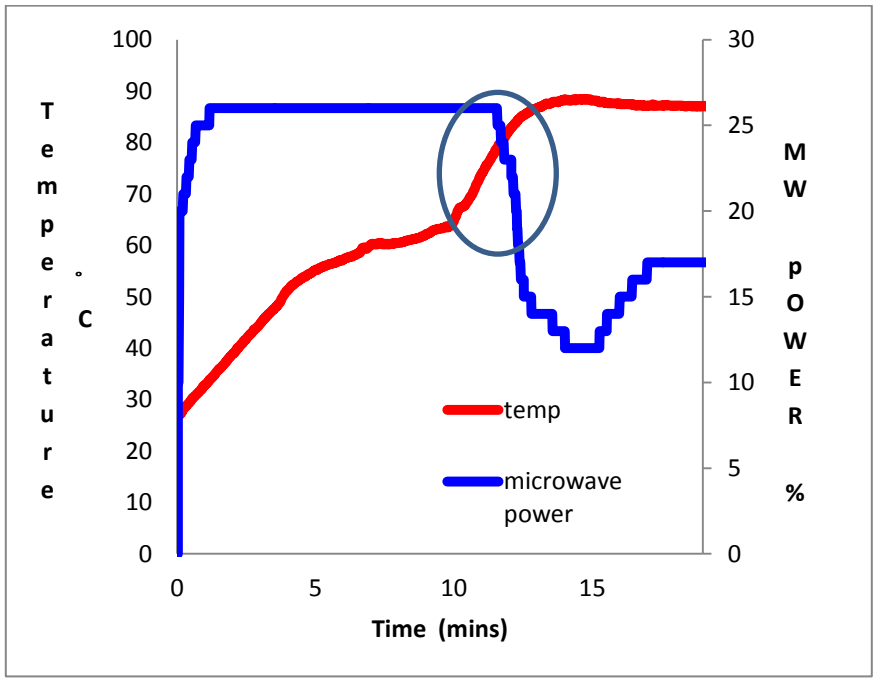


Figure 1.3.7.4: Illustration of thermal run-away under microwave heating

Despite the chance of thermal run-away and the potential heating capabilities of microwaves, the actual amount of energy supplied to a material is below the energy required to break bonds. Microwaves do not have adverse effects on the actual material being heated, they just facilitate this process, allowing a faster and a more uniform heating process[45].

1.3.7.1 The microwave oven

The majority of microwave heating is performed in a microwave oven and a modified form of this was used in this research. Microwaves are generated by a magnetron; vacuum diodes that are made up of circular resonating cavities around a cathode immersed in a perpendicular magnetic field[46].

Albert Hull created the magnetron in the 1920's, and this was then further investigated by Harry Boot and John Randall in the 1930's and the early 1940's. Eventually in 1947, Dr Percy Spenser made the first microwave oven[47].

The microwave oven differs from that used in domestic applications in four aspects.

A) The power control system has been modified so that there are two, rather than the usual one transformer to supply the current to the magnetron filament and provide the accelerating potential. This configuration means that the power can be switched on and off more rapidly, leading to better temperature control.
B) The incorporation of a metal reflector within the oven. The reflector is made of a 1mm thick square piece of aluminium that rotates while the microwave is on. This allows for the microwave energy to be focused onto the material been heated, aiding the whole heating process and allowing the desired temperature to be reached at a faster rate.
C) The use of a fibre optic temperature probe to accurately measure the temperature of the sample within the oven. The temperature is monitored by a fibre optic probe with a fluorescent chemical (phosphorescent chemical) at the tip. This chemical is excited by a light pulse sent down the fibre via a control unit. The fluorescent chemical then re-emits the light over a period of time (milliseconds) and this is proportional to the actual temperature of the material

been heated. The control unit measures the time it takes for the fluorescent chemical to re-emit the light and calculates the temperature which is then sent and seen on the computer. The operating range for the fibre optic probe is from 0°C to 300°C[48].

D) The use of bespoke control and acquisition software that allows the microwave power to be set to any desired level in real-time and records both the power and the fibre optic probe temperature as a function of time. For a visual picture of the microwave cavity, refer to Chapter Two, Section 2.2, and Figure 2.2.1.3.

1.4 Techniques used in the analysis of pharmaceutical formulations

To evaluate the success of any pharmaceutical formulation careful analysis is required. Some of the techniques used within the pharmaceutical industry for the analysis of formulations are: Particle size analysis, X-ray diffraction (XRD), scanning electron microscopy (SEM), differential scanning calorimetry (DSC), fourier transform infrared spectroscopy (FT-IR), isothermal titration calorimetry (ITC), thermal activity monitoring (TAM), and *in vitro* dissolution. All these techniques use different principles to help determine how a formulation behaves and the compatibility of the drug and excipients. These techniques will also show if any damage or degradation has occurred to the drug during the formulation process or potential storage.

For the purpose of this research, analysis was limited to the five most appropriate techniques, namely

1. Isothermal titration calorimetry,
2. Differential scanning calorimetry,
3. Scanning electron microscopy,
4. Thermal activity monitoring,
5. *In vitro* dissolution.

1.4.1 Isothermal Titration Calorimetry (ITC)

Calorimetry is the measurement of heat evolved or absorbed by a chemical or physical process[49].

All chemical and physical changes are accompanied by a change in heat content or enthalpy. Therefore all chemical reactions, including solid-state, solution-phase, gas-phase and biological reactions can be studied using calorimetric techniques[50].

One of these calorimetric techniques is isothermal titration calorimetry (ITC). ITC is a highly sensitive technique that investigates weak interactions between molecules and by investigating this, it provides thermodynamic and kinetic information for the reaction[51]. Therefore ITC measures binding interactions between, for example, drug molecule-carriers, and these interactions can be detected by the associated heat absorbed or released during a reaction[52]. From this, ΔH (enthalpy), and ΔS (entropy) can be calculated and a significant amount of information about an interaction can be concluded. It is only possible to calculate ΔH, and therefore ΔS, because nearly all binding interactions are accompanied by a change in enthalpy. Therefore a full thermodynamic profile can be gained from one single ITC experiment[53].

For a reversible association between D and C then the following applies:

$$D + C \leftrightarrow DC$$

Which is characterised by its association binding constant (bonding affinity between two molecules at equilibrium), K_b, defined by the following:

$$\frac{[DC]}{[D]\,[C]} = K_b \qquad \text{Equation 1.4.1.1}$$

[DC] = Drug-excipient complex,

[D] = Drug

[C] = Excipient

In addition, the association constant, K, is related to standard free energy, ΔG, by:

$$\Delta G = -RT\ln K \qquad \text{Equation 1.4.1.2}$$

Where R = Gas constant (8.314 J mol^{-1})

T = Absolute Temperature (K)

Furthermore, the standard free energy is composed of a heat term ΔH, (enthalpy) and ΔS (entropy) and related by:

$$\Delta G = \Delta H - T\Delta S^{54\text{-}58} \qquad \text{Equation 1.4.1.3}$$

ΔG = Standard free energy (kJ mol^{-1})

ΔH = Enthalpy (kJ mol^{-1})

T = Absolute Temperature (K)

ΔS = Entropy (kJ mol^{-1})

1.4.1.1 ITC Instrumentation

ITC comprises two identical cells, a reference cell and a sample cell (1.8mL in volume). These two coin-shaped cells are enclosed in an adiabatic shield or jacket, illustrated in Figure 1.4.1.1.1. The temperature difference between the reference cell and the jacket is continuously monitored to maintain a constant temperature[58]. A feedback system monitors the difference in temperature between the sample and reference through a thermocouple that is positioned between the two cells[58]. This thermocouple allows for a highly sensitive response to fluctuations in temperature between the cells and the jacket[59]. Therefore the feedback signal is the measured signal.

The sample cell contains a solution of the chosen excipient (titrand), and the injection syringe contains a solution to be injected into the sample cell called a titrant (drug), that will cause a heat change. The injection syringe injects this solution into the sample cell in a stepwise manner, usually between 5-10μL at each step and produces a

response. Along with delivery into the sample cell, the syringe rotates and stirs the mixture at the same time. This mixing of the interacting species is rapid and allows response times of the instrument to be less than ten seconds.

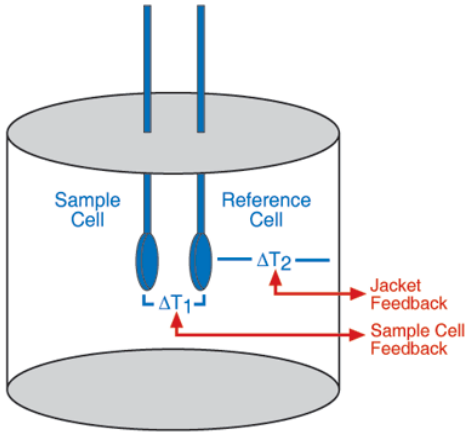


Figure 1.4.1.1.1 – A typical ITC cell[60]

ITC provides information on thermodynamic parameters to be investigated by direct measurements of the enthalpy over the course of a titration. This information can then be used to provide an insight into stability, specificity and stoichiometry of numerous biomolecular interactions.

ITC is just one calorimetric method, there are many more including non-isothermal methods such as differential scanning calorimetry (DSC).

1.4.2 Differential Scanning Calorimetry (DSC)

Thermal analysis is a group of techniques in which a property of a sample is monitored against time or temperature while the temperature of the sample, in a specific atmosphere is varied[61-65]. The chosen program may involve heating or cooling of the sample at a fixed temperature rate, holding at a specific temperature, or any sequence of these[61-65]. DSC is a technique that measures the energy difference (heat flow) between the sample and the reference[61-65].

DSC is the most often used thermal analysis method, mainly because of its speed, simplicity and availability. DSC however also provides detailed information on physical and energetic properties of a substance (for example, melting points, re-crystallisation, and glass transitions)[66]. It offers the analyst quantitative information

about exothermic, endothermic and heat capacity changes as a function of temperature and time[66].

To conduct these measurements, the sample is placed into a small pan usually made of aluminium. The reference is also an aluminium pan but usually left empty, they may also have lids that have a hole pierced into the top of them[67]. The sample size is usually between 5-10mg and the temperature range is typically 25-700°C[67].

There are variations in the type of DSC instrumentation available and this research used the common 'heat-flux' form.

In heat-flux DSC the difference in heat flow into the sample and reference is measured while the sample temperature is changed at a constant rate[66]. Both the sample and reference pans are heated by a single heating unit, and heat flows into the sample and reference via an electrically heated thermoelectric disk[66]. The differential heat flow into the two pans is directly proportional to the difference in the temperature between the two pans.

1.4.3 Thermal Activity Monitoring (TAM)

The thermal activity monitor (TAM), is an isothermal calorimetric system designed to monitor a wide range of chemical and biological reactions. It works on the principle that all chemical and biological processes are accompanied by a heat exchange with their surroundings, and therefore the system can observe and quantify both exothermic (heat-producing) and endothermic (heat-absorbing) processes[68-73]. The TAM can be used to obtain information on the rate, and extent of basic chemical reactions, phase changes, changes in structure and metabolism of living systems. Any thermal events that these reactions or changes provide, even in the microwatt range (μW) can be observed by the TAM. This means that any temperature differences less than 10^{-6}°C can be detected[68-73].

TAM utilises the heat flow or heat leakage principle (Figure 1.4.3.1), where heat produced from the sample in a thermally-defined vessel flows away in an effort to establish thermal equilibrium with the surroundings. Thermal stability is achieved by

using a 25L thermostated water bath which surrounds the reaction vessel and acts as an infinite heat sink. Any reaction can be studied within the temperature range of 5-80°C (working temperature of the thermostat) and up to four individual samples can be held and measured in the water bath. The temperature is maintained constantly to allow the smallest changes to be accurately measured[68].

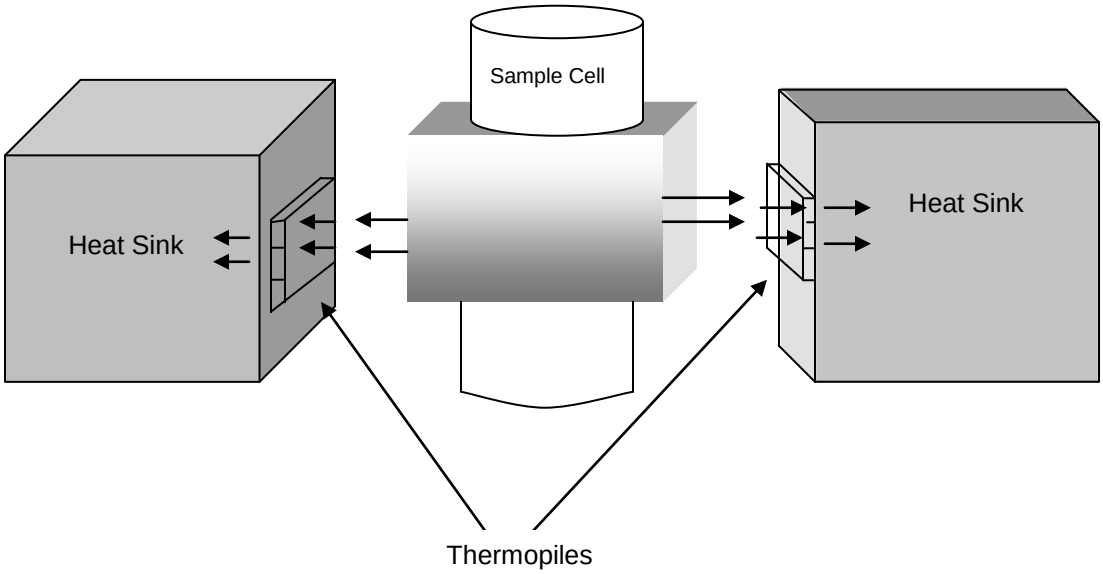


Figure1.4.3.1: Heat flow principle[68].

Heat energy from the sample in the reaction vessel (glass ampoule) is channelled through sensitive thermopile blankets, called the peltier elements, before escaping to the heat sink[68].

The peltier elements act as thermoelectric generators using the seebeck effect. These are bimetal devices made from semi-conductor materials, and can respond to temperature gradients of less than one millionth of a °C. These peltier elements are made up of a large number of semiconductor junctions joined in a series. These highly sensitive detectors convert heat energy into a voltage signal which is proportional to the heat flow. The results are presented on a computer and are a measure of thermal energy produced by the sample per unit of time. Interactions involving liquids, solids, and gases can be measured[68].

1.4.3.1 Instrumentation

The TAM itself is a free-standing multichannel microcalorimeter. Continuous heat leakage measurements are conducted under isothermal conditions.

The two main functions of the system are precise control of the isothermal temperature with the water thermostat, and detection of thermal events by a measurement system[68].

The samples are placed in the TAM via measuring cylinders (glass ampoules) which are maintained at constant temperature by the water thermostat. Each cylinder, together with a signal amplified, forms the measuring channel. Up to four channels can be operated at the same time in the TAM[68].

In all channels, measurements take place in the measuring cup which is between a pair of peltier thermopile heat sensors. In each cylinder there is a single peltier element mounted on the base of each cup, and the samples are introduced to each cup in sealed ampoules after a pre-equilibration period. This equilibrium period is carried out in the neck of the cylinder and outside of the neck is in direct contact with the water from the thermostat bath. This allows for rapid exchange of heat between the ampoules and the water bath via the neck[68].

The TAM is fitted with two amplifiers, one for each channel. The output signal from any thermal event within the sample is fed directly to the appropriate channel amplifier and the signal is monitored by a computer.

In summary, calorimetric techniques can provide an array of information about the behaviour of a pharmaceutical sample as it undergoes chemical or physical changes. However it does not allow the analyst to visually see any differences. To achieve this form of analysis requires a technique such as scanning electron microscopy (SEM).

1.4.4 Scanning Electron Microscopy (SEM)

Scanning electron microscopy can image and analyse bulk materials, with magnification up to <1000x. This type of magnification is possible with SEM and not light microscopy because SEM uses electrons to produce the image rather than photons. However because of this all images are in black and white. SEM has many advantages over light microscopy including: large depth of field allowing more of the sample to be focused at one time, and higher resolution which allows closely spaced specimens to be magnified at a much higher level[74-76].

1.4.4.1 SEM Instrumentation

Two major components are the electron column and control console (Figure 1.4.4.1.1). The electron column consists of an electron gun and two or more electron lenses, which influence the path of electrons travelling down the evacuation tube. The electron gun generates electrons and accelerates them to an energy in the range of 0.1 to 30 KeV[74-76]. The electron beam finally emerges from the last lens and into the sample chamber, where it interacts with the sample to a depth of approximately 1µm and generates a signal which is used to form an image. All of this is carried out under vacuum, to prevent any electrons colliding with air molecules which would result in a distorted image[74].

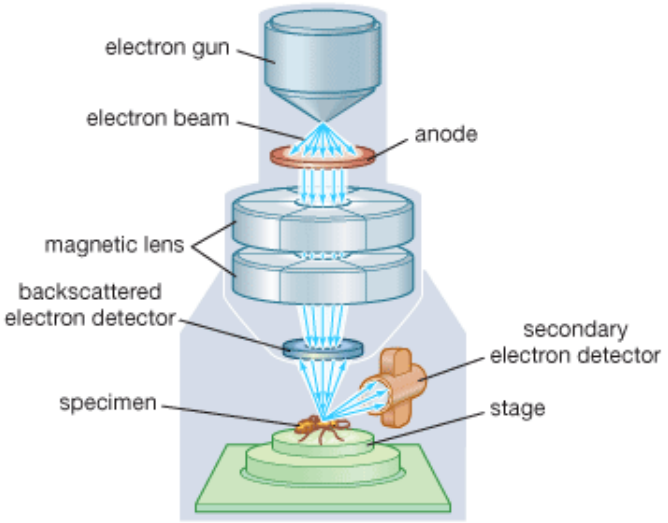


Figure 1.4.4.1.1 – Illustration of SEM instrumentation[77]

Two pairs of electromagnetic deflection coils (scan coils) sweep the electron beam across the sample. The first pair of coils deflect the beam from an optical axis within the microscope and the second pair bends the beam back onto the axis at the pivot point of the scan[74]. Once the electron beam interacts with the sample, a number of signals are generated. The electronics of the detector system converts these signals to point-by-point intensity changes which are passed to a computer that reads the signals and produces an image[74].

The two most important signals that are used to produce an SEM image are secondary and backscatter electrons (SE and BSE). These signals are capable of carrying information about the sample composition, shape (topography), surface textile, and thickness. Secondary electrons are loosely bound outer shell electrons from the sample atoms. These receive sufficient kinetic energy during the scattering of the electron beam and are ejected from the sample and set in motion. Secondary electrons are defined on the basis of their kinetic energy and all electrons that are emitted from the sample with energy less than 50eV are classed as secondary electrons[74].

Backscatter electrons are a beam of electrons whose trajectories occur because of an interception with the surface of the sample. Backscatter electrons remove a significant amount of the total energy from the primary beam and the number of these electrons that reach the detector is proportional to the mean atomic number of the sample[74-76].

Two types of detectors are used to identify the secondary and backscatter electrons these are then used to provide information on the sample. However for the electron beam to interact with the sample and for SE and BSE to be produced, the sample must be a solid and conducting. Samples that are not conducting are coated with a thin layer of a conducting material, such as gold, by a device called a ‘sputter coater’.

All the above techniques provide information concerning the formulated product, however it is also important to consider how formulation choices affect the subsequent drug release profile. One technique that can help in this respect is *in vitro* dissolution analysis.

1.4.5 Dissolution analysis

Dissolution studies of pharmaceutical compounds are exceptionally important because the dissolution behaviour will govern the bioavailability of the drug[78].

Dissolution is defined as the process by which a solid substance enters into a solvent yielding a solution. Simply, dissolution is the process by which a solid substance dissolves[79]. Dissolution testing is generally carried out on pharmaceutical dosage forms, including solid and solid-liquid dispersed formulations and mainly for quality control between batches[78-80].

Once a dosage form is administered to the body, it undergoes dissolution in the biological media, followed by absorption of the drug[79]. However for any of this to occur, the drug must dissolve before absorption can take place (*in vivo*). Dissolution (*in vitro*) can help to predict how well the drug will dissolve, therefore help to predict *in vivo* activity (*in vivo*, *in vitro* correlation, IVIVC).

$$\text{Solid} \xrightarrow{\text{Dissolution}} \text{Solution} \xrightarrow{\text{Absorption (ingestion)}} \text{Blood}$$

Many factors can affect dissolution, including: the manufacturing process of the drug/excipient (granulation, tablet punch pressure, composition of the formulation), drug properties (solubility/permeability, particle size, wettability, pH, pKa) and the dissolution method (paddle/basket method, rotation speed, temperature, volume and pH)[79-80].

If absorption is slow (drug dissolves, but diffusion, or active transport of drug over GI tract restricted) when compared with dissolution then absorption is the rate determining step. However if dissolution is the rate determining step then the factors that affect dissolution will control the overall process[81].

The dissolution rate is described by the Noyes-Whitney equation (this relates the rate of dissolution of solid to the properties of the solid and the dissolution medium)[82-83]:

— — Equation 1.4.5.1

M = Mass of solute dissolved in time, t.

dm/dt = Mass rate of dissolution (mass/time)

D = Diffusion coefficient of solute in solution

S = Surface area of exposed solid

h = Thickness of diffusion layer

Cs = Solubility of solid

C = Concentration of solute in bulk solution at time, t.

t = Time

If diffusion is the rate determining step, Fick's Law of diffusion can be used. Also if the drug concentration at various distances from the surface of the solid are measured then a concentration gradient can be seen[81].

Fick's Law of diffusion

Rate of Solution = ———— Equation 1.4.5.2

D = Diffusion coefficient

A = Surface area

Cs = Solubility of drug

Cb = Concentration of the drug in bulk solution

h = Thickness of diffusion layer

1.4.5.1 Methods of dissolution

There are a number of methods, but the most common and the official BP method is the rotating basket and paddle method for testing solid oral dosage forms. The rotating basket method was developed by Pernarowski in 1968[84], and then soon after Hayes developed the paddle method in 1969[85] which was further improved by Poole in 1969. The basket method uses a wire mesh basket to hold a solid dosage form

which is in the dissolution media allowing for wetting of the formulation and release of the drug.

For the paddle method, the solid dosage form is dropped into the dissolution media and the paddle rotates the media and the solid dosage form allowing for the wetting of the formulation and release of the drug[4,79].

1.4.5.2 Instrumentation

The dissolution instrument comprises of six 200mL dissolution cells and two further one litre cells containing a blank and the other, a standard solution. The dissolution cells stand in a water bath maintained at 37°C±0.1°C. Drug dissolution is monitored using a UV-Vis spectrometer monitoring a chosen wavelength for the drug of interest. The solution is circulated from the cells to the UV-Vis using a peristaltic pump while software (Icalis) allows a real-time dissolution profile for each of the cells to be determined. Beer-Lambert calibration plots were constructed to allow the absorbance values to be converted to percentage drug release.

1.4.5.3 Buffers

The definition of a buffer is a ‘substance which by its presence in solution increases the amount of acid or alkali that must be added to cause a unit increase in pH[85]. A buffer contains a weak acid and its conjugated base (or a weak base and its conjugated acid). This type of solution can maintain a constant pH when a small amount of acid or base are added, and are widely used where a change in pH may have detrimental effects.

Dissolution is pH sensitive and so dissolution studies frequently use buffer solutions to ensure reliable results as some drugs are acidic in solution. In addition, the use of buffers can simulate the pH of parts of the gastrointestinal system to increase the realism of the dissolution study[85].

For the current research, a buffer comprising 0.2M Di-sodium hydrogen orthophosphate dodechydrate and 0.2M Di-hydrogen orthophosphate di-hydrate was used to maintain a pH of 8 as found in the small intestine.

1.5 Materials used in this research

There were four drugs and four different excipients chosen for the current study. These were ibuprofen, ketoprofen, flurbiprofen and paracetamol. These particular drugs were chosen because all are non-steroidal anti-inflammatory drugs (NSAID's) commonly used. Consequently there is extensive knowledge on these drugs, i.e. they are well characterised. Each of these drugs properties are summarised in Table 1.5.1 to 1.5.3.

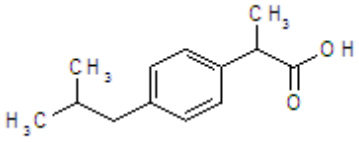
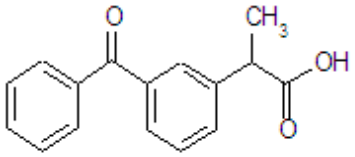
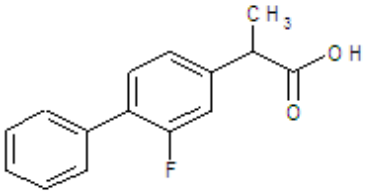
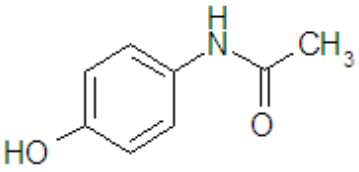
Drug	Chemical Name	Structure
Ibuprofen	[(±)-2-(4'-isobutylphenyl) propanoic acid	
Ketoprofen	2-(3-benzolphenyl)-propionic acid	
Flurbiprofen	2-(2-fluro-4-biphenyl) propionic acid	
Paracetamol	Acetaminophen	

Table 1.5.1 – Structural summary of the four drugs used[86-108]

Drug	Therapeutic Dose (mg)	Solubility (mg/mL) at 25°C	Appearance	pKa
Ibuprofen	200-1200	0.06	White Crystalline powder	4.5
Ketoprofen	200-1000	0.30	White Crystalline powder	4.5
Flurbiprofen	200-1000	0.08	White Crystalline powder	4.5
Paracetamol	500-1000	20.90	White Crystalline powder	9.5

Table 1.5.2 – Summary of chemical properties of the drugs used in this work[86-108]

Drug	logP	MP (°C)	BCS	Dosage Forms
Ibuprofen	3.6	75-77	2	Tablets Capsules Liquids Gels
Ketoprofen	0.97	95-97	2	Capsules Injections Suppositories Gels
Flurbiprofen	4.2	114-117	2	Tablets Capsules Eye Solutions
Paracetamol	0.49	169-170	1	Tablets Capsules Suspensions Suppositories

Table 1.5.3 – Pharmaceutical properties of the drugs used in this research[86-108]

Ibuprofen, ketoprofen and flurbiprofen have poor aqueous solubility because they are weak acids with pKa values in the range 4-5 i.e. when they dissociate, hydrogen ions are released. The more hydrogen ions that are released the more acidic the solution becomes, this then inhibits the solubility of these drugs because weak acids dissolve to a greater extent when in mild basic solutions. Therefore the solubility is pH dependant and increases with increasing pH, related by the following equations (Equations 1.5.1-1.5.2)[86-108]

$$pKa = -\log_{10}(Ka) \qquad \text{(Equation 1.5.1)}$$

$$Ka = \frac{[H^+]\,[A^-]}{[HA]} \qquad \text{(Equation 1.5.2)}$$

[H+] = Hydrogen ions

[A-] = Ionised drug

[HA] = Unionised form of drug

1.5.1 Previous research

Previous research for ibuprofen solid dispersions and inclusion complexes has included a number of methods to incorporate ibuprofen into polyvinylpyrrolidone (PVP), stearic acid (SA) and β-cyclodextrin (BCD). These include wet granulation[109], the solvent method[110], spray drying[111], and freeze drying[112-113]. This previous work suggests that these excipients can help control the release of the drug or improve the solubility using the chosen formulation method.

Other research which is directly relatable to this work incorporated ibuprofen into the above excipients by melting[114-115] using conventional heating. Referring to references 27-31, Bergese et al, and Moneghini et al formulated ibuprofen with PVP and BCD using microwaves to produce solid dispersions or inclusion complexes to improve the properties of the drug. All suggest that microwave heating, with the use of ibuprofen, could be advantageous and help to control the release of the drug. This research, although demonstrating the potential of microwave heating, had drawbacks in terms of accurate temperature measurement and power control that the current work seems to address. In addition, a wider range of drug-excipient systems were studied than previously considered.

Previous research for ketoprofen solid dispersions and inclusion complexes has covered a number of methods including incorporation of ketoprofen into PVP and BCD. These include freeze drying to produce a solid dispersion[116-117], spray drying[118], kneading and co-evaporation[119]. However, little has been published on the use of the melt method for the formulation of this drug with the chosen excipients other than two papers published in 2008 by Cirri et al[120-121]. In both the published papers ketoprofen was tumble mixed with β-cyclodextrin, methyl-β-cyclodextrin and egg phosphatidylcholine in various ratios. Each different mixture was then subjected to microwave heating for varying amounts of time and power. It was seen in all cases that an improvement for the dissolution of the drug occurred. However despite another method of microwave heating illustrating the potential, these methods still illustrated drawbacks which have previously been discussed and seem to be taken into consideration in the current project. Another novel aspect of this research is the incorporation of ketoprofen into PVP, SA and 2HPBCD using the melt method.

Previous research into flurbiprofen has been carried out using various methods that include co-precipitation, co-evaporation and spray drying[122-126]. However, no known research has incorporated flurbiprofen into the chosen excipients via the different heating methods.

Paracetamol was the last drug incorporated into this research, however little research was found relating to this work. The only paper found that illustrated paracetamol and β-cyclodextrin mixed together was published in 1992 by Tasic et al. The solid dispersions of paracetamol were prepared by mixing the drug with β-cyclodextrin via a kneading method (mortar and pestle) and a water-ethanol solvent mixture.

In addition to varying the drugs under investigation, this research focuses on varying excipients, namely stearic acid (SA), β-cyclodextrin (BCD), polyvinylpyrrolidone (PVP) and 2-hydroxypropyl-β-cyclodextrin (2HPBCD).

1.5.2 Excipients

The choice of excipient is important to any drug formulation. This choice can affect the solubility of the drug and therefore the dissolution[4]. Excipients are generally added to a drug to provide a specific function. This can be to mask an unpleasant taste provided by the drug, it can provide protection for the drug so it is not damaged before it reaches its target site, and they can be added to increase solubility and increase or decrease the kinetics of drug release[4]. However the magnitude of the effects will depend upon the drug, the quantities, properties of the excipient[4] and the formulation method. A summary of the different excipients used within this research, stearic acid, β-cyclodextrin, polyvinylpyrrolidone, and 2-hydroxypropyl-β-cyclodextrin can be seen in Table 1.5.1.1.

Excipient	Chemical formula	Solubility	Appearance	MP (°C)	Uses
SA	$C_{18}H_{36}O_2$	Insoluble	Waxy solid	66-70	oral and topical formulations Lubricant and binder
BCD	$(C_6H_{10}O_5)_2.3H_2O$	Soluble (0.18g/mL)	White powder	280	Improve solubility by forming inclusion complexes
2HPBCD	$(C_6H_{10}O_5)_2.3H_2O.$ $CH_2CH(OH)CH_3$	Soluble (1g/mL)	White powder	280	Improve solubility by forming inclusion complexes
PVP	$C_6H_{10}NO_n$	Cross-Linked PVP Insoluble	White Powder	300	Complex formation with pharmaceutical drugs

Table 1.5.1.1 – Summary of the four different excipients employed for this research[128-132]

Stearic acid (Figure 1.5.1.1), is a long chain fatty acid and previous research has utilised it with ibuprofen to aid or control the release of the drug[132]. However in this research the stearic acid and ibuprofen mixture was heated using conventional heating to encapsulate the drug.

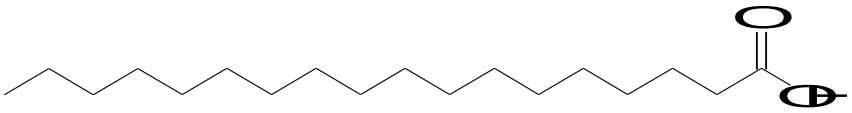


Figure 1.5.1.1: Structure of Stearic acid

Cyclodextrins are natural or semi-synthetic cyclic oligosaccharides with α-, β- and γ- the most commonly used, consisting of six, seven and eight D-glucopyranose units respectively[133]. Each of these units are linked by an α-1,4, glycosidic bond and because of the chair formation of the glucopyranose units, the cyclodextrin takes the shape of a truncated cone[134-140]. As each cyclodextrin increases in glucopyranose units, their cavity also increases in size and therefore larger drug molecules can be included (β-cyclodextrin has a cavity size around 6-6.5Å)[141]. The cavity is hydrophobic and forms inclusion complexes preferentially with hydrophobic drugs[134-147].

Cyclodextrin complex formation usually results from a combination of electrostatic interactions, van der Waal's, hydrogen-bonding and charge-transfer interactions[146-147] and some papers have suggested that these complexes form in a 1:1 ratio[134-147]. The structure of β-cyclodextrin (BCD) is illustrated in Figure 1.5.1.2.

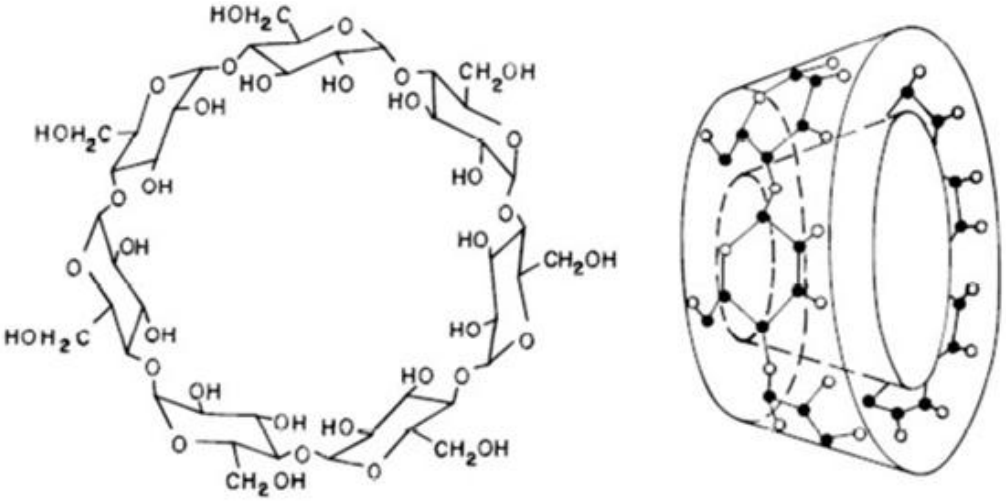


Figure 1.5.1.2 – Structure of β-cyclodextrin, front and side view[144]

2-Hydroxypropyl-β-cyclodextrin (2HPBCD) has gained much interest over the years because of its increased solubility when compared to the parent β-cyclodextrin[148-150]**.** It is produced from β-cyclodextrin by hydroxypropylation of the hydroxyl groups of the cyclodextrin[151]. It is chemically stable and the degree of substitution is the average number of hydroxypropyl groups per cyclodextrin. The structure is illustrated in Figure 1.5.1.3 and the hydroxypropyl group is $CH_2CH(OH)CH_3$, substituted onto the cyclodextrin in the R position.

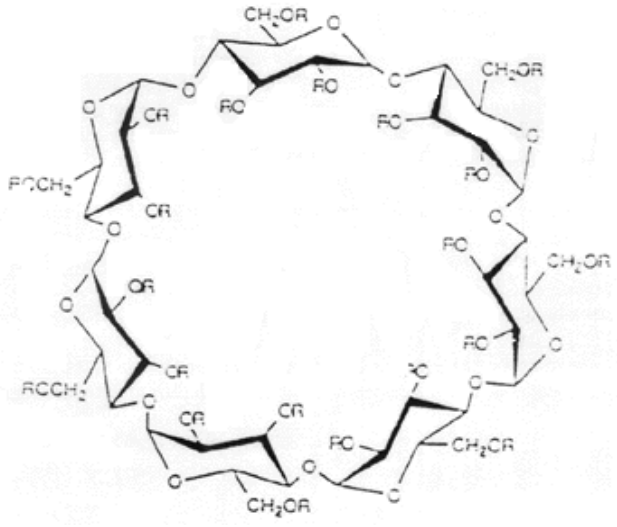


Figure 1.5.1.3 Structure of β-cyclodextrin

the R groups show where the hydroxypropyl group can be substituted[151]

The cavity retains its hydrophobic nature and the hydroxypropyl groups give an increased water solubility[148-155]. The degree of substitution of these hydroxypropyl groups also allows some control over the bonding to any drug molecule.

Polyvinylpyrrolidone (PVP) is widely used because of the following properties: it is highly hydrophilic, it has good biological compatibility, rapid water uptake, low toxicity, good swelling properties, adhesive characteristics, it is relatively inert against salts and acids, and it is resistant to thermal degradation[156-160].

PVP falls into two different categories based on aqueous solubility. However for the purpose of this research only the insoluble form of PVP was utilised. This is synthesised by polymerisation of N-vinylpyrrolidone which yields mainly a cross-linked polymer[156-160]. It is widely used in the pharmaceutical industry as a swelling polymer (absorbs water) with selective absorptive properties, and it also has favourable disintegration effects for tablets[160]. The structure of this excipient is illustrated in Figure 1.5.1.4.

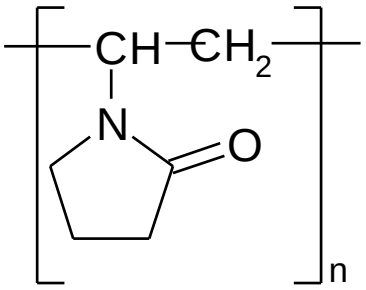


Figure 1.5.1.4: Structure of PVP

Previous research has incorporated a number of drugs into PVP to help improve the dissolution behaviour. Methods used to incorporate drugs into the structure of PVP include co-precipitation[157-159], solid dispersions[161-165], spray drying[160], solvent evaporation, [161-165], and mixing[166]. Previous research suggests that PVP does help to improve solubility and dissolution, because PVP may inhibit crystal growth[167-168]

1.6 Aims and objectives

The aims of this project were as follows:

A) To determine the thermodynamic parameters associated with the binding between the chosen drug and excipients, and to analyse whether this is temperature dependant.

B) To compare and contrast the behaviour of drug-excipient formulations prepared using conventional and microwave heating.

Each of these aims was determined by analysing the product formulations via a range of analytical techniques including calorimetry, microscopy, and dissolution studies. These chosen techniques were used to help illustrate the effectiveness of the formulation process. Three objectives were identified to complete the aforementioned aims and these are discussed in Chapter Six (p209-217).

Although previous researchers have indicated that microwave heating may have benefits in drug formulation, their work largely used relatively primitive microwave equipment where, critically, the temperature of the mixture or the microwave power was not monitored or controlled.

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Chapter 2

Materials and Methods

Chapter 2

In this research a series of drug-excipient formulations were manufactured using conventional heating and microwave heating methods. All resultant products were then subjected to an array of analytical techniques to fully characterise their properties and behaviour.

Materials and Methods

2.1 Materials

Ibuprofen was a gift from Galpharm, UK. Paracetamol, stearic acid, β-cyclodextrin, polyvinylpyrrolidone and 2-hydroxypropyl-β-cyclodextrin were purchased from Sigma-Aldrich, Dorset UK.

Ketoprofen and Flurbiprofen were purchased from TCI chemicals (Manchester UK). Di-sodium hydrogen orthophosphate dodechydrate and sodium di-hydrogen orthophosphate di-hydrate were purchased from Fisher Scientific, UK. All chemicals were ≥99% purity and used as received with no further purification undertaken.

2.2 Methods

Figure 2.2.1.1 is an illustration of dry and wet formulation, seen on p55.

2.2.1 Formulation methods

Two methods of heating the drug-excipient mixture during the formulation process were investigated, namely conventional heating and a novel microwave heating method. In both cases it was possible to undertake the process both with, and without, the presence of water as a solvent.

Method one: Conventional Heating, Wet Formulation[1]

1. 10g of the drug and excipient were prepared in a 1:1, 3:1, and a 1:9 mass ratio.
2. The dry powders were then tumble mixed for a period of five minutes.
3. A sample mass of powder (2g) was added to a beaker containing deionised water to achieve a 10% w/v solution.
4. This was then transferred to a hotplate, the temperature was adjusted until the water reached 85°C, as monitored by a fibre optic probe.
5. The temperature was monitored and maintained over a five minute period to ensure all contents were at the required temperature.
6. The beaker was then removed from the hotplate and allowed to cool.
7. When the contents of the beaker were at 45°C, the resultant formulation was collected through vacuum filtration and dried overnight in a desiccator over silica gel.

2.2.1.2 Conventional Heating, Dry Formulation

1. 10g of the drug and excipient were prepared in a 1:1, 3:1, and a 1:9 mass ratio.
2. The dry powders were then tumble mixed for a period of five minutes.
3. A sample mass of powder (2g) was added to a crucible and placed in an oven set at 85°C.
4. This was then left for a twenty minute period at this temperature.
5. The crucible and contents were removed from the oven and allowed to cool to room temperature.

Method two: Microwave Heating, Wet Formulation.

1. 10g of the drug and excipient were prepared in a 1:1, 3:1, and a 1:9 mass ratio.
2. The dry powders were then tumble mixed for a period of five minutes.
3. A sample mass of powder (2g) was added to a beaker containing deionised water to achieve a 10% w/v solution.
4. This was then transferred to the microwave oven.
5. The power was manually adjusted until the water temperature reached 85°C, as monitored by the fibre optic probe, Figure 2.2.1.2 and Figure 2.2.1.3.

6. This temperature was then monitored and maintained for a five minute period to ensure all contents were at the required temperature.
7. To mimic the conditions on the hotplate, the microwave power was then adjusted to allow cooling of the water.
8. When the temperature reached 45°C, the product was collected through vacuum filtration and dried overnight in a desiccator over silica gel.

2.2.1.4 Microwave Heating, Dry Formulation

1. 10g of the drug and excipient were prepared in a 1:1, 3:1, and a 1:9 mass ratio.
2. The dry powders were then tumble mixed for a period of five minutes.
3. A sample mass of powder (2g) was added to a crucible and placed in the microwave oven.
4. The microwave power was then manually adjusted until the temperature reached 85°C, as monitored by the fibre optic probe, Figure 2.2.1.2 and Figure 2.2.1.3.
5. This temperature was maintained and monitored for a five minute period to ensure all the contents were at the required temperature.
6. The microwave power was then adjusted to allow the sample to cool.

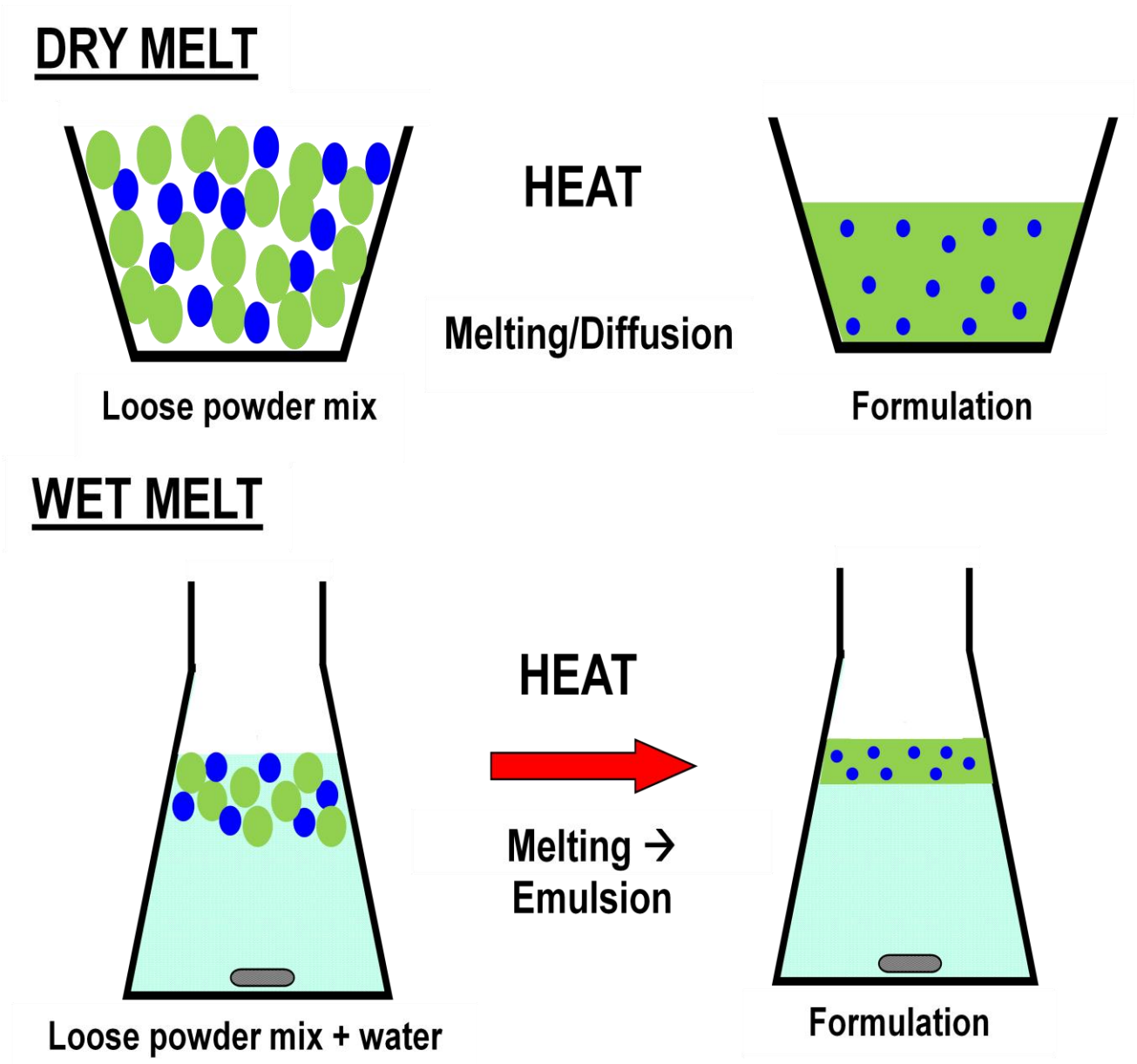

Figure 2.2.1.1: Illustration of dry and wet formulation process carried out using microwave and conventional heating.

Figure 2.2.1.2 demonstrates the full microwave oven and power control unit (Arrow 1 and 2 respectively). Figure 2.2.1.3 illustrates the inside of the microwave cavity and arrow 3 and 4 illustrate the novel parts of this equipment in terms of the fibre optic probe (arrow 3) and the aluminium reflector (arrow 4).

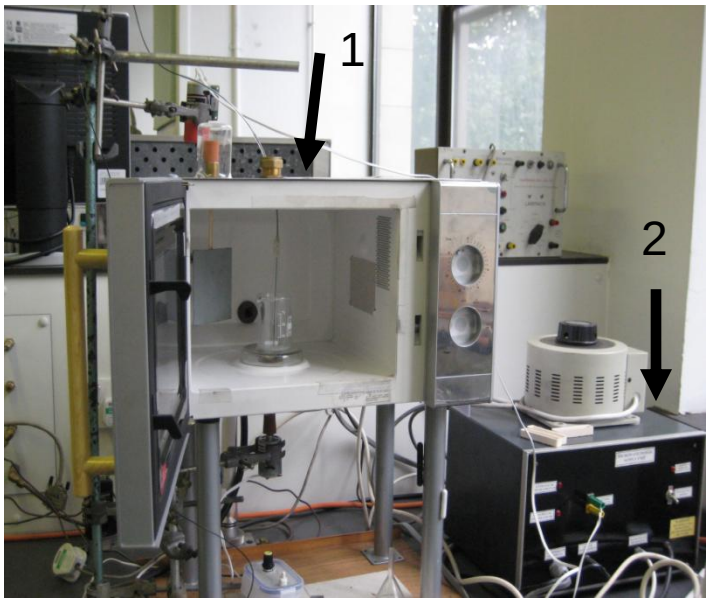

Figure 2.2.1.2 – Microwave and Control unit

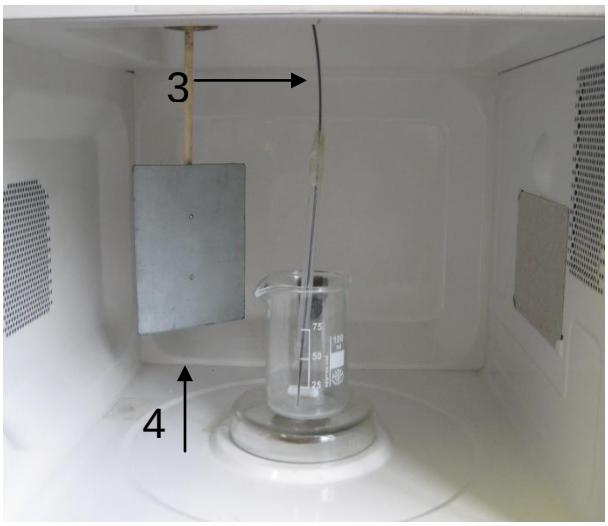

Figure 2.2.1.3 – Microwave Cavity

The following pages show examples of the types of experimental profiles that were obtained for selected formulation experiments using the microwave oven. In all cases the blue line represents the applied microwave power, shown as a percentage of the total power (800W), while the red line shows the formulation temperature as monitored by the fibre optic probe. During an experiment the user adjusts the microwave power, in 1% steps, as required to obtain the desired temperature. At the end of the formulation period the microwave power was set to 0% so that the cooling profile could be recorded.

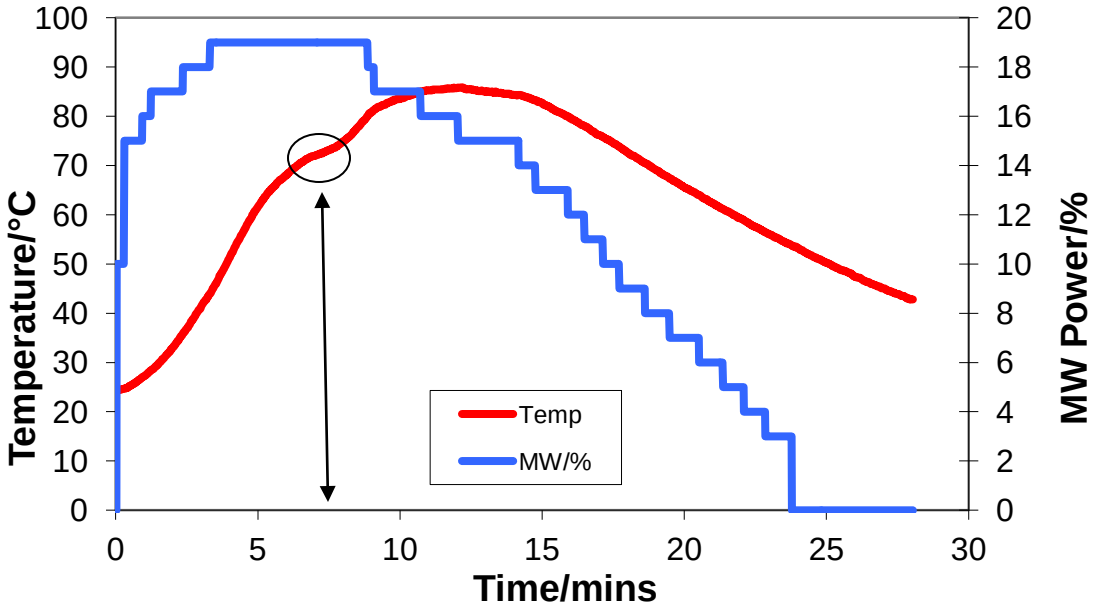

Figure 2.2.1.4 - The above graph shows the heating of ibuprofen and PVP, 1:1 without water. A small step in the temperature can be seen around seven minutes as the ibuprofen melts and its loss factor increases.

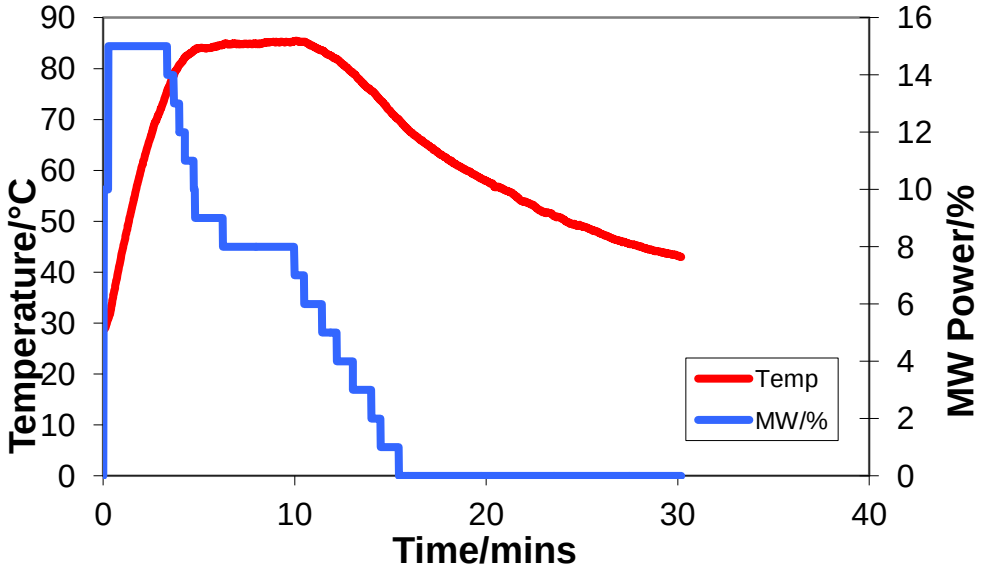

Figure 2.2.1.5 – The above graph shows the heating of ibuprofen and BCD, 1:1 with water. This demonstrates the accuracy with which the temperature can be monitored at a chosen power level.

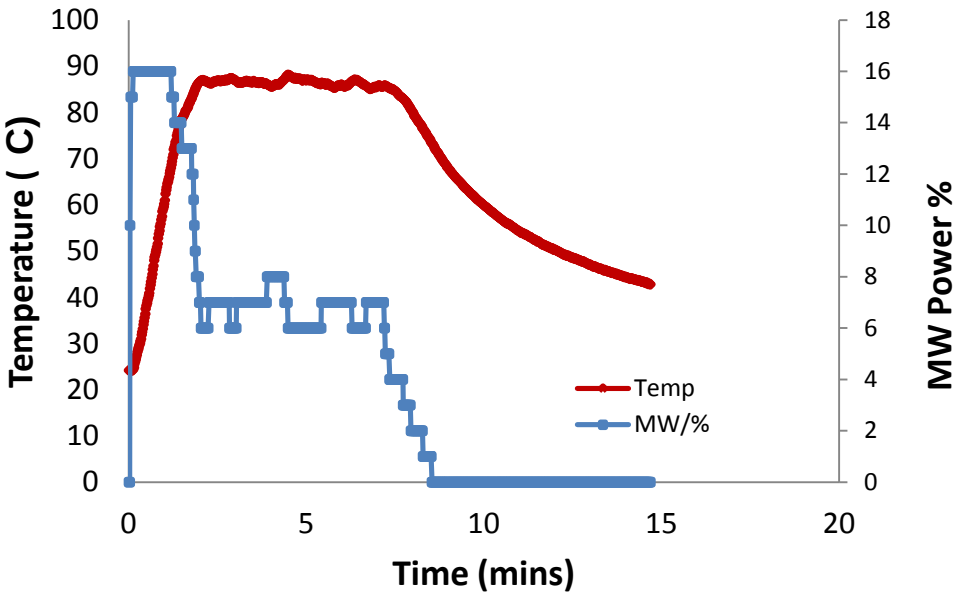

Figure 2.2.1.6 – The above graph shows the heating of ketoprofen and BCD, 1:9 without water.

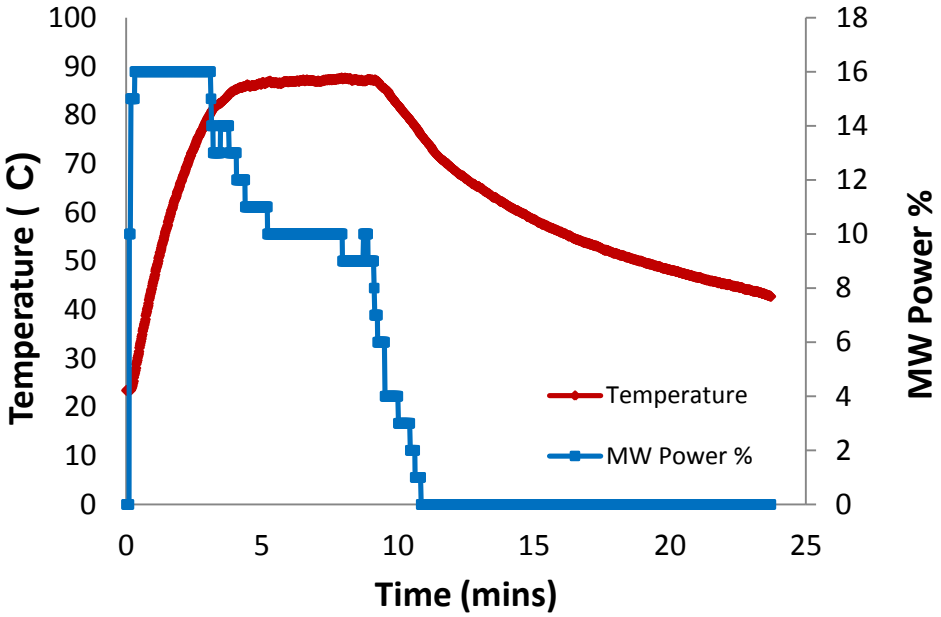

Figure 2.2.1.7 – The above graph shows the heating of ketoprofen and BCD, 1:9 with water.

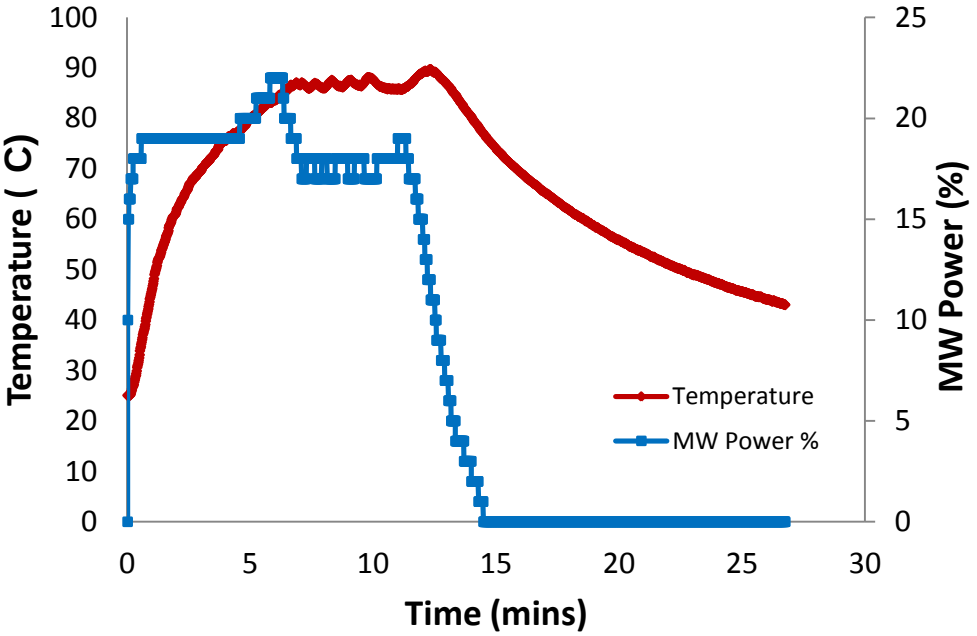

Figure 2.2.1.8 – The above graph shows the heating of flurbiprofen and PVP, 1:9 without water.

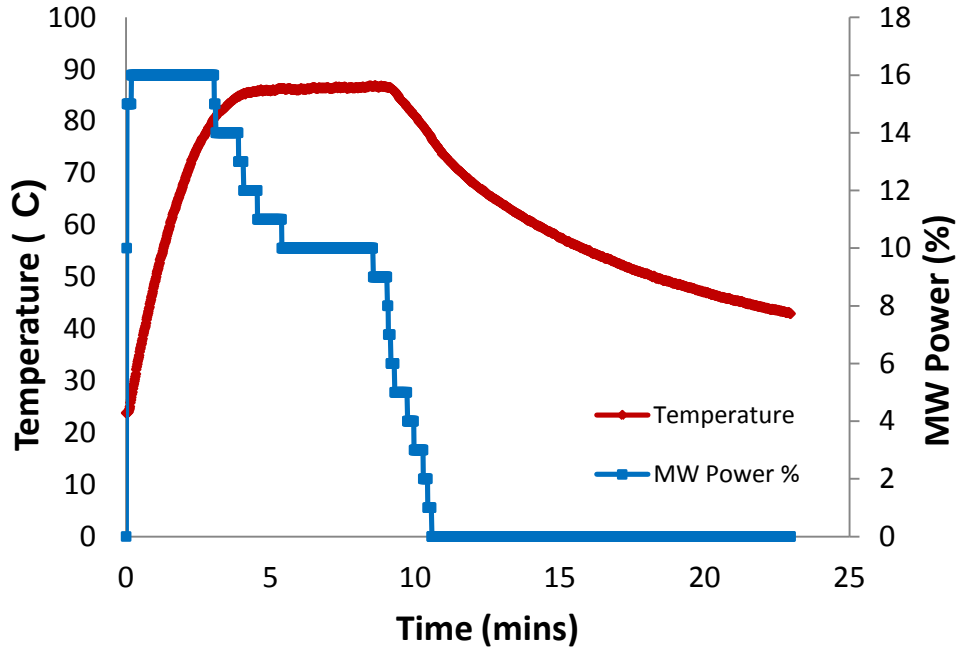

Figure 2.2.1.9 – The above graph shows the heating of flurbiprofen and PVP, 1:9 with water.

Overall, the effect of the relative loss factor for each of the formulations is also noticeable with some requiring more power and taking longer to reach the desired temperature. Figure 2.2.1.4 is for ibuprofen and PVP, 1:1 without water, and this graph shows that it can be difficult to heat, requiring a large amount of microwave energy to reach the target temperature (85°C).

Surprisingly when Figure 2.2.1.4 is compared with Figure 2.2.1.6 which is for ketoprofen and BCD, 1:9 without water it can be seen that to enable ibuprofen to reach the maximum temperature, 19% microwave power was needed compared with 16% for the ketoprofen and BCD formulation. This can also be seen when Figure 2.2.1.4 and Figure 2.2.1.6 are compared with Figure 2.2.1.8 which is for flurbiprofen and PVP, 1:9 without water. For this formulation to reach maximum temperature, 24% microwave power was required.

It is also apparent from the graphs that when water is present within the formulation it requires less power and time to reach target temperature and maintain it. This is partly because water interacts strongly with the microwave energy, and water is present to a greater extent when compared to the actual drug and excipient mixture.

Another key factor of this method is the ability to maintain the temperature, by reducing or increasing the microwave power the maximum temperature can be sustained. This illustrates that a temperature of a formulation can be kept constant for as long as required.

The fibre optic probe can be removed from the microwave, and was used to measure the temperature for all experiments performed using conventional heating. By removing the probe, it allowing for accurate temperature monitoring and control even for this method. The graph for a conventional method is shown in Figure 2.2.1.10. The graph has no microwave power profile as the heat is generated by an external conventional method (oven or hotplate). This enabled some disadvantages to be noticed about the conventional method, including the fact that it is more difficult to control and maintain the maximum temperature. This also took longer to be reached, putting the formulation under more thermal stress and the experiment as a whole also took longer.

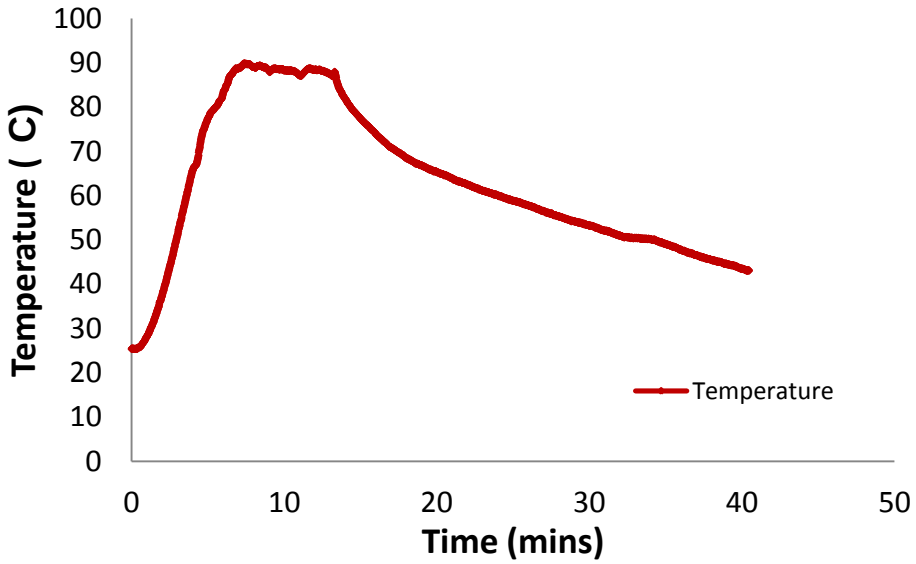

Figure 2.2.1.10 – An illustration of temperature monitoring (red line) using the conventional heating method, in this case for flurbiprofen and PVP, 1:1 with water.

In summary, two heating methods were employed in this research to formulate a series of pharmaceutical formulations. To completely characterise all samples then required the application of several analytical techniques.

2.2.2 Analytical methods

2.2.2.1 Isothermal Titration Calorimetry (ITC)

All ITC experiments were conducted using a Microcal VP-ITC Microcalorimeter. The sample and reference cell were enclosed in an adiabatic outer shield jacket (to maintain temperature and prevent loss of heat to surroundings), and during all experiments both the sample and reference cell were completely filled. It should be noted that the sample cell fill volume was 1.8mL. Experiments initially involved a primary temperature equilibration period for the sample in the cell, followed by a secondary equilibration with the syringe in place. Periodic calibration was conducted to confirm the validity of the data using a known chemical calibration reaction, namely barium chloride and 1,4,7,10,13,26-hexaoxacyclooctadecane (18-crown-6)[2-5]

Experimental

1. The drug and cyclodextrin solutions were weighed out and placed in pH8 buffer solution. Drug concentration ranged from 0.01M to 0.03M, with the cyclodextrin concentrations ranging from 0.0005M to 0.001M.
2. All solutions were then de-gassed using a Thermovac for two minutes.
3. The reference cell was filled with pH8 phosphate buffer with no significant difference in mass recorded before and after degassing. The sample cell was filled with a known concentration of cyclodextrin solution up to 1.8mL, and the syringe was filled with a drug solution of a known concentration up to 290µL.
4. The syringe was then placed in the sample cell with the stirring speed of the syringe maintained at 300rpm to ensure thorough mixing throughout the experiment.
5. Twenty nine injections were then injected in to the sample cell, each of 10µL volume with sufficient time allowed between injections.
6. All experimental data was monitored via VP-ITC origin software, and this was used to analyse all data with a standard fit model. This allowed reaction stoichiometry (n), binding constant (K_b) and enthalpy to be calculated. The change in Gibbs free energy was calculated using the derived Kb value and the van't Hoff isotherm with the change in entropy also calculated.
7. All six drug-cyclodextrin complexes were studied at three different temperatures, namely 298, 303, 310K to determine the significance of temperature on the complex formation.
8. All experiments were repeated in a minimum of triplicate for statistical validation with all contributions from heats of dilution subtracted from isotherms.
9. A typical ITC graph is illustrated in Figure 2.2.2.1.1. It can be seen from the titration curve that a number of peaks are present which correspond to each injection and each peak is the differential power between the sample and the reference cell (µCal sec^{-1}). Each peak is deflected in the negative direction showing an exothermic reaction had occurred. Towards the end of the titration it can be seen that the exothermic peaks begin to reduce as all the possible binding sites become saturated. From the titration curve and with the non-linear

least squares fit model the following parameters can be determined: K_b, ΔH and consequently ΔG and ΔS. Kb is the binding constant and is determined from the shape of the curve and is dependent on the concentration of the components, enthalpy change (ΔH) is calculated from each injection and from the end point of the titration (saturation point)[6].

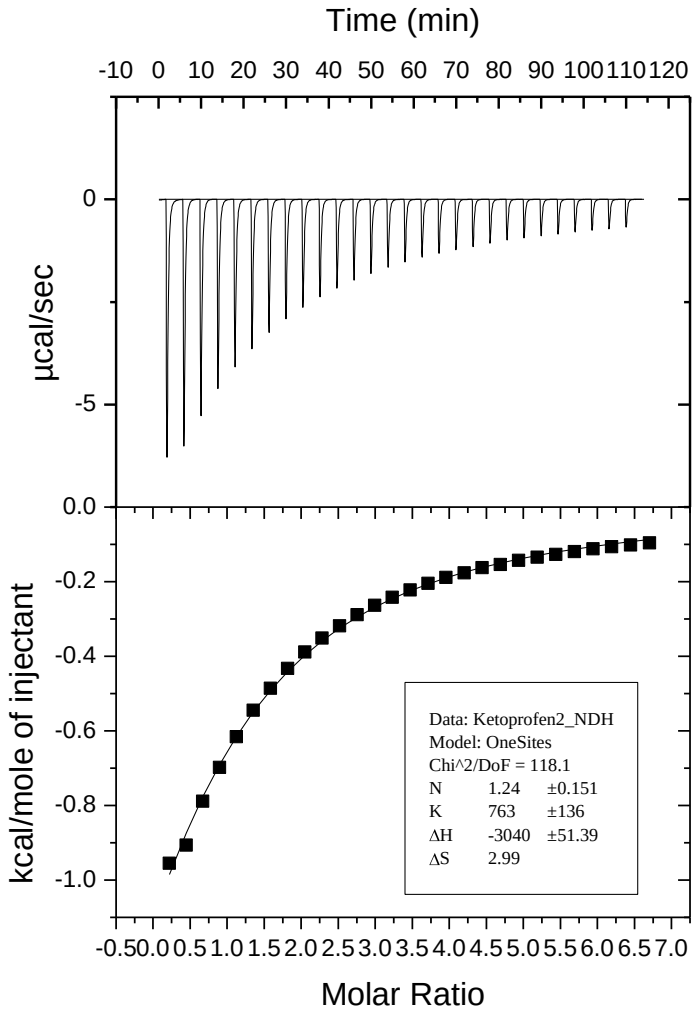

Figure 2.2.2.1.1- A typical ITC graph displaying the raw data and calculated data for a drug-excipient interaction, in this case ketoprofen at 298K with BCD

As a result, at the end of each experiment the computer software (Origin) can then be used to analyse the data and provide thermodynamic information on the above parameters. Titration calorimetry is the only technique capable of defining all the above parameters in a single experiment resulting in a nearly completed thermodynamic profile of the reaction.

2.2.2.2 Differential Scanning Calorimetry (DSC)

Calorimetric experiments were performed using a DSC Mettler Toledo 822. Periodic calibration was performed using Benzil to confirm temperature and enthalpy values.

Experimental

1. Between 5-10mg of the samples were weighed out into a 40μL aluminium pan,
2. The lid for the sample pan was pierced using a pin and then crimped.
3. The samples were subjected to a heating and cooling method starting from 25° and finishing at 125°C, 135°C, or 185°C (depending on the formulation) with an isotherm of ten minutes after each stage. The heating rate was 10°C min^{-1} with a gas flow of nitrogen at 80mL min^{-1}.

2.2.2.3 Thermal Activity Monitor (TAM)

All experiments were performed using an isothermal calorimeter, (2277 TAM) and the system was electronically calibrated to ensure the validity of the results.

Experimental

1. 100mg of each formulation was placed in a 5mL ampoule.
2. The cap was then crimped onto the ampoule.
3. The TAM was set at an isothermal temperature of 30°C and the samples were lowered into it and allowed to equilibrate for a forty minute period.
4. The sample was then left running isothermally at 30°C for a four day period.
5. Heat changes were monitored and recorded using computer software that recorded in real-time to allow a heat time profile to be determined.

2.2.2.4. Scanning Electron Microscopy (SEM)

All experiments were carried out using SEM instrument and model JEOL LSM-6060LV.

Experimental

Each different formulation was taken from distant, intermediate and close up ranges to provide a representative image of the samples.

2.2.2.5 Drug dissolution analysis

All dissolution studies were performed using a Pharmatest PTW III dissolution bath, and a Cecil 3021, series 3000 UV visible spectrophotometer and a peristaltic pump. A diagram of the dissolution apparatus can be seen in Figure 2.2.2.5.1. Figure 2.2.2.5.2 and Figure 2.2.2.5.3 display the laboratory set-up for the dissolution apparatus.

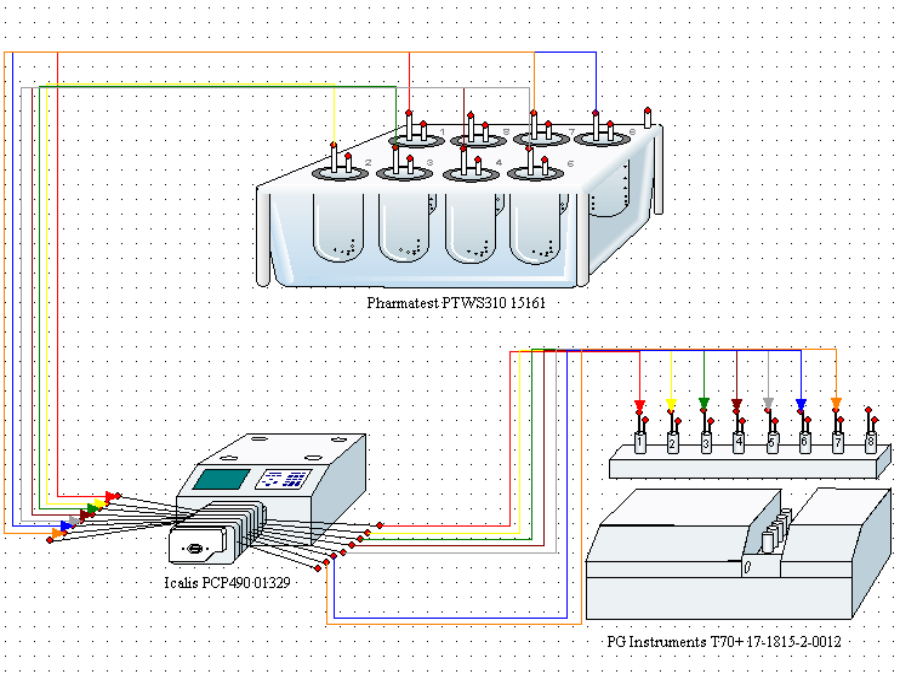

Figure 2.2.2.5.1 Systematic diagram of the dissolution apparatus[7]

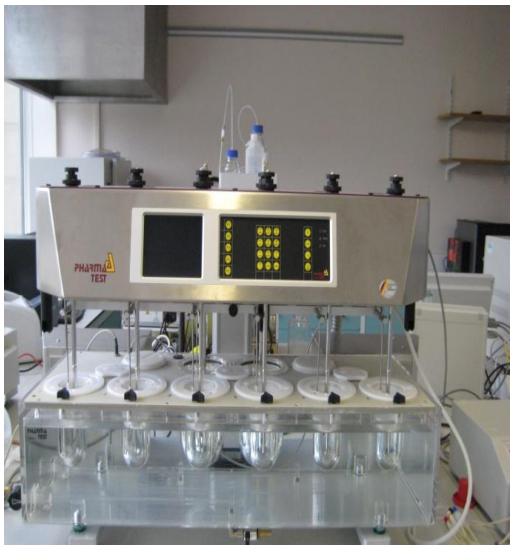

Figure 2.2.2.5.2 – Dissolution Bath

Figure 2.2.2.5.3 – Bath, pump and UV

Experimental – Formulations analysed in phosphate buffer (pH8) and deionised water

1. Drug and excipient formulations were weighed into six separate containers.
2. Each container had 200mL of aqueous phosphate buffer (0.2M monobasic and 0.2M dibasic sodium phosphate mixed together to produce a solution with pH8) or deionised water maintained at 37±0.1°C.
3. A method was set, allowing a paddle speed of 50rpm, a relevant wavelength (ibuprofen 265nm, ketoprofen 235nm, flurbiprofen 260nm and paracetamol 294nm) and a certain number of measurements to be taken over the time period. The buffer/water from each cell was pumped round the system using a peristaltic pump at a flow rate 10mL min^{-1}.
4. Drug release profiles were established with sink conditions maintained throughout the analysis.
5. All experiments were repeated in triplicate with the percentage drug release determined in concordance with the Beer-Lambert plot.

Determination of Beer-Lambert plots

To allow for the percentage drug release to be determined for each drug a Beer-Lambert plot was established. A number of solutions with known concentrations were tested in the dissolution bath. The absorbance was determined and the linear equation was related to the percentage drug release for all formulations tested.

In summary, several analytical techniques were employed to characterise each formulated sample to achieve a comprehensive understanding of the structure and behaviour of the products. By combining all of the resultant data it was possible to achieve an understanding of the application of microwave heating to pharmaceutical formulations.

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7. A schematic of the dissolution apparatus as seen on the Icalis software program (Version 3.0)

Chapter Three

Drug-Excipient Binding

(Analysis of Formulations using ITC)

Chapter 3

3.1 Introduction

One of the most fundamental methods of analysing a material is to monitor its response as it is heated in a controlled manner, or maintained at a constant temperature, and these responses can be measured by a range of calorimetric methods. A way to investigate the interactions and compatibility of a drug and excipient is to heat the two components and measure any changes that occur during this process or combine drugs and excipients at one temperature. With this, important changes on a molecular level and valuable conclusions about the sample, previous history, preparation, chemical nature, and behaviour of the sample during its proposed use can be determined.

Chapter Three concentrates on a technique called ITC, which provides information on thermodynamic properties including binding constants, stoichiometry, enthalpy, entropy and Gibb's free energy associated with the interactions between drugs and excipients. Also investigated will be the potential application of ITC to thermodynamically differentiate the complex formation for three guest molecules (ibuprofen, ketoprofen and flurbiprofen) of pharmaceutical interest with two forms of cyclodextrins over a range of temperatures. This information can then be used to determine and understand the complexation process including the strength of the interaction between the drug and cyclodextrin and whether the interaction is favourable.

3.1.1 Overview of ITC

A full discussion of ITC can be found in Chapter One. ITC is a calorimetric technique that is kept at one constant temperature throughout an experiment (isothermal). The unit directly measures heat evolved or absorbed in liquid samples (heat changes) as a result of mixing precise amounts of reactants (direct enthalpic measurements). It contains two identical coin-shaped cells (sample and reference) that are filled with liquid throughout the experiment. Both these cells are enclosed in an adiabatic outer shield (jacket) and any temperature difference between the sample and reference are monitored and measured. The entire experiment is computer controlled and the user inputs the experimental parameters (temperature, number of injections,

injection volumes). Origin software is then used to analyse the ITC data using fitting models which can then be used to calculate binding constants, reaction stoichiometry (n), enthalpy, entropy and Gibbs free energy thus providing a complete thermodynamic profile of the molecular interaction in a single experiment. Equations can be seen in Chapter One (p17).

Once the various parameters have been determined, ITC can be used to determine the strength of the drug and excipient interaction, the effect of temperature on this interaction and the ratio of the drug to the excipient molecule.

A typical ITC titration curve is illustrated in Figure 3.1.1.1 for barium chloride and 18-crown-6 which is used for calibrating the ITC. The barium chloride forms a 1:1 complex with the crown ether which has a well characterised enthalpy of -33kJ mol^{-1}[1(1-2)].

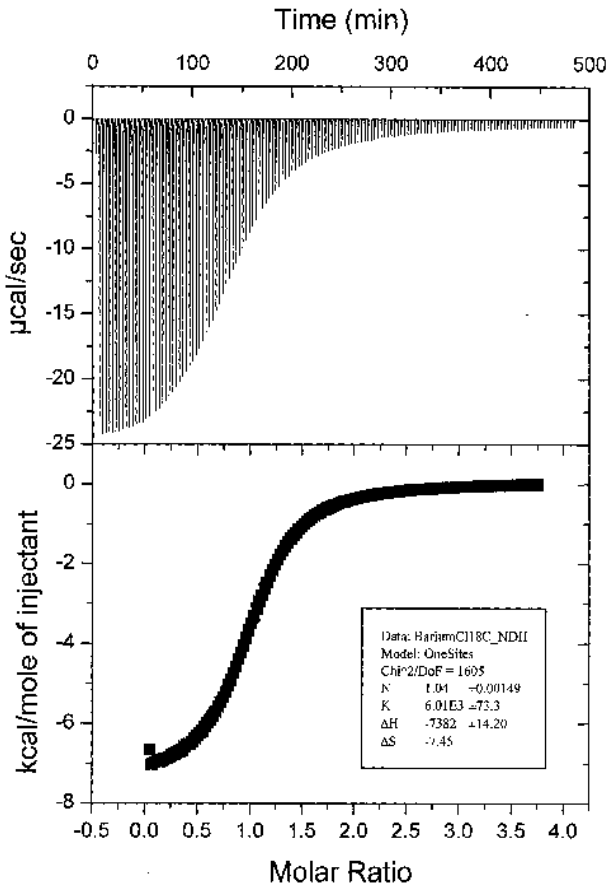

Figure 3.1.1.1 – A typical ITC titration curve including raw data and calculated values for barium chloride and 18-crown-6

The reaction for this particular compound shows a 1:1 interaction, with a ΔH value that equals to -31±0.4kJ mol^{-1} which is in agreement with the literature (after taking into consideration experimental and instrumental error). It can be seen from the graph, the ΔH value is in calories therefore this value was converted from calories to Joules and then Joules to kJ mol^{-1} to give the recognisable ΔH value.

3.2 Previous research

Extensive research has incorporated non-pharmaceutical compounds into cyclodextrins to investigate the thermodynamic parameters and these include complexes with benzene[5], hexanol[6], cyclohexanol[7], butanediol[8], benzoic acid[9-10], amino acids[11-12], glucose[13], and aspartame[14]. Despite the importance of understanding the binding process of drugs to a significant excipient, little research has investigated the thermodynamics of pharmaceutical complexes such as a drug to a cyclodextrin molecule. However two papers published in 2007 and 2009 by Todorova et al and Xing et al investigated the incorporation of ibuprofen and flurbiprofen into β-cyclodextrin[15-16]. The former paper investigated the thermodynamic parameters of the reaction between ibuprofen and β-cyclodextrin using a thermal activity monitor at a single temperature (298K) and at pH7 (Tris-HCl buffer). The latter paper investigated the reaction between flurbiprofen and β-cyclodextrin using ITC, over two different temperatures (293K and 313K) and a sodium phosphate buffer to give pH6 and pH8. However, the current research is the first to investigate three different drugs (ibuprofen, ketoprofen and flurbiprofen), into two different cyclodextrin compounds (β-cyclodextrin, and 2-hydroxypropyl-β-cyclodextrin) at three temperatures 298, 303, and 310K using ITC.

3.3 Experimental

Six different guest-host interactions were investigated, each at three specific temperatures, namely 298, 303, and 310K. In each case the reference cell was filled with degassed phosphate buffer (pH8) and the sample cell was filled with one of the cyclodextrin solutions. The stirring speed of the syringe was maintained at 300rpm to ensure thorough mixing throughout the experiment. A total of twenty-nine consecutive injections (10μL each) of the drug solution were then injected into the sample cell. Drug concentrations in the syringe varied from 0.01-0.03M with the cyclodextrin concentrations in the cell ranging from 0.0005-0.001M. All experiments were carried out in triplicate to allow for an average to be determined, and in all cases heats of dilution were investigated and subtracted from the final titration curves. To understand the complexation process, it is important to realise the binding mechanism. An interaction will occur once the drug molecule enters the cyclodextrin cavity in a reversible way, and the more lipophilic (hydrophobic) part of the molecule will enter the cavity (lipophilic cavity) with the more hydrophilic part remaining exposed to the bulk solvent[16].

3.4 Results and discussion

ITC was used to determine the stoichiometry (*n*), binding constant (K_b) and change in enthalpy (ΔH) for a total of eighteen complexation events. From these values it is possible to calculate thermodynamic properties, i.e. changes in Gibbs free energy (ΔG) and entropy (ΔS) for each complex formation. The results obtained can be seen in Table 3.4.1 below with an example of the experimental data for a typical ITC result seen in Figure 3.4.1 which has the corresponding binding isotherm alongside (stoichiometry, binding constant and enthalpy were determined from this).

Drug	Cyclodextrin	Temperature (K)	Drug: CD Ratio	10^3 K_b ($dm^3.mol^{-1}$)	ΔH (kJ mol^{-1})	ΔG (kJ mol^{-1})	ΔS (kJ mol^{-1})
Ibuprofen	BCD	298	1:1	8.34 (± 0.6)	-10.6 (± 0.4)	-22.4 (±0.2)	0.04 (± 0.002)
		303	1:1	6.72 (± 0.3)	-12.2 (±0.6)	-22.2 (±0.1)	0.03 (± 0.002)
		310	1:1	9.51 (± 0.5)	-12.8 (±0.2)	-23.6 (±0.3)	0.03 (± 0.002)
	2-(hydroxypropyl)-BCD	298	1:1	1.58 (± 0.1)	-7.2 (±0.3)	-18.2 (±0.1)	0.04 (± 0.002)
		303	1:1	2.1 (± 0.8)	-8.9(±1.0)	-19.3 (±0.8)	0.03 (± 0.002)
		310	1:1	2.52 (± 0.7)	-11.1 (±1.1)	-20.2 (±0.9)	0.03 (± 0.002)
Ketoprofen	BCD	298	1:1	1.09 (± 0.1)	-14.2 (±1.1)	-17.3 (±0.1)	0.01 (±0.001)
		303	1:1	1.14 (± 0.1)	-16.0 (±0.5)	-17.7 (±0.2)	0.01 (± 0.002)
		310	1:1	1.14 (± 0.1)	-17.4 (±0.1)	-18.1 (±0.1)	0.01 (±0.001)
	2-(hydroxypropyl)-BCD	298	1:1	0.48 (± 0.1)	-10.2 (±0.1)	-15.3 (±0.5)	0.02 (±0.001)
		303	1:1	0.72 (± 0.1)	-10.8 (±0.9)	-16.7 (±0.1)	0.02 (± 0.002)
		310	1:1	0.82 (± 0.1)	-12.9 (±0.2)	-17.3 (±0.1)	0.01 (±0.001)
Flurbiprofen	BCD	298	1:1	14.93 (± 0.6)	-15.1 (±1.4)	-23.8 (±0.1)	0.03 (± 0.002)
		303	1:1	8.83 (± 0.8)	-15.0 (±1.9)	-22.9 (±0.6)	0.03 (± 0.002)
		310	1:1	5.44 (± 0.4)	-15.0 (±0.6)	-22.2 (±0.1)	0.02 (± 0.002)
	2-(hydroxypropyl)-BCD	298	1:1	5.29 (± 0.1)	-15.8 (±0.1)	-21.2 (±0.1)	0.02 (± 0.002)
		303	1:1	6.46 (± 0.1)	-16.8 (±0.1)	-22.1 (±0.1)	0.02 (±0.001)
		310	1:1	6.53 (± 0.1)	-18.5 (±0.2)	-22.6 (±0.1)	0.01 (±0.001)

Table 3.4.1 – All ITC data conducted with ibuprofen, ketoprofen and flurbiprofen binding to BCD and 2HPBCD.

It can be seen from the table that all the interactions between the three different drugs and the two different cyclodextrins have a stoichiometry of 1:1 and are independent of temperature. It is apparent from the data that, despite differences in the size of the molecules, that a 1:1 stoichiometry is maintained between the drugs and both forms of cyclodextrins. This ratio was also unaffected by temperature over the range studied. However, there are significant differences in the binding constants, ΔH, and consequently ΔG. The results are discussed in greater detail in the following sections.

Previously to this research only the interaction between flurbiprofen and BCD at 298 K, and 303 K in pH6 and pH8 buffer was published with an enthalpy of –17 kJ mol^{-1} and 19 kJ mol^{-1} [15]. The enthalpy values presented in this work for this particular binding process were all –15 kJ mol^{-1} across the range of temperatures. The results obtained correlated well with the published enthalpy values and suggests an unchanged binding

mechanism. The slight discrepancy in the enthalpy values may have come from experimental and/or instrumental error. In addition to flurbiprofen, experimental data was published for ibuprofen and BCD at 298 K which again showed similar ΔH values (─14 kJ mol^{-1}) to those presented in this research (─10 to ─12 kJ mol^{-1}) after variation within buffer and instrumentation has been taken into consideration. However despite these slight discrepancies which are accountable for, it is possible to say that the data obtained in this research is accurate and reliable and is a consequence of the interaction between the drug and excipient.

Any differences seen within the reaction (binding constant, ΔH, ΔG and ΔS) can be associated with the following differences: logP value of the drug, the choice of cyclodextrin (BCD and the more sterically hindered 2HPBCD), and the chosen temperature range.

Section 3.4.1 and onwards is a separation and explanation of the three individual drugs with BCD and 2HPBCD. Each section investigates the results obtained and any trends that can be seen between the drug and the two excipients. Section 3.4.2 is a comparison of all the results obtained, each drug is then compared to determine any differences in the thermodynamic parameters. All results are illustrated in Table 3.4.1.

3.4.1 Ibuprofen and BCD

It can be seen from Table 3.4.1 that as the temperature increases from 298-310K there is a slight difference in the binding constant but it is largely unchanged. This therefore suggests that an increase in temperature has minimal effect on the equilibria for the formation of the ibuprofen-cyclodextrin complex.

The enthalpy change for ibuprofen and BCD increases over the temperature range, showing the bonding becomes more exothermic as the temperature increases. An enthalpy change arises mainly as a result of change in the interaction, for example hydrogen bonding[17-18]. ΔG also shows a slight decrease to a more negative value with an increase in temperature. The negative values for ΔG indicates that the complex has less free energy than the free drug and cyclodextrin, and consequently the negative value for enthalpy, negative values for Gibb's free energy suggests binding is favoured and this promotes the complex formation.

3.4.2 Ibuprofen and 2HPBCD

The reaction between Ibuprofen and 2HPBCD was also investigated. From the results obtained, it can be seen that as the temperature increases so do the values for ΔH, and ΔG. This shows that there is an increase in the strength of bonding interaction as the temperature increases. For all the complexation events between ibuprofen, BCD and 2HPBCD, the observed values are negative and it can be said that the process of binding is exothermic and enthalpically driven. However when both the binding constants and therefore the enthalpy, Gibb's free energy and entropy were compared for ibuprofen binding to BCD and ibuprofen to 2HPBCD it can be seen that ibuprofen does form a complex with 2HPBCD but it is a relatively weak process (ibuprofen and BCD show significantly higher negative values when compared to 2HPBCD). To hypothesise, this result could be occurring because 2HPBCD has seven substituted hydroxypropyl groups ($CH_2CH(OH)CH_3$) attached in the C6 position of each unit of the cyclodextrin making it more sterically hindered. This will then make it more difficult for any drug to bind to the cavity of the cyclodextrin thus lowering the binding constants, ΔH, and ΔG.

3.4.3 Ketoprofen and BCD

For ketoprofen with BCD the binding constant showed little change over the temperature range (298-310 K) and as a result the ratio of drug and excipient binding is unaffected by an increase in the temperature of the reaction. However when the temperature increases, there is a change in the enthalpy, and consequently Gibb's free energy. As the temperature increases, the enthalpy (ΔH) for the reaction also decreases with ─14.2 kJ mol^{-1} obtained at 298 K and ─17.4 kJ mol^{-1} at 310 K. This illustrates a more exothermic process is occurring, which may suggest that the strength of the interaction between ketoprofen and the cyclodextrin cavity has increased.

Along with this decrease in enthalpy, there is an increase in negativity in the Gibb's free energy with a value of ─17.3 kJ mol^{-1} (±0.1) obtained for the reaction at 298 K and ─18.1 kJ mol^{-1} (±0.1) obtained at 310 K. Consequently the resultant complex has less free energy than the free drug and BCD molecules and therefore binding is favoured.

3.4.4 Ketoprofen and 2HPBCD

After ketoprofen and BCD, 2HPBCD was also investigated. From the results obtained it is apparent that as the temperature increases, there is an increase in enthalpy, and as a result the Gibb's free energy. When the temperature is kept isothermally at 298 K, the enthalpy was calculated at ─10.2 kJ mol^{-1} (±0.1) and at the maximum temperature of 310 K the enthalpy was ─12.9 kJ mol^{-1} (±0.2). Therefore the interaction between ketoprofen and 2HPBCD is temperature dependant. The interaction becomes more exothermic suggesting an increase in strength between the drug and 2HPBCD as the temperature increases. This is also the case with the Gibb's free energy because at 298 K it is calculated at ─15.3 kJ mol^{-1} (±0.5) and at maximum temperature of 310 K the Gibbs free energy is ─7.3 kJ mol^{-1} (±0.1). As a result an increase in temperature causes the Gibb's free energy to become more negative. This shows that the complex has less free energy than the free drug and cyclodextrin.

It is apparent from the results that the interaction seen between ketoprofen and 2HPBCD is weaker when compared with ketoprofen and BCD. This therefore may be suggesting that the substituted groups seen in the structure of 2HPBCD may make it difficult for the drug to interact and bind to the cavity of the particular cyclodextrin.

3.4.5 Flurbiprofen and BCD

When the flurbiprofen, BCD and 2HPBCD complexes were analysed a number of trends were seen. In the case of flurbiprofen with BCD, the binding constant goes down with increasing temperature which was not witnessed previously (temperature has no usual affect on the binding constant). When the enthalpy for each reaction was calculated it was seen to remain constant over the temperature range studied, (─15.0 kJ mol^{-1}) suggesting that the binding mechanism is unchanged from 298 to 310K. There is also a slight decrease in the Gibb's free energy, at 298 K this value was calculated at ─23.8 kJ mol^{-1} (±0.1) but as the temperature increased to 310 K the value calculated decreased to ─22.2 kJ mol^{-1} (±0.1). These results suggest that a complex is formed and favoured but the strength of it is reduced as the temperature becomes elevated. As previously mentioned flurbiprofen with BCD at 298 K has been investigated

prior to this research[15]. The enthalpy values presented in this work for this particular binding process were all −15 kJ mol^{-1} (±1.3 kJ mol^{-1}) across the range of temperatures.

3.4.6 Flurbiprofen and 2HPBCD

For the binding between flurbiprofen and 2HPBCD, the binding constant, enthalpy and Gibb's free energy all increase with increasing temperature which is a trend previously seen with ibuprofen and ketoprofen. Again the binding constant increases with temperature, and also the binding enthalpy decreases across the studied range of 298 to 310 K. This result therefore suggests that the bond between the flurbiprofen drug molecule and the cyclodextrin cavity increases in strength with increasing temperature. It also shows that the reaction becomes more exothermic at higher temperatures. There is an increase in ΔG which shows that at higher temperatures, there is less free energy in the complex than the free drug and cyclodextrin.

When the two different excipients were compared to each other for the interaction with flurbiprofen, significant differences were seen. For flurbiprofen and BCD the binding constant decreases with increasing temperature, but for flurbiprofen and 2HPBCD the binding constant increases with increasing temperature. When the enthalpy for each of the reactions was calculated it became apparent that this remains constant for the interaction of flurbiprofen and BCD but an increase in the enthalpy was seen for the drug and 2HPBCD. This result shows that the interaction between flurbiprofen and BCD decreases or becomes less favourable as the temperature increases, however the opposite is witnessed for the interaction of the drug and 2HPBCD. This result is also seen in the Gibb's free energy, with a slight decrease for the interaction of flurbiprofen and BCD and an increase for the drug and 2HPBCD. All results obtained show that something is occurring to the flurbiprofen and BCD when the temperature increases. To hypothesise, the presence of fluorine within the drug compound may have a subsequent impact on hydrogen bonding potential both with water and the host cyclodextrin, which only becomes apparent when a range of temperatures was investigated.

3.4.7 Comparison of ibuprofen, ketoprofen and flurbiprofen with BCD and 2HPBCD

From analysis of all the results obtained there appears to be differences not only between the drug and the choice of cyclodextrin but also between the different drugs. Each drug does have some similarities but the main differences include the structures and the partition coefficients of the drugs (logP).

Ketoprofen has the lowest logP of 0.97[19], then ibuprofen with a logP of 3.6[19], while flurbiprofen has the highest logP of 4.2[20]. Upon analysis of the results there appears to be a clear correlation between the lipophilicity of the drug molecule and the experimentally determined binding constant and enthalpy of binding. For example at 298K the binding constant for ketoprofen is 1.09×10^3 dm^3mol^{-1}, ibuprofen has a binding constant of 8.34×10^3 dm^3mol^{-1} and flurbiprofen has a binding constant of 14.93×10^3 dm^3mol^{-1}. From this it can be seen that the higher the partition coefficient, and thus the greater the lipophilicity, the stronger the interaction between the drug molecule and the cyclodextrin. This could therefore be a reflection of the greater affinity of the lipophilic compound towards the less polar internal cavity of the cyclodextrin when compared with water.

This trend can be seen throughout the scenarios and over the temperature range until 310 K, where the decrease in binding constant, ΔH and ΔG for flurbiprofen and BCD causes this result to become smaller than the ibuprofen and BCD scenario at this temperature. This consequently suggests another explanation may be involved in this result. In addition to the lipophilic difference, another hypothesis is the structural difference for flurbiprofen when compared with ibuprofen and ketoprofen. Flurbiprofen has a fluorine atom attached to the first benzene ring from the carboxylic group. This may have a subsequent impact on the hydrogen bonding potential with the cyclodextrin cavity causing a decrease in strength as the temperature increases.

3.5 Overall summary

To summarise this chapter, the ITC analysis allowed thermodynamic data to be calculated that was associated with three different drugs, namely ibuprofen, ketoprofen and flurbiprofen. Each of these drugs were analysed with two different cyclodextrins over a range of temperatures (298K to 310K). Analysis of the data confirms all complexes formed were in a 1:1 stoichiometric ratio, and all binding constants and enthalpies of binding increase with increasing temperature. This trend applies throughout the analysis apart from flurbiprofen and BCD which shows a decrease as the temperature increases, which could be because of the presence of fluorine affecting the interaction. Furthermore, there appears to be a positive correlation between drug lipophilicity and the measured binding constant and the binding enthalpy, suggesting the more lipophilic the drug the stronger the interaction, and consequently stronger the bond. This also suggests that the drug had a greater affinity for the less polar cavity of cyclodextrin. In general, all complexes that were formed are thermodynamically favourable, for example enthalpies and Gibb's free energies are negative with slightly positive entropy and as a result binding is favourable and a complex is likely to be formed. Overall, the most favourable complex that was formed appeared to be flurbiprofen with BCD at 298K, (K_b = 14.93x10^3 (±0.6) dm^3mol^{-1}, ΔH = ─15.1 (±1.4) kJ mol^{-1}, ΔG = ─23.8 (±0.1) kJ mol^{-1} and ΔS = 0.03 (±0.002) kJ mol^{-1}), however for all processes it is enthalpic rather than an entropically driven complex formation process.

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Chapter 4

Formulation Stability

Chapter 4

The previous chapter looked into how the drug and excipient bond and the energy associated with that mechanism. This chapter presents analytical results of the formulated products.

For clarity, the chapter is separated into three different techniques, namely differential scanning calorimetry (DSC), scanning electron microscopy (SEM) and thermal activity monitoring (TAM). These techniques will allow the compatibility of the drug and excipient to be determined, how each formulation appears, the stability of the drug/excipient mixture and if there are any differences between the formulation methods (heating and the presence of water).

4.1 Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry (DSC) is a thermal analysis technique that measures the physical and chemical properties of a sample as a function of temperature or time. DSC is useful within the pharmaceutical industry because it helps to determine the physical properties of the drug and the excipient and then a mixture of the two. Therefore DSC can help to illustrate whether or not the drug and excipient are compatible[1-4].

To determine the compatibility of the drug and excipient and to investigate if the formulation method changed the thermal behaviour, analysis considered each of the four different drugs and excipients in isolation. Also, all of the different formulations prepared using microwave and conventional heating, and with or without water present. The illustrated DSC traces are for the initial melt of the formulations and consequently only a short section of the trace is illustrated. Each sample weighed 8mg (±0.5mg) and was placed within an aluminium pan with a pierced lid. The sample was then placed into a heat flux DSC and subjected to a heating program (10°C/min) to mimic the formulation process, and to determine the behaviour of the sample.

4.1.1 Pure components

Each of the four different drugs, ibuprofen, ketoprofen, flurbiprofen and paracetamol were first investigated in isolation using DSC. Secondly the four different excipients were also investigated in isolation. The results are illustrated below in Figure 4.1.1.1 - 4.1.1.8. Each of the pure drugs and excipients were subjected to a heating program (illustrated by the red line on the graph) with a maximum temperature of 125°C. This consequently allowed the drug to melt (unless otherwise stated) and also determine the behaviour of the drug at the formulation temperature (represented by the green line).

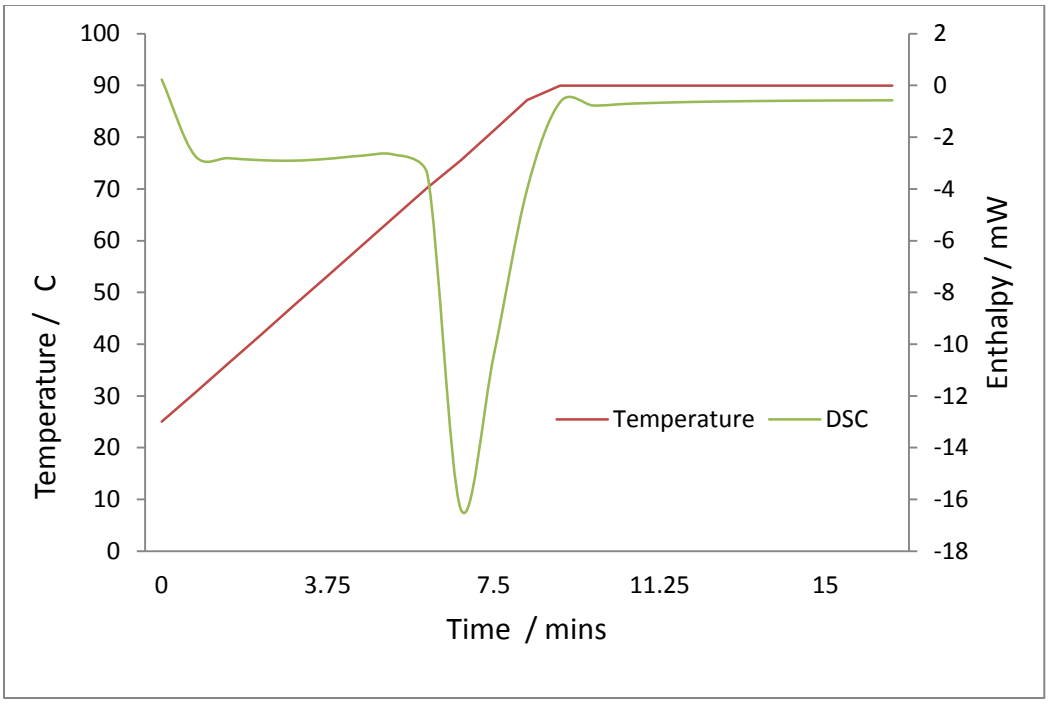

Figure 4.1.1.1 - DSC trace for pure ibuprofen

Figure 4.1.1.1 shows the melting of pure ibuprofen at 77°C as revealed by the endothermic peak. Recrystallisation was often not observed on cooling liquid ibuprofen and literature suggests it can remain in a metastable form for a considerable period of time[5].

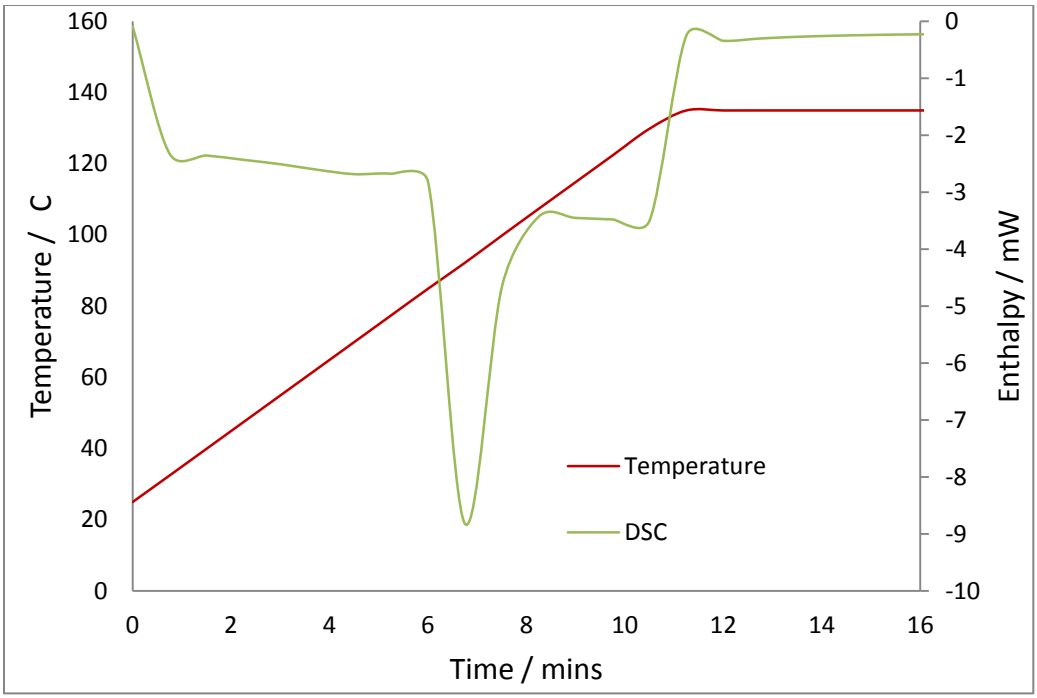

Figure 4.1.1.2 - DSC trace for pure ketoprofen

Figure 4.1.1.2 is for pure ketoprofen, it can be seen from the graph that an endothermic peak is present which represents the melt of the drug at around 95°C.

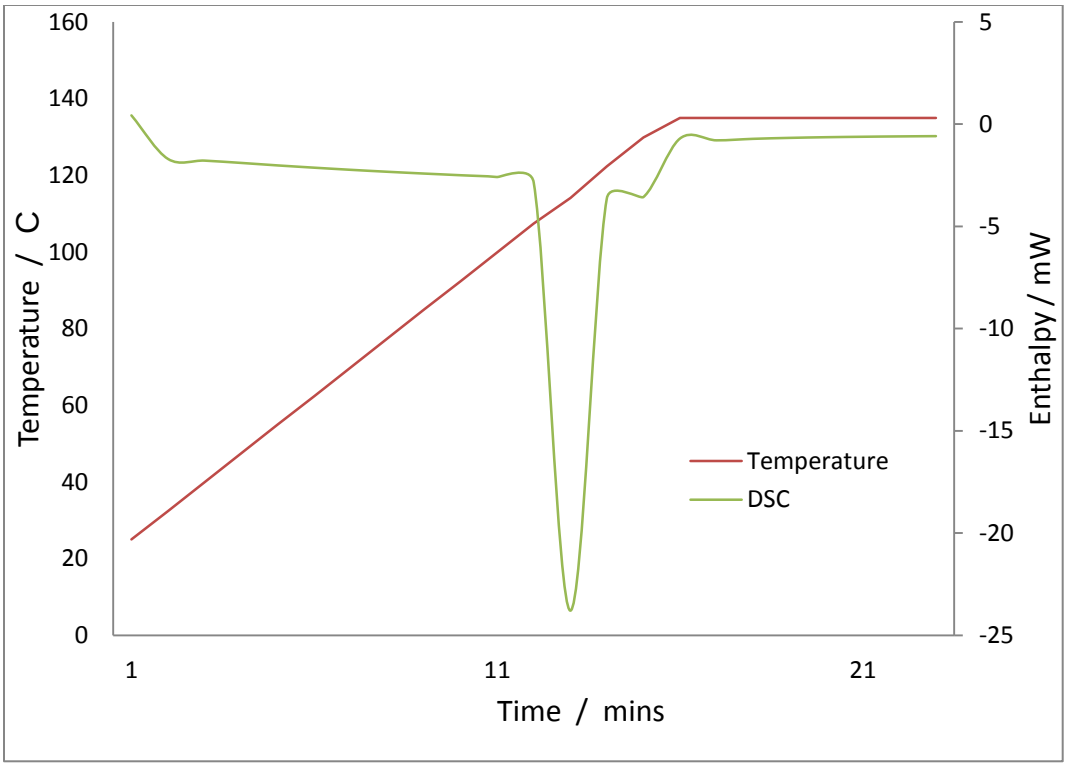

Figure 4.1.1.3 - DSC trace for pure flurbiprofen

Figure 4.1.1.3 illustrates the thermal behaviour of flurbiprofen and it can be seen that an endothermic peak is present. This corresponds to the melt of the drug with a temperature of 115°C. The final drug analysed using DSC was paracetamol and similarly to the other three drugs, an endothermic peak is seen for the melt of the drug, which occurred around 169°C.

After all the drugs were analysed, each of the different excipients were investigated. Each of the excipients were analysed up to 125°C, however in the case of BCD, PVP and HPBCD these were heated to 300°C to determine how they behaved when taken to their decomposition temperature. This however was for interest purposes only and because the formulation temperature was 85°C, only the thermal behaviour up to 125°C is illustrated.

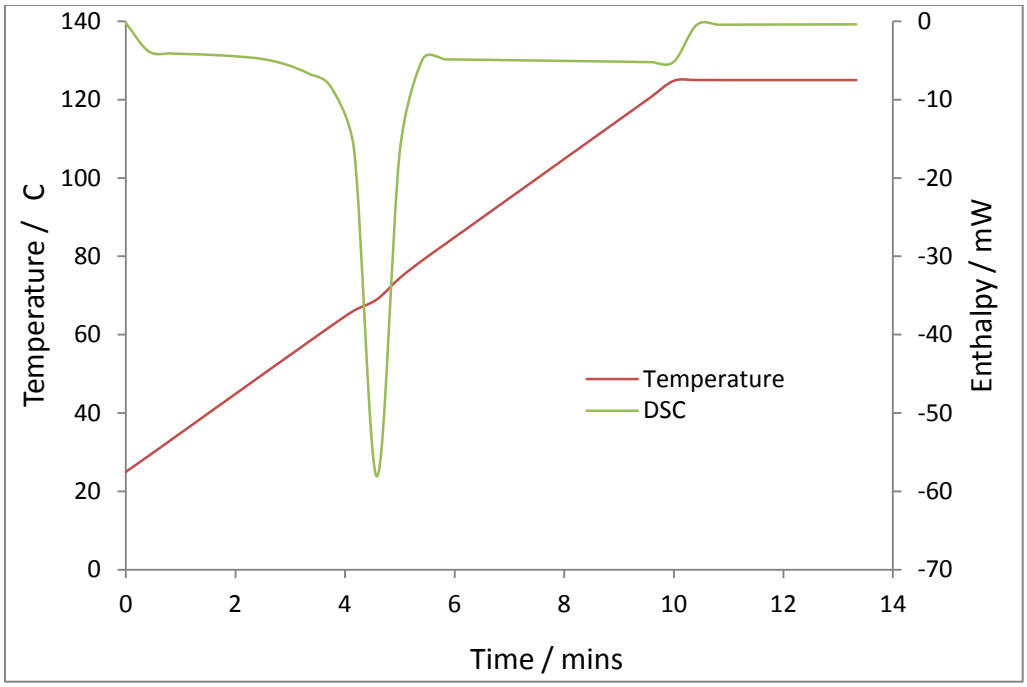

Figure 4.1.1.4 - DSC trace for pure stearic acid (SA)

Figure 4.1.1.4 shows the thermal behaviour for pure stearic acid (SA), and there is an endothermic peak present for the melt of this compound.

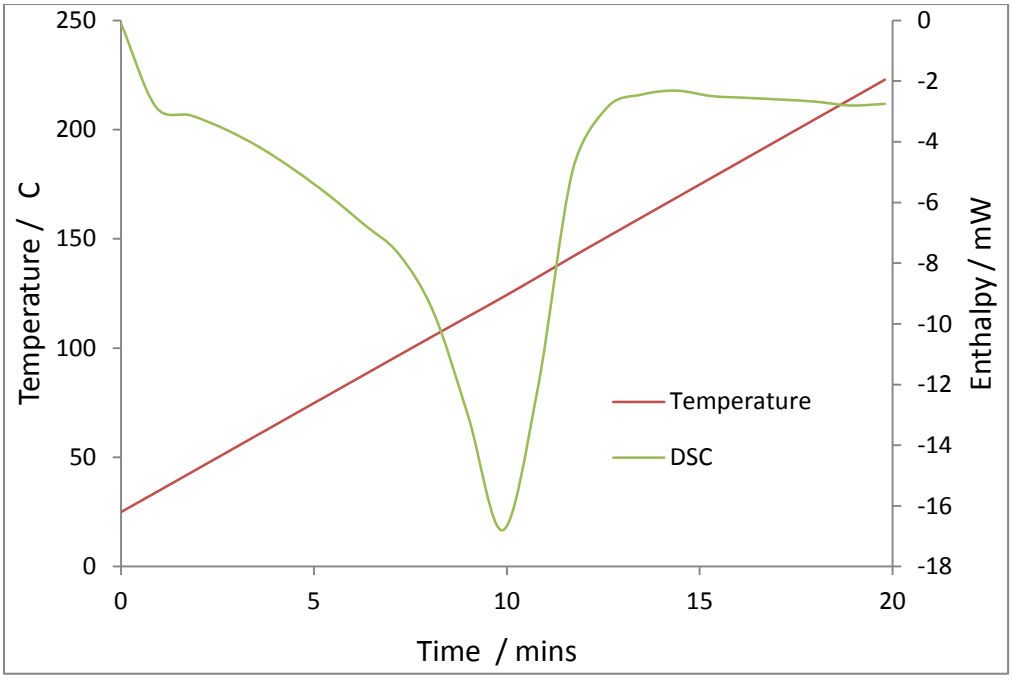

Figure 4.1.1.5 - DSC trace for pure β-cyclodextrin (BCD)

From Figure 4.1.1.5 it can be seen that a broad endothermic peak is present when BCD is heated to and above the formulation temperature. This broad endothermic peak occurs around 120°C, which could correspond to the release of water from the BCD cavity. The BCD used is a hydrate.

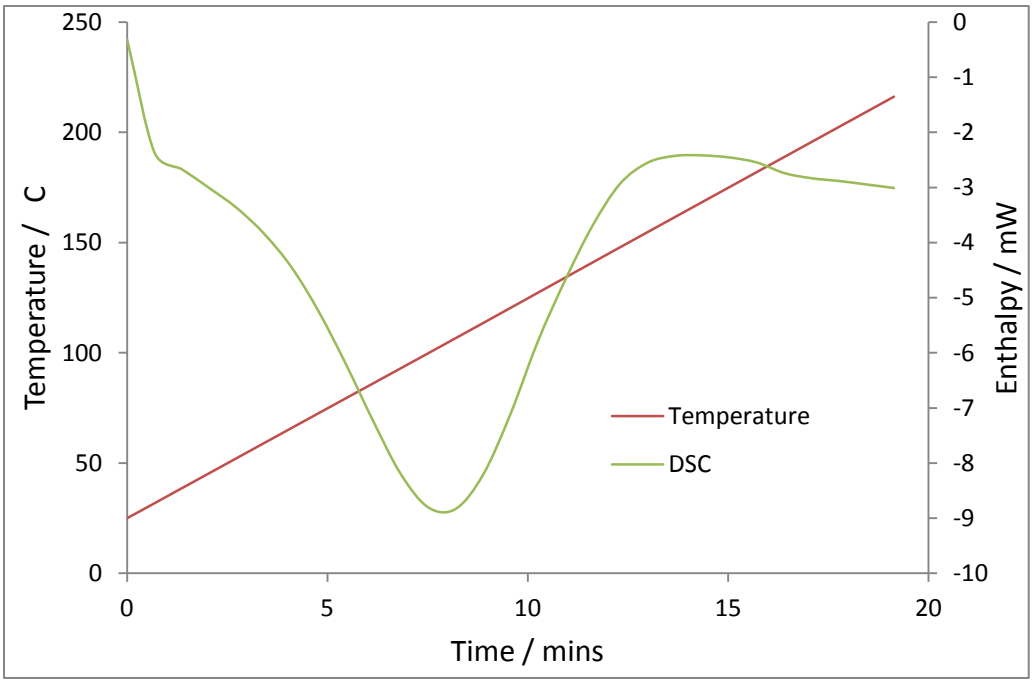

Figure 4.1.1.6 - DSC trace for pure 2-hydroxypropyl-β-cyclodextrin (2HPBCD)

Figure 4.1.1.6 shows the DSC result for 2HPBCD. Again, there is a clear peak around 100°C which again could be the loss of water from the cavity.

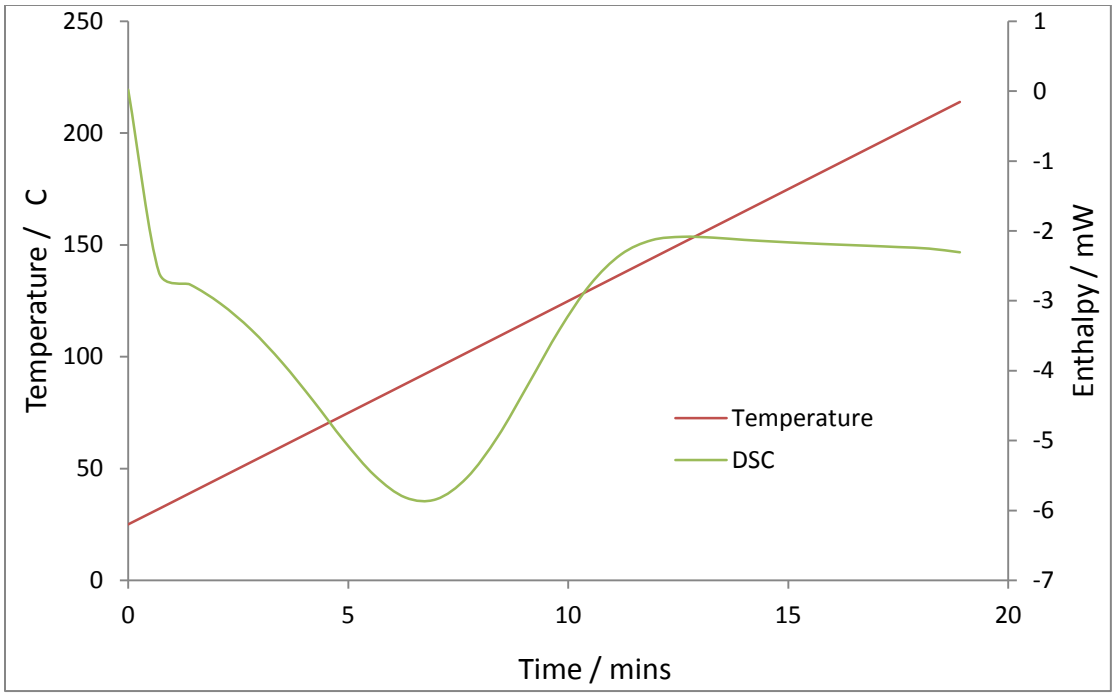

Figure 4.1.1.7 - DSC trace for pure polyvinylpyrrolidone (PVP)

Figure 4.1.1.7 shows the DSC profile for PVP, It is clear from the trace that this excipient is not crystalline, and the peak that is seen could be from the loss of water trapped in the structure of the polymer.

Each of the four drugs were analysed with the four different excipients formulated using microwaves and the conventional heating method (with and without water present).

4.1.2 Ibuprofen and SA

A total of four different formulations were analysed for this drug and excipient combination. Two microwave formulations (with and without water) were investigated and the same for the conventionally heated. An example of the DSC result is illustrated in Figure 4.1.2.1.

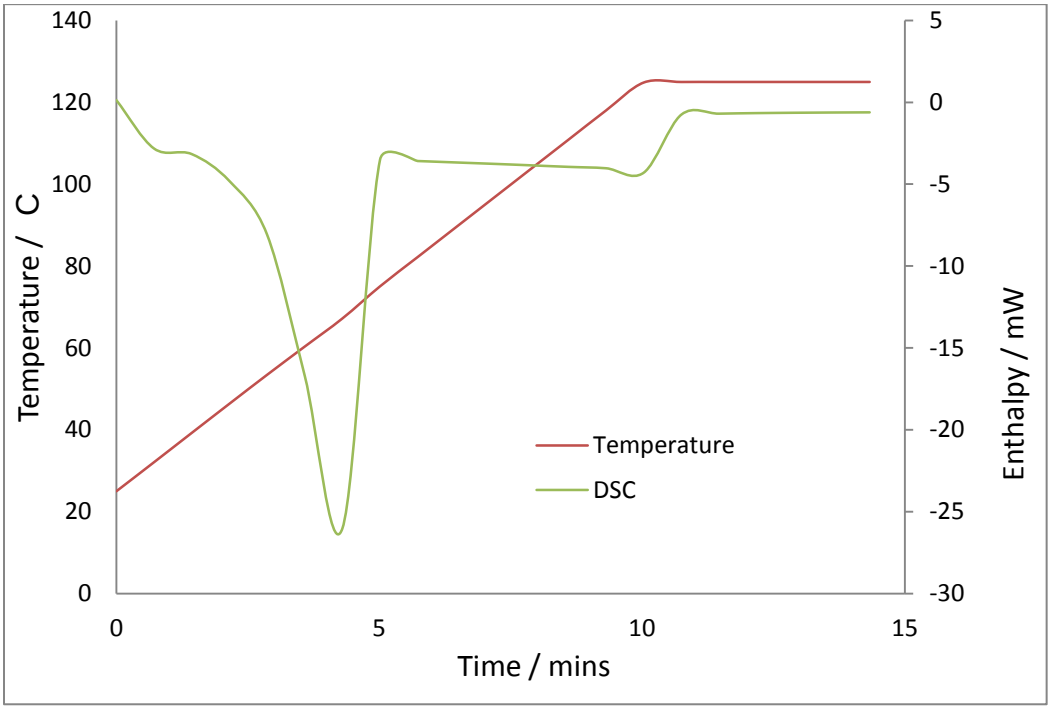

Figure 4.1.2.1 - DSC trace for microwave ibuprofen and stearic acid (SA) without water present in the formulation process

Ibuprofen and SA was formulated with and without the presence of water. When these traces are compared with the pure compounds significant differences can be seen. Firstly there is only one peak seen for the melting of the drug and excipient which could suggest an overlap and consequently a possible interaction between the two compounds after formulation. Another point that may suggest an interaction is the reduction in the temperature of the peak associated with the melting, for pure ibuprofen the melting point is around 77°C and for SA it is 70°C. However for the microwave formulation the melt appears at 65°C, which shows a decrease of 12°C for the drug and 5°C for the excipient. Upon analysis of the formulation prepared using conventional

heating without water present, there is again only one peak present that represents the melt of the formulation. There is also a decrease in the temperature of the melt (65°C) when compared with the pure drug and excipient. All of these findings suggest that an interaction between the drug and excipient has occurred after the formulation method. When the two formulations with water were compared, no significant differences were seen between microwave and conventional heating and also no differences were seen when compared with the formulations prepared without water.

4.1.3 Ibuprofen and BCD

The next formulation analysed was ibuprofen with BCD. Ibuprofen and BCD were formulated in a 1:1 and 1:9 ratio using microwaves and conventional heating (with and without water present). An example of a DSC trace for this formulation can be seen in Figure 4.1.3.1.

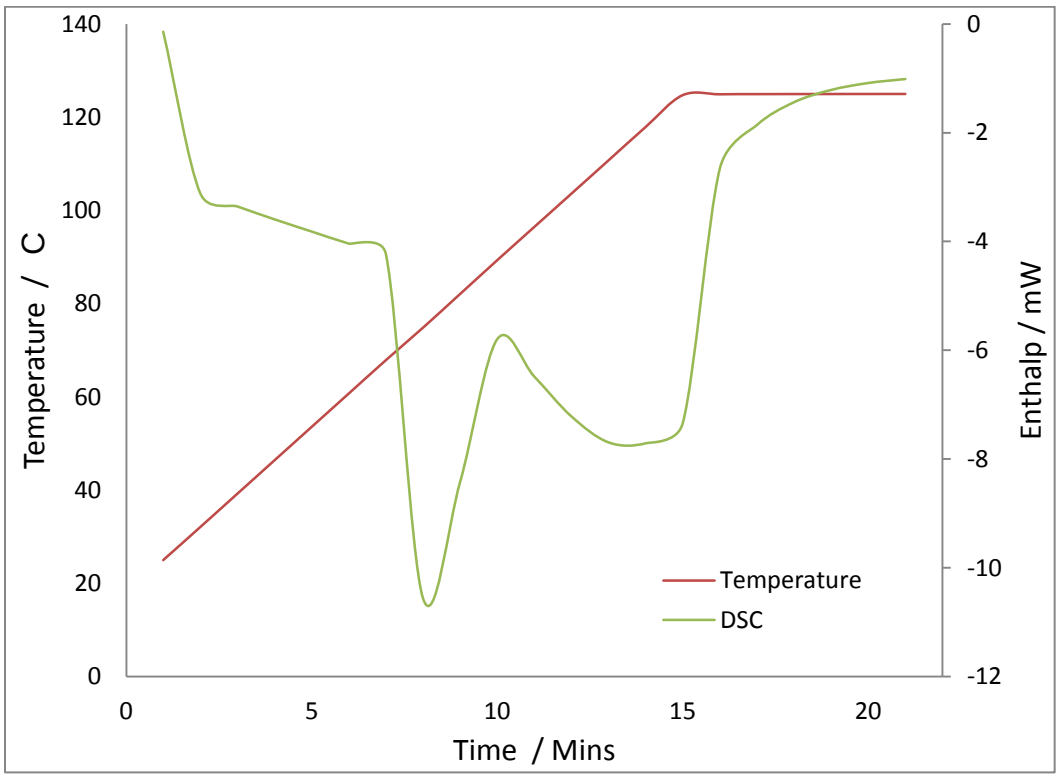

Figure 4.1.3.1 - Microwave formulated ibuprofen and BCD, 1:1 without water present in the formulation process

Figure 4.1.3.1 is an example of ibuprofen formulated with BCD without water present and in the 1:1 ratio. The first peak occurs at about 75-80°C which corresponds to the melt of ibuprofen, the second peak appears around 100°C which corresponds to the loss of water from the cyclodextrin cavity. After these results were compared with the pure compounds it appears no significant differences occurred. The melt for ibuprofen has not been affected by the addition of the excipient and the loss of water from the cyclodextrin cavity is also unaffected. This is also the case for ibuprofen and BCD formulated using conventional heating either with or without water present during the method. Ibuprofen with BCD in a 1:1 ratio either using microwaves or conventional heating appears to not affect the drug's behaviour when subjected to thermal analysis.

Upon comparison of all results obtained for ibuprofen and BCD in the 1:1, it appears that there is little or no significant difference between the two heating methods and consequently it can be said that the thermal behaviour of this formulation is unaffected. Ibuprofen and BCD was also formulated in 1:9 ratio with or without the presence of water, and Figure 4.1.3.2 is an example of a result obtained.

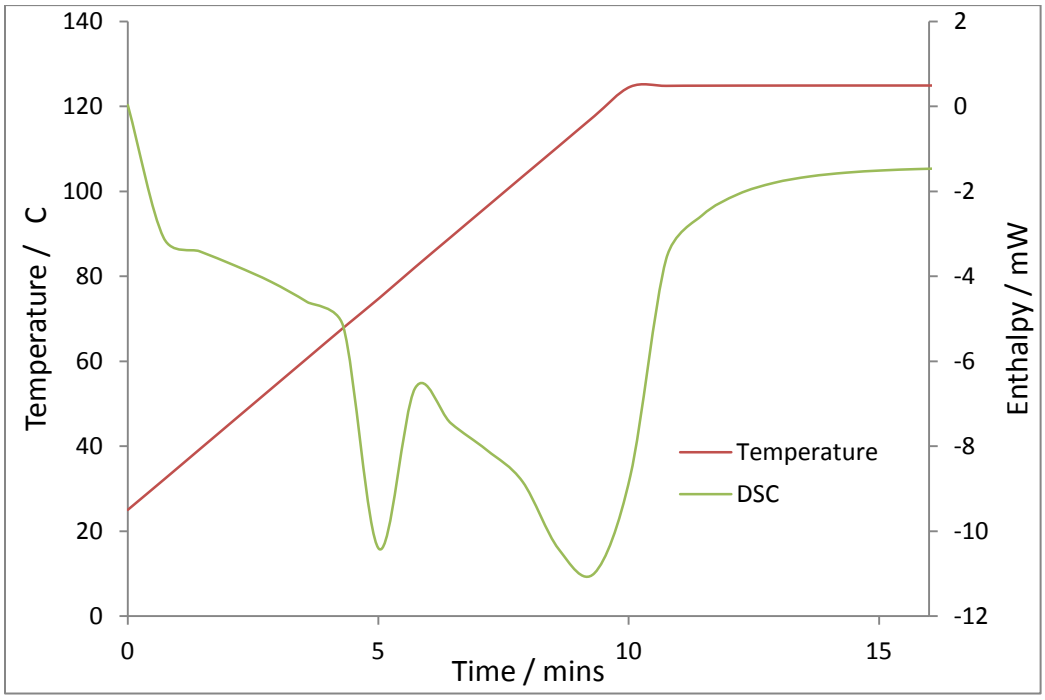

Figure 4.1.3.2 - Microwave formulated ibuprofen and BCD, 1:9 without water present in the formulation process

Figure 4.1.3.2 shows the DSC traces for ibuprofen and BCD in a ratio of 1:9 formulated using microwave heating. When the formulation is heated without the presence of water, two peaks can clearly be seen. The first peak appears to correspond to the melt of ibuprofen which is around 76°C and the dehydration of the cyclodextrin cavity, at 100°C. These temperatures are very similar to the pure drug and excipient, which may suggest that the formulation has had no affect on the thermal behaviour of the two components. This was also the case for the formulation prepared with water, this again suggests that the choice of heating method doesn't affect the thermal behaviour of the drug.

4.1.4 Ibuprofen and 2HPBCD

Due to the potential loss of the drug and excipient within the formulation solvent i.e. the water, only ibuprofen and 2HPBCD without water was formulated. An example can be seen in Figure 4.1.4.1.

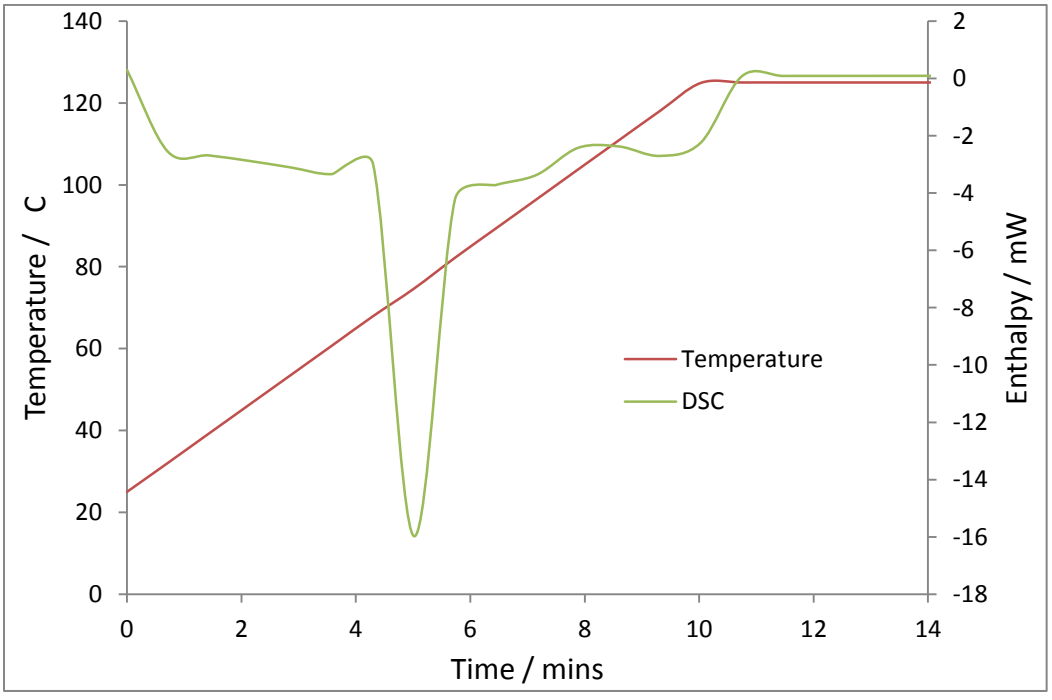

Figure 4.1.4.1 - Microwave formulated ibuprofen and 2HPBCD, 1:1 without present in the formulation process

Figure 4.1.4.1 is for microwave formulated ibuprofen and 2HPBCD. From the graph it can be seen that only one peak is present with a temperature of 75°C which appears to correspond to ibuprofen. As a result, it is possible to say that the formulation method has had little or no effect on the behaviour of the drug.

This is also the case for the conventionally formulated ibuprofen and 2HPBCD. The only peak present has a melting point of 75°C indicating it is the drug that is melting, consequently this example is not illustrated.

Ibuprofen and 2HPBCD was also analysed in a 1:9 ratio, an example can be seen in Figure 4.1.4.2.

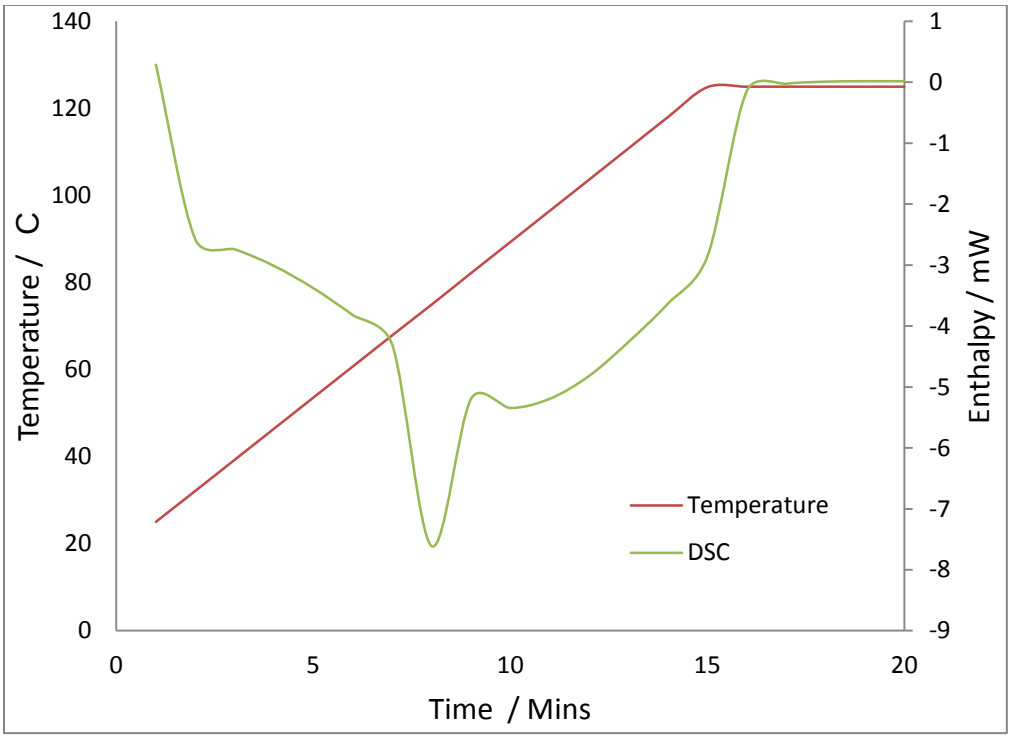

Figure 4.1.4.2 - Microwave formulated ibuprofen and 2HPBCD, 1:9 without water present in the formulation process

The above DSC traces are for microwave formulated ibuprofen and 2HPBCD, 1:9. From analysis and comparison of the formulated compounds with the pure components little or no difference is seen for the drug when formulated.

4.1.5 Ibuprofen and PVP

After ibuprofen was analysed with 2HPBCD, the next excipient formulated with the drug was PVP. The results are illustrated in Figures 4.1.5.1 – 4.1.5.2.

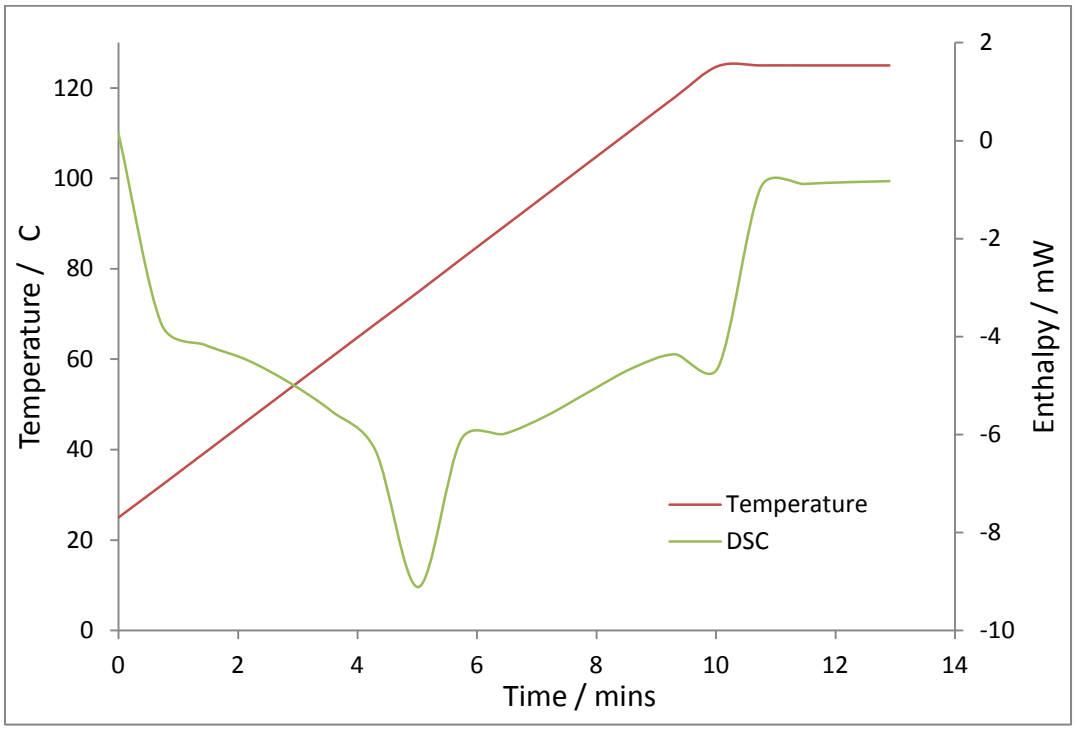

Figure 4.1.5.1 - Microwave formulated ibuprofen and PVP 1:1 without water present in the formulation process

Figure 4.1.5.1 is for the microwave formulated product without water in the 1:1 ratio. Upon comparison of this trace to the pure compounds, there appears to be similarities. The only peak present has a temperature of 76°C which relates to the melting point of ibuprofen. Therefore it appears that the formulation process and the combining of the drug and excipient has made no difference to the behaviour of the two compounds.

However when water is present in the formulation process, two peaks become present with a slight overlap. The first peak has a temperature of 75°C which could be the melting point of ibuprofen (slight decrease) and the second peak has a temperature of 90°C which could relate to the removal of water from the polymer. For the latter when this was compared with the pure PVP trace a difference was noticed, with the formulation the removal of water occurs at 90°C, which is a 10°C decrease to the pure

compound (100°C). It is possible that because ibuprofen is poorly water soluble, when water is present it is more likely to bond to the polymer chain. This would then be seen by an easier removal of water from the polymer and as a result a reduction in the temperature of the excipient peak.

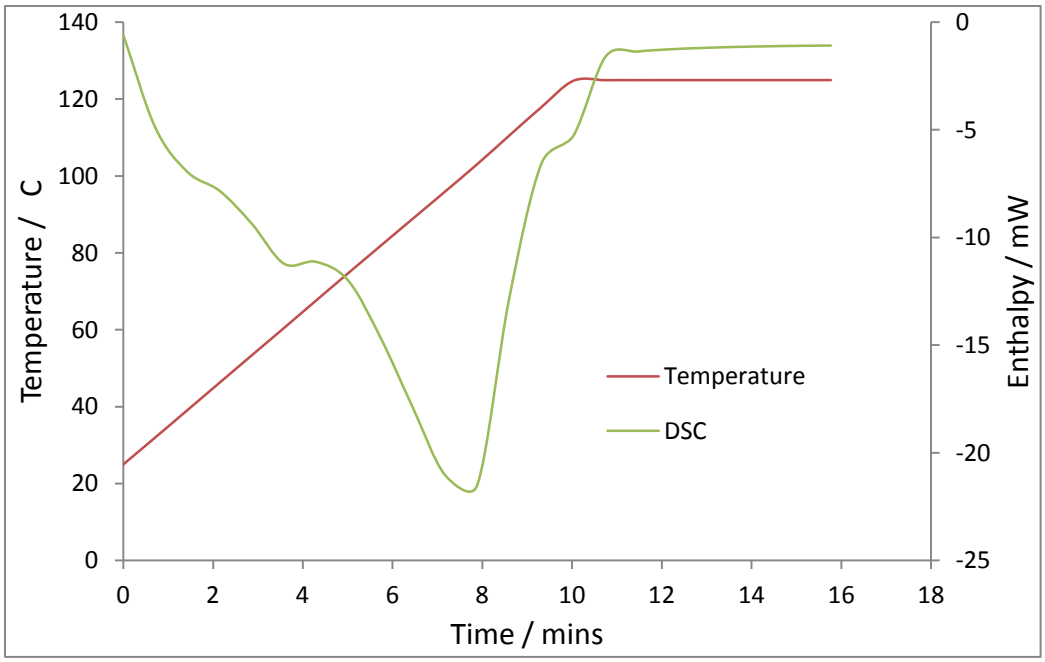

Figure 4.1.5.2 - Conventional formulated ibuprofen and PVP 1:1 with water present in the formulation process

Figure 4.1.5.2 is for ibuprofen and PVP heated conventionally with water, and it can be seen that a single peak is present. From analysis of the temperature at which this occurs, around 75-80°C, it can be said that this peak corresponds to the melt of the drug. This was also seen when ibuprofen and PVP was conventionally formulated without water and consequently this is not illustrated.

After ibuprofen and PVP were analysed in a 1:1 ratio, this drug and PVP were also investigated in a 1:9 ratio. Figures 4.1.5.3 - 4.1.5.4 are examples of the DSC traces for ibuprofen and PVP, in a ratio of 1:9.

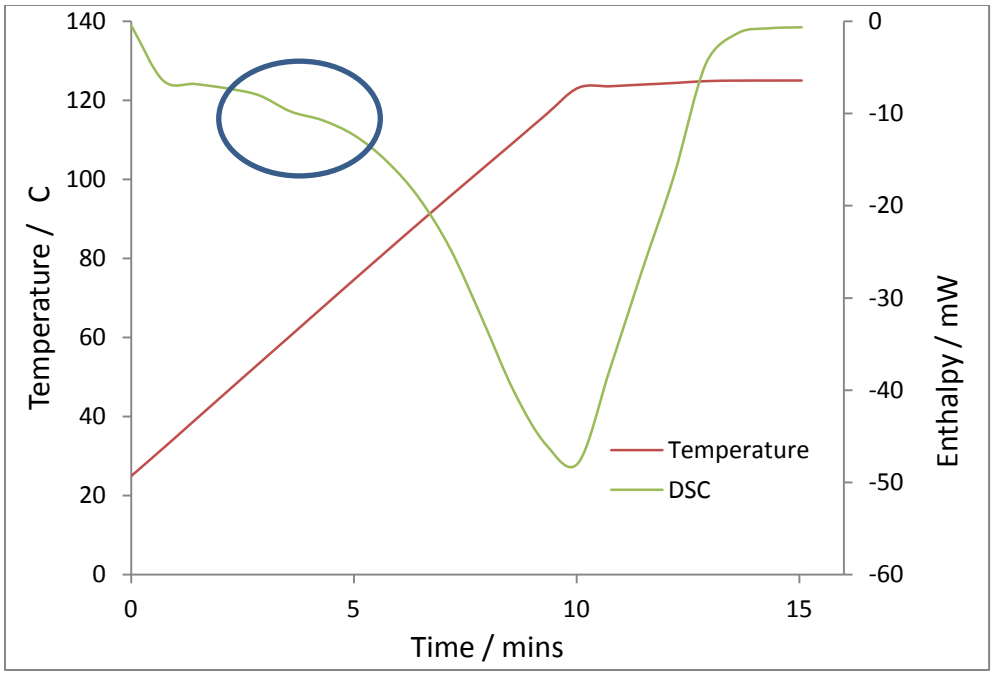

Figure 4.1.5.3 - Microwave formulated ibuprofen and PVP, 1:9 with water present in the formulation process

Figure 4.1.5.3 is an example of microwave formulated ibuprofen and PVP in a ratio of 1:9. For the formulation prepared with water, a clear overlap of the two peaks has occurred with a significant reduction in the melting point of ibuprofen. For pure ibuprofen this melts around 77°C, but in Figure 4.1.5.3 the melt is 60°C which shows a difference of 17°C (illustrated by circle). There is also an increase in the second peak temperature from around 100°C to 116°C. This is again a difference of 16°C, and these results show that after formulation a difference in the behaviour of ibuprofen and PVP has occurred. The overlapping peaks and the decrease in the melt for ibuprofen suggest an interaction has occurred.

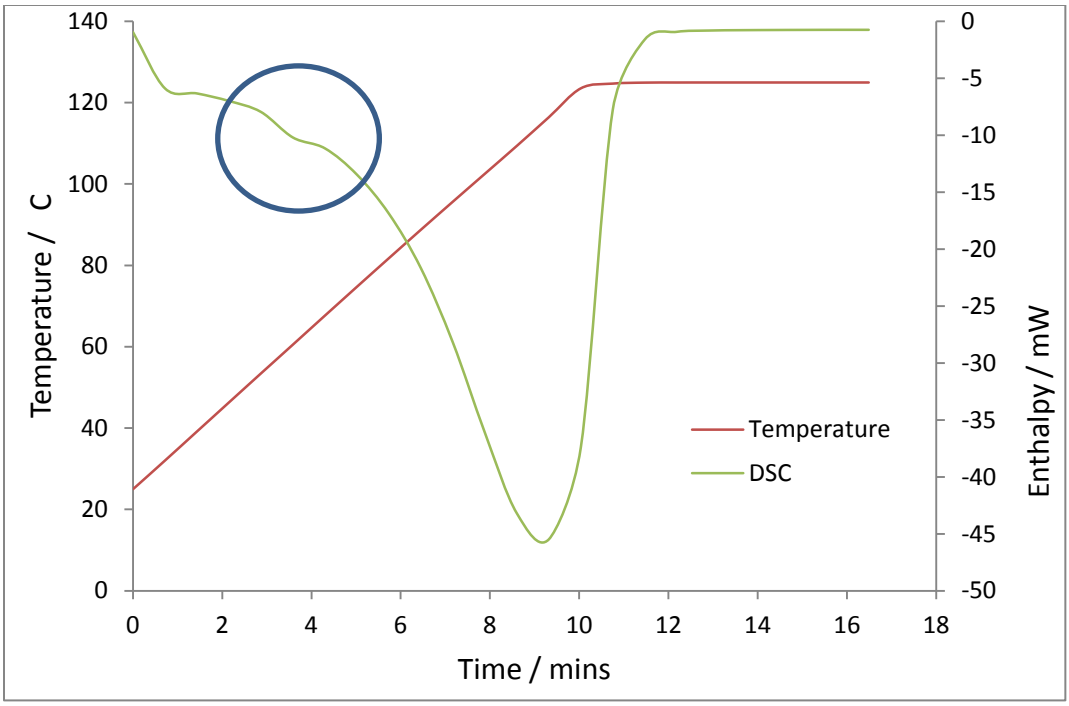

Figure 4.1.5.4 - Conventional formulated ibuprofen and PVP, 1:9 with water present in the formulation process

Figure 4.1.5.4 shows ibuprofen and PVP, 1:9 formulated using conventional heating. It can be seen from the DSC trace that two peaks are present. The first peak corresponds to the melt of ibuprofen (illustrated in the circle) and it occurs at 65°C and the second peak occurs around 110°C. These results suggest that the formulation process has made a difference to the drug and excipient behaviour during thermal analysis with a decrease in the melt for ibuprofen and an increase in the expulsion of water from the polymer chain. This therefore shows that an interaction may have occurred and a complex may have formed between the two compounds.

From all the results obtained it appears that there are no overall significant differences between the two heating methods, however there seems to be a difference between the ratios with a complex more likely to form between the 1:9 ratio compared with the 1:1 ratio.

4.1.6 Ketoprofen and SA

Figure 4.1.6.1 and Figure 4.1.6.2 show the DSC profiles for ketoprofen and SA formulated using microwave and conventional heating. From analysis of the four different formulations, in all cases only one peak is present (see illustrated examples).

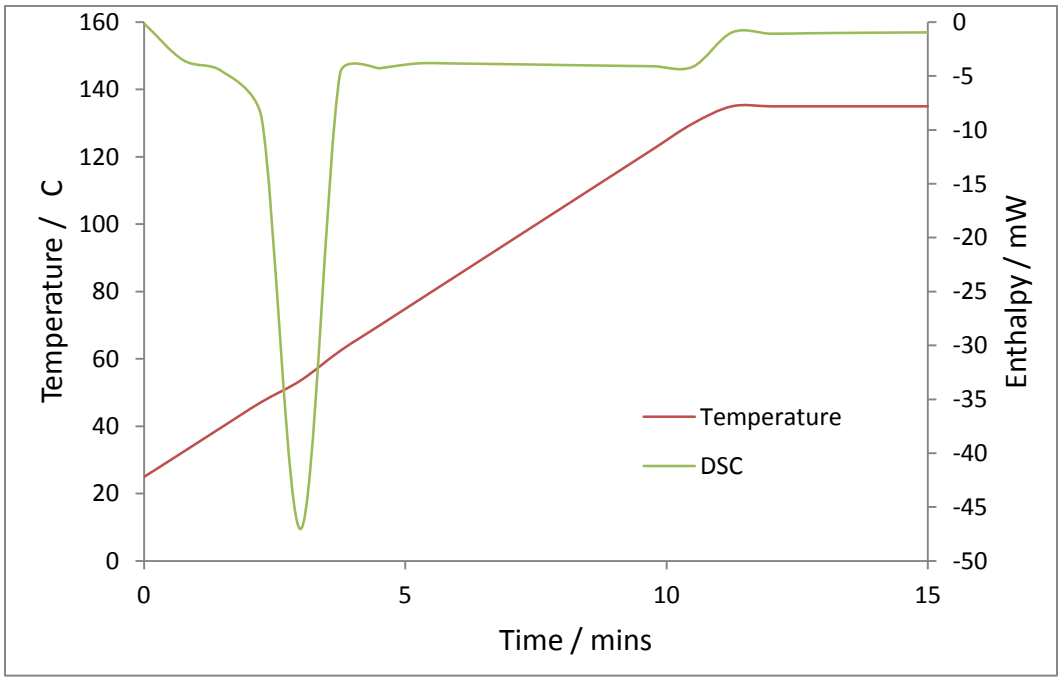

Figure 4.1.6.1- Microwave formulated ketoprofen and SA, with water present in the formulation process

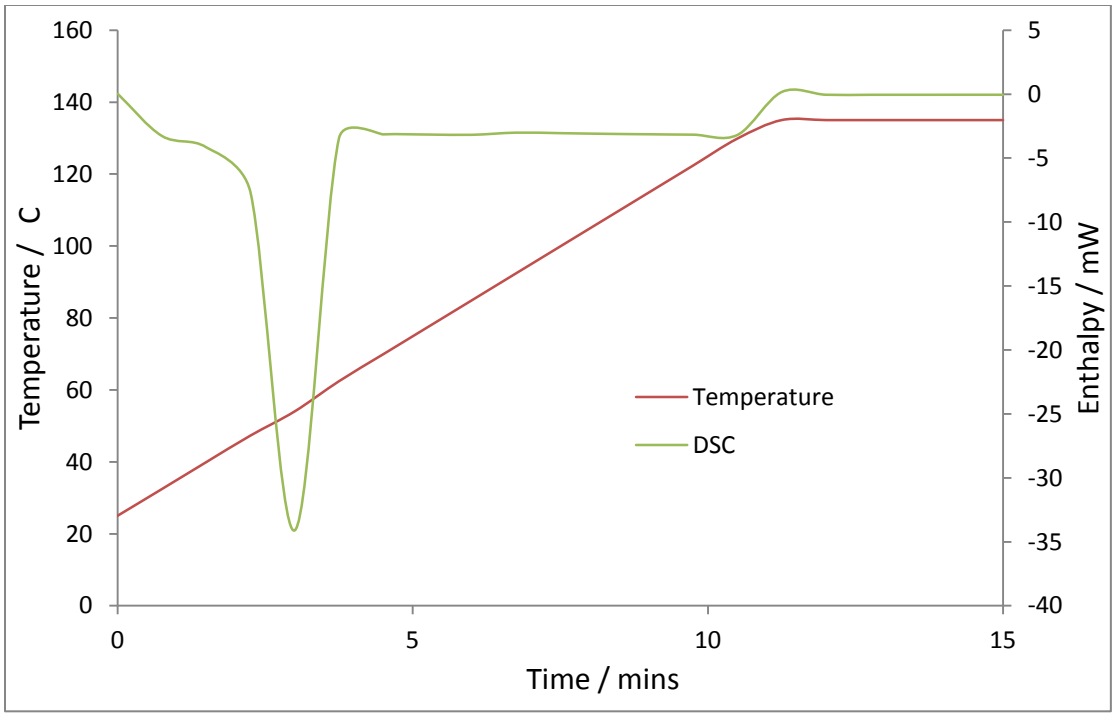

Figure 4.1.6.2 - Conventional formulated ketoprofen and SA, without water present in the formulation process

Figure 4.1.6.1 and 4.1.6.2 illustrates ketoprofen and SA formulated using microwaves and conventional heating. It can be seen that a single peak is present and from analysis of the temperature, it appears that this thermal event occurs around 55°C. It is therefore likely this event corresponds to the melting point of the excipient, however there is a decrease in this temperature when compared to the pure compound (70°C to 55°C). This may suggests that an interaction has occurred between ketoprofen and SA. However, there is no peak that corresponds to the melting point of the drug which may show that a reduction in the melting point of the drug has occurred and the single peak present is actually both the excipient and the drug. However, another possibility is that the formulation is not as homogenous as expected. Ketoprofen doesn't melt at the formulation temperature (85°C) and as a consequence the resultant formulation may not be homogenous throughout. Also a small amount of formulation is taken for analysis, therefore weight error may have been introduced. If the prior statement is the case then a way to overcome this problem would be to increase the initial mixing time, and also to grind and re-mix the formulation after the heating process.

4.1.7 Ketoprofen and BCD

Ketoprofen and BCD were formulated using microwaves and conventional heating with and without the presence of water. The following results are examples of these formulations and are illustrated in Figures 4.1.7.1 - 4.1.7.2.

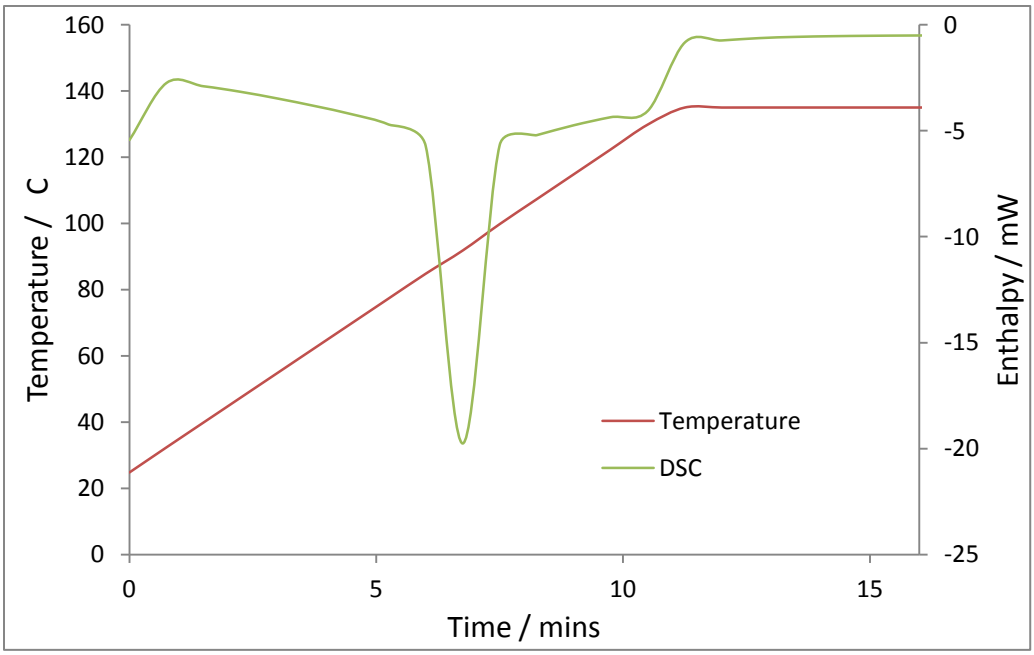

Figure 4.1.7.1 - Microwave formulated ketoprofen and BCD, 1:1 without water present in the formulation process

Figure 4.1.7.1 shows ketoprofen and BCD, 1:1 formulated using microwaves without the presence of water. It is evident from the graph that a single peak is present with a temperature of 90°C, which is likely to correspond to the melt of the drug. This shows a decrease in the melt of the drug and there is also no peak for the removal of water from the cyclodextrin cavity. Therefore these results suggest that the formulation process has made a difference to the thermal behaviour and it is possible an interaction has occurred between the drug and excipient. The result obtained for this particular formulation was also illustrated for the conventionally heated formulation (consequently example not illustrated), this suggests that the choice of heating method makes no difference to the way the compounds behave once formulated.

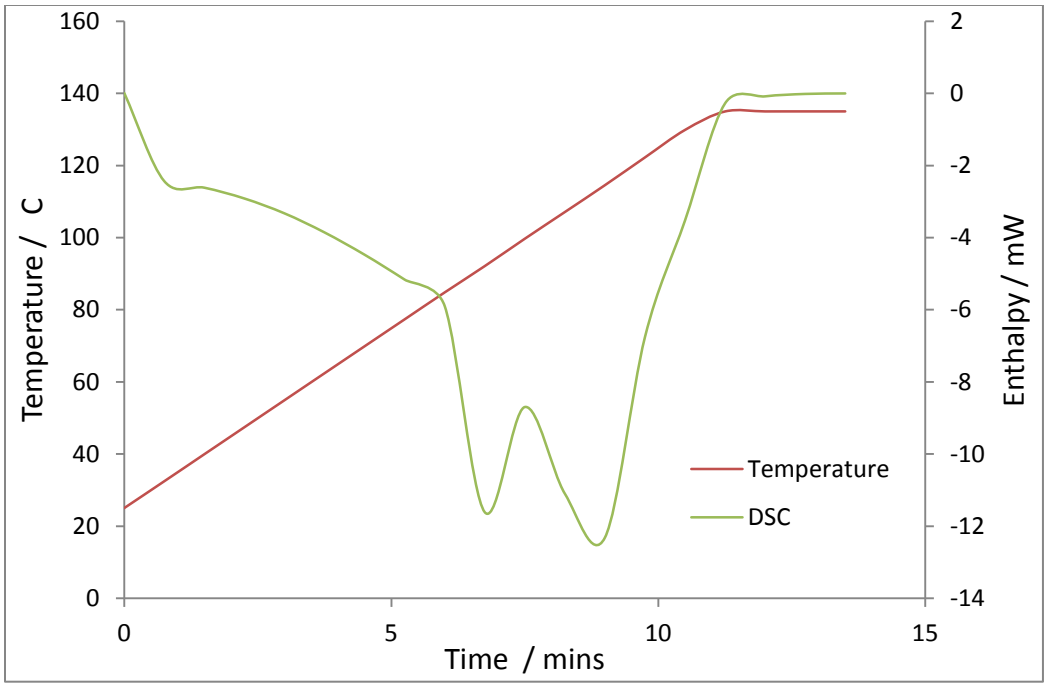

Figure 4.1.7.2 – Microwave formulated ketoprofen and BCD, 1:9 without water present in the formulation process

Figure 4.1.7.2 displays the thermal analysis for ketoprofen and BCD, 1:9 formulated using microwaves, and without the presence of water. It is clear from the graph that two peaks are present, with the first having a corresponding temperature of 85°C and the second peak temperature of 110°C. This shows a decrease for the melt of the drug and an increase for the removal of water from the cyclodextrin cavity, therefore it is possible an interaction occurred between the two compounds. This is justified by a change in the thermal behaviour of the drug and excipient after the formulation process. This was also seen for the conventional formulation and is consequently not illustrated.

4.1.8 Ketoprofen and 2HPBCD

Ketoprofen and 2HPBCD was formulated using microwave and conventional heating, without the presence of water. The results are illustrated in Figures 4.1.8.1 to 4.1.8.2.

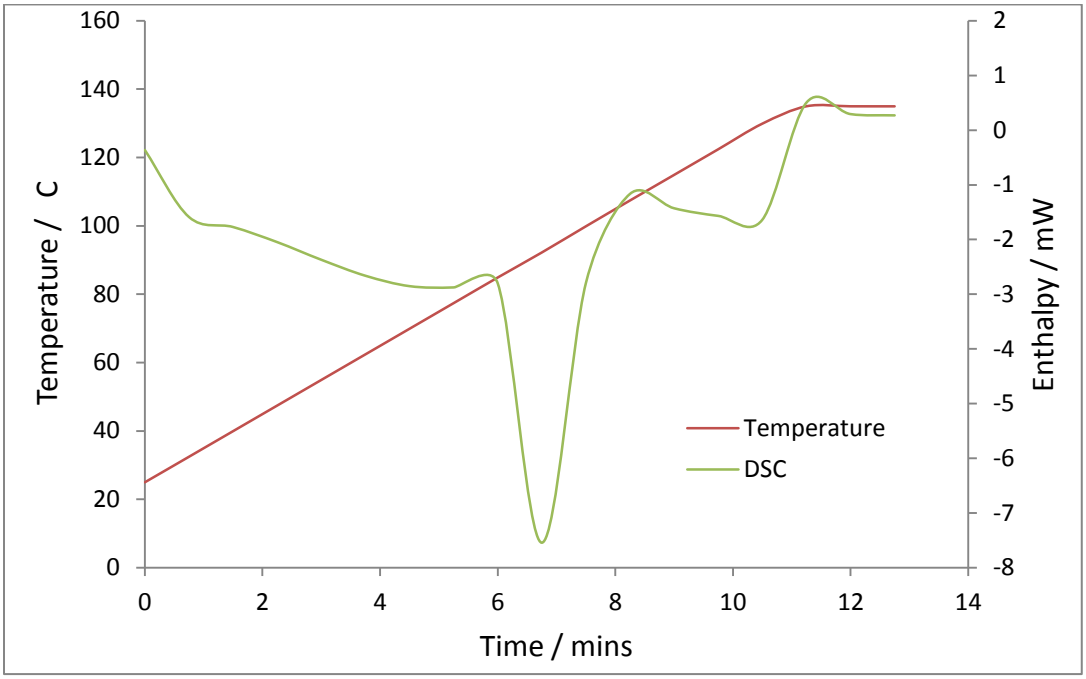

Figure 4.1.8.1 - Microwave formulated ketoprofen and 2HPBCD 1:1, without water present in the formulation process

Figure 4.1.8.1 displays the DSC traces for ketoprofen and 2HPBCD in the 1:1 ratio formulated using microwave heating, and without the presence of water. It can be seen that a single peak can be seen with a temperature of 90°C. This is likely to correspond to the melt of the drug, and as a result it is possible to say that the formulation process has had little or no effect on the thermal behaviour of the drug. It is also a possibility that a single peak is present because the dehydration of the cyclodextrin cavity occurred during the heating method and no water was present to prevent this from happening. This occurred for both formulations and therefore there is no significant difference between the two heating methods.

After ketoprofen and 2HPBCD were analysed in the 1:1 ratio, it was also investigated in the 1:9 ratio and the results are illustrated in Figure 4.1.8.2.

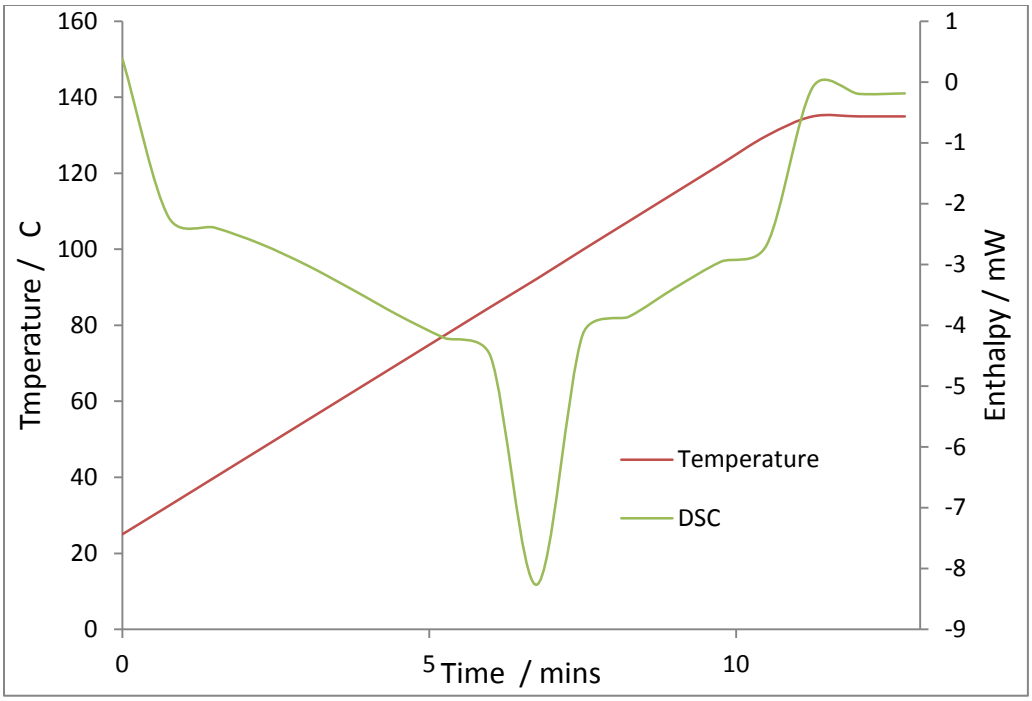

Figure 4.1.8.2 - Conventional formulated ketoprofen and 2HPBCD, 1:9 without water present in the formulation process

Figure 4.1.8.2 shows the formulation prepared using conventional heating. It is evident from the DSC result that a single peak is present with a temperature of 90°C. This temperature corresponds to the melt of the drug and as a consequence the formulation process appears to not have made a difference to the thermal behaviour of the drug.

4.1.9 Ketoprofen and PVP

Ketoprofen was formulated with PVP in the 1:1 and 1:9 ratios, using microwave and conventional heating, with or without the presence of water. Figures 4.1.9.1 and 4.1.9.2 displays ketoprofen and PVP in the 1:1 and 1:9 ratios.

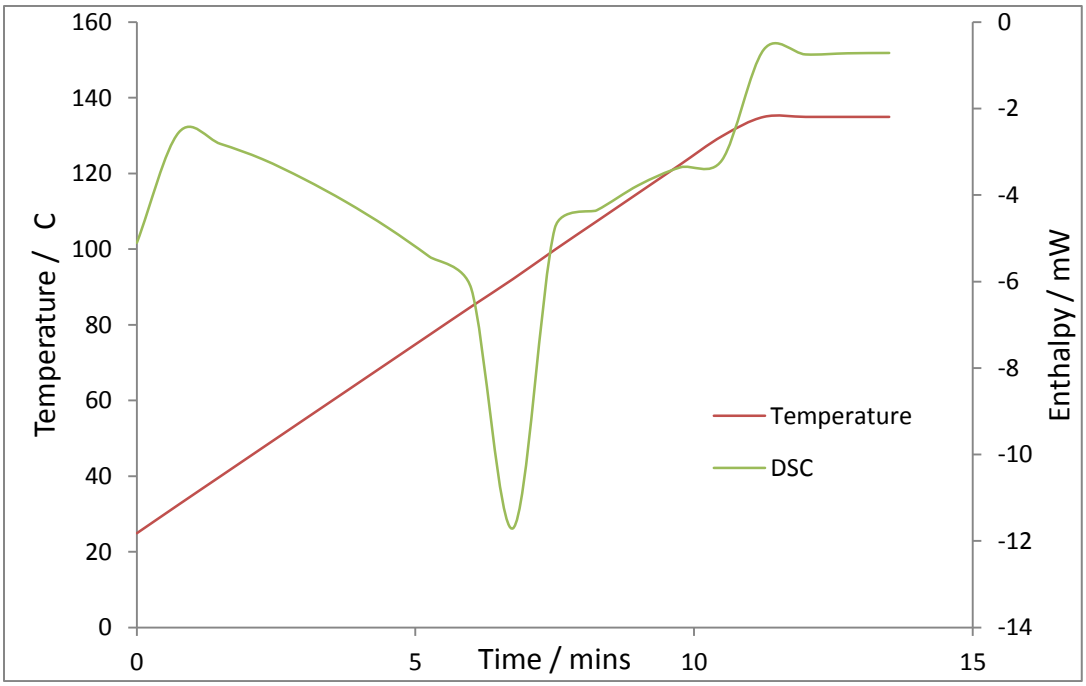

Figure 4.1.9.1 – Microwave formulated ketoprofen and PVP, 1:1 without water present in the formulation process

Figure 4.1.9.1 shows the microwave formulation prepared without water present, it can be seen that the peak is sharp and has a temperature of 90°C. This is likely to correspond to the melt of the drug and for that reason it seems that the formulation process has not affected the thermal behaviour of the drug. The absence of the polymer dehydration peak may be because the heating method has already removed any moisture and as a result it will not be present in the DSC trace.

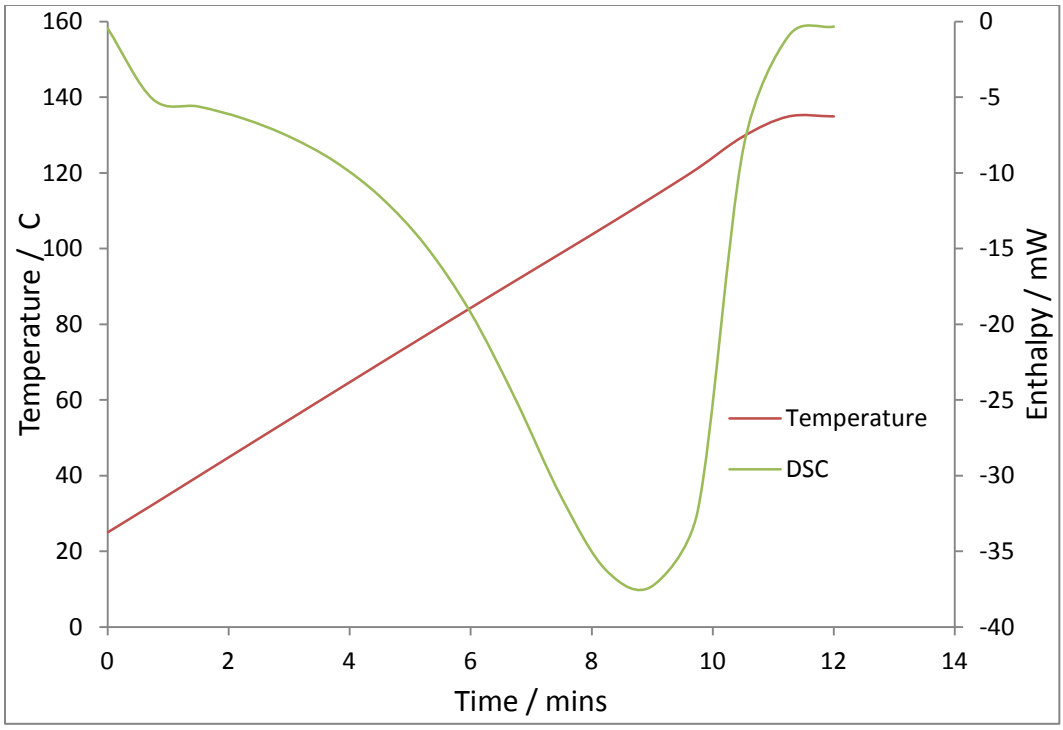

Figure 4.1.9.2 - Microwave formulated ketoprofen and PVP, 1:9 with water present in the formulation process

Figure 4.1.9.2 is an example of microwave formulated ketoprofen and PVP with water present during the formulation method. It is evident from the graph that only a single peak is present, with a temperature of around 90°C which is likely to correspond to the melt of ketoprofen. This may suggest that no significant difference has occurred to the thermal behaviour of the drug once formulated.

4.1.10 Flurbiprofen and SA

Flurbiprofen and SA were analysed in a 1:3 ratio. A total of four different formulations were prepared and analysed. However as previously seen only a few examples are illustrated unless significant differences occurred between the formulations.

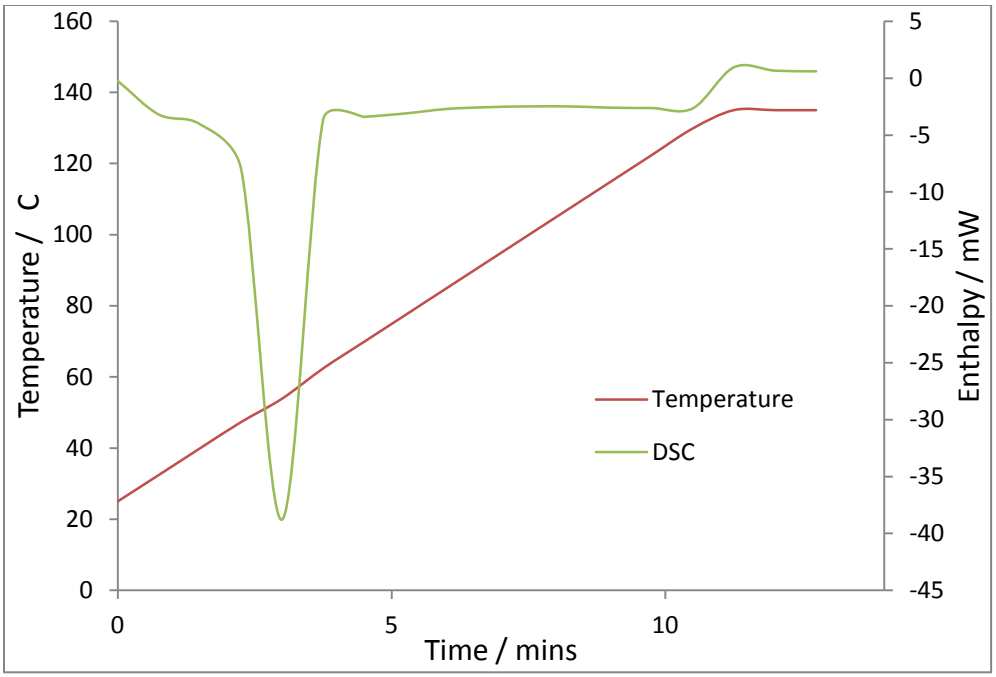

Figure 4.1.10.1- Microwave formulated flurbiprofen and SA, 1:3 without water present in the formulation process

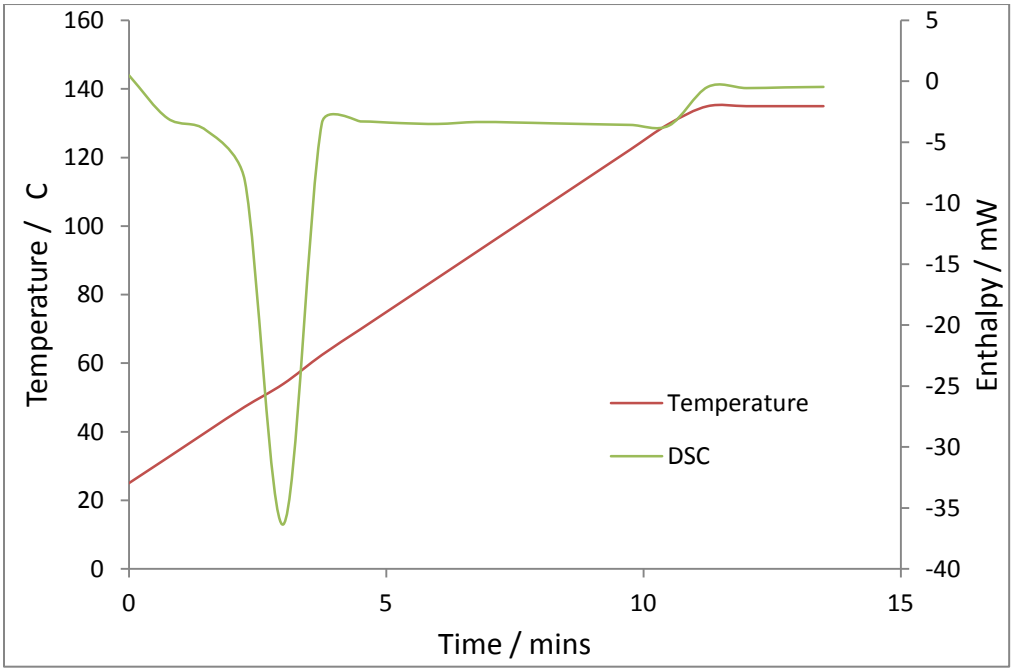

Figure 4.1.10.2 - Conventional formulated flurbiprofen and SA, 1:3 with water present in the formulation process

It can be seen from Figure 4.1.10.1 and 4.1.10.2 that only a single melting peak is present. In both cases a peak temperature of 55°C was seen. This shows a clear decrease in the temperature when compared with the pure components. This could signify an interaction between the drug and excipient has occurred and an overlap of two melting points is evident. However, for flurbiprofen to overlap with the melt for the excipient, the melt for the drug would have to decrease by over 60°C. Other possibilities therefore include that the formulation is not as homogenous as expected and as a result when a small amount of the formulation is taken for analysis it may not contain any of the drug. Nevertheless, there is still an apparent decrease in the melt for the peak that is present. Another possibility could be that at the formulation temperature of 85°C, only the SA melts, this could cover the drug, encapsulate it and it may then hide it and prevent it from showing up on the DSC trace.

4.1.11 Flurbiprofen and PVP, 1:1 and 1:9

Flurbiprofen and PVP were formulated in the 1:1 and 1:9 ratios, using microwave and conventional heating, with and without the presence of water.

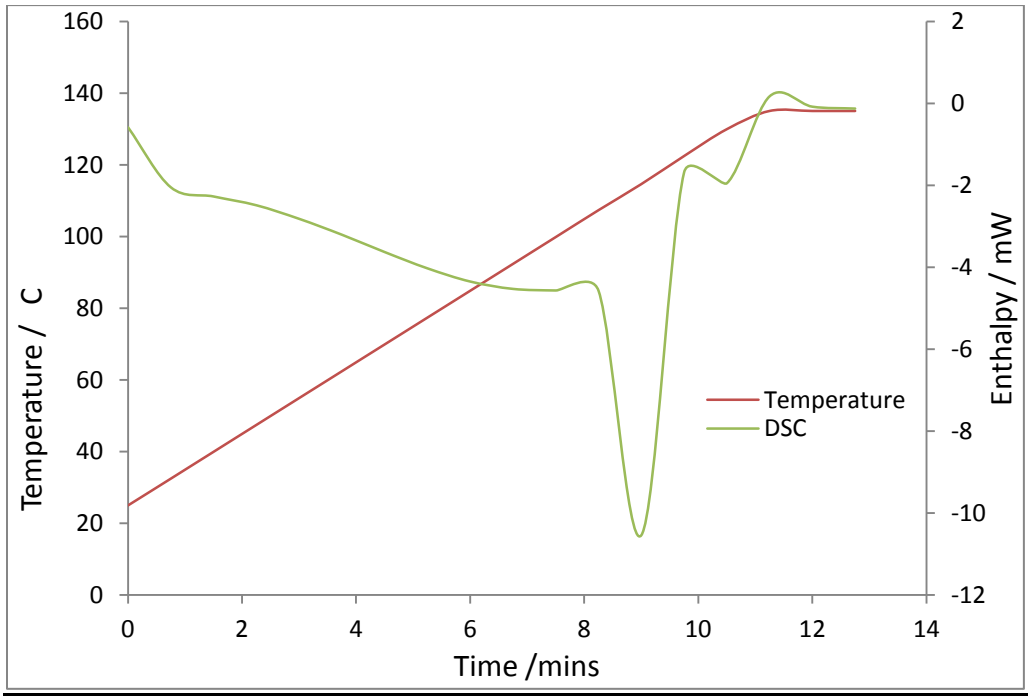

Figure 4.1.11.1 - Microwave formulated flurbiprofen and PVP, 1:1 without water present in the formulation process

Figure 4.1.11.1 is for flurbiprofen and PVP, in the 1:1 ratio formulated using microwaves and without water present. It is evident from the DSC trace that a single peak is present, with a temperature of 115°C which corresponds to the melting point of the drug. This shows that the formulation process has not affected the thermal behaviour of the drug, but it may have dehydrated the excipient and that is why only a single peak is present. The results obtained for the microwave formulations were also observed in the formulations prepared using conventional heating, and this shows that there is little or no significant difference between heating methods.

After the 1:1 formulations were analysed, flurbiprofen and PVP were investigated in the 1:9 ratio, illustrated in Figure 4.1.11.2.

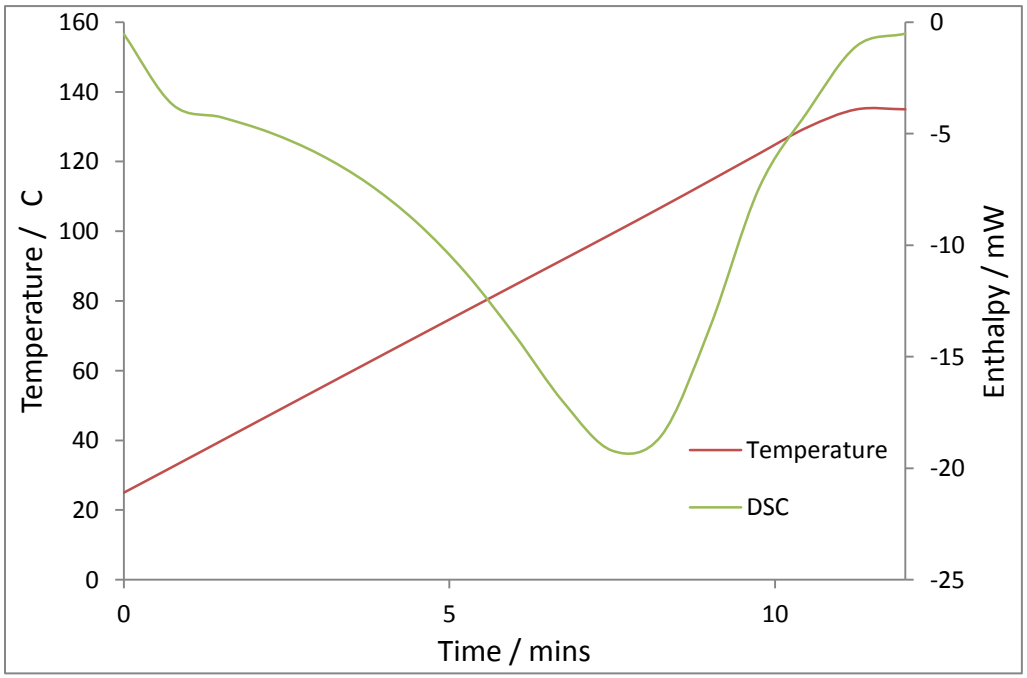

Figure 4.1.11.2 - Microwave formulated flurbiprofen and PVP, 1:9 with water present in the formulation process

Figure 4.1.11.2 is for flurbiprofen and PVP, 1:9 with water. It is evident that a single peak is present with a temperature around 100°C which could be the loss of water from the excipient. It is broad which makes it difficult to determine if there is a peak present for the melting point of the drug. This also occurred for the conventional formulation.

The last drug that was formulated with the four different excipients was paracetamol. The results for this drug are illustrated in Section 4.1.12.

4.1.12 Paracetamol and SA

Paracetamol and SA were formulated without water using microwaves and conventional heating in a 1:3 ratio which can be seen in Figure 4.1.12.1 and Figure 4.1.12.2.

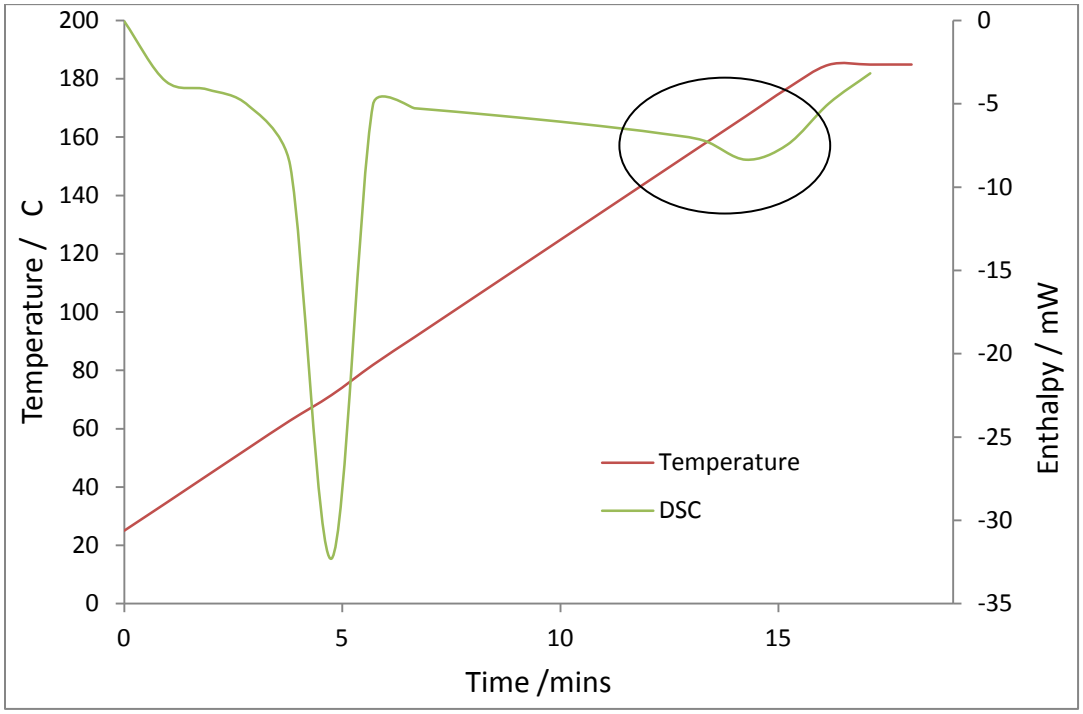

Figure 4.1.12.1 – Microwave formulated paracetamol and SA, 1:3 without water present in the formulation process

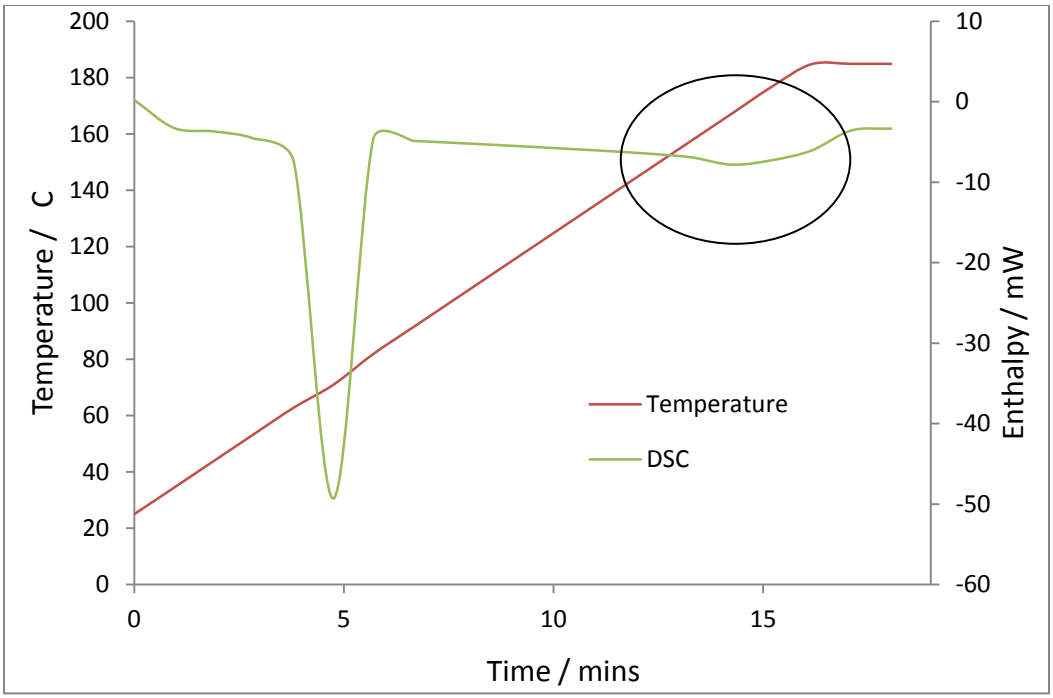

Figure 4.1.12.2-Conventional formulated paracetamol and SA, 1:3 without water present in the formulation process

Figure 4.1.12.1 is for paracetamol and SA formulated using microwaves, and it can be seen from the DSC trace that the first peak has a temperature of 70°C which corresponds to the melt of the excipient, SA. The second peak has a temperature of 170°C, and this corresponds to the melt of the drug (illustrated by the circle). From these results it is apparent that the formulation process has made no significant difference to the thermal behaviour of the drug and excipient. This result was also obtained for the formulation prepared using conventional heating, seen in Figure 4.1.12.2. No significant difference may have occurred in the thermal behaviour because only the excipient melts and may not encapsulate the drug to a maximum extent. This result also indicates that the choice of heating method makes no difference to the overall formulation after the heating process.

4.1.13 Paracetamol and BCD, 1:1 and 1:9

Paracetamol was formulated with BCD in the 1:1 and 1:9 ratios using microwaves and conventional heating, without the presence of water.

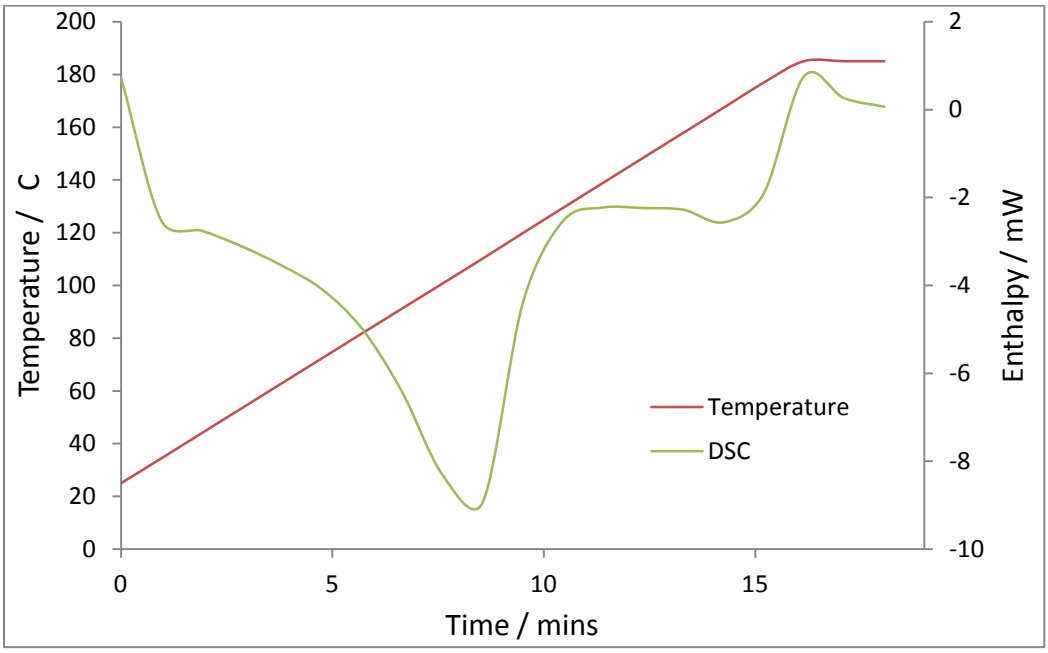

Figure 4.1.13.1 - Paracetamol and BCD, 1:1 formulated using microwave heating without the presence of water

Figure 4.1.13.1 illustrates paracetamol and BCD formulated in the 1:1 ratio using microwave heating, without the presence of water. It can be seen from both DSC traces that two peaks are present, the first has a peak temperature of 110°C which corresponds to the dehydration of the cyclodextrin cavity, a result seen throughout. The second peak has a temperature of 170°C which illustrates the melt of the drug. The about result was also seen for the conventional formulation and consequently this is not illustrated.

Paracetamol and BCD were also formulated in the 1:9 ratio, and the results are illustrated in Figure 4.1.13.2.

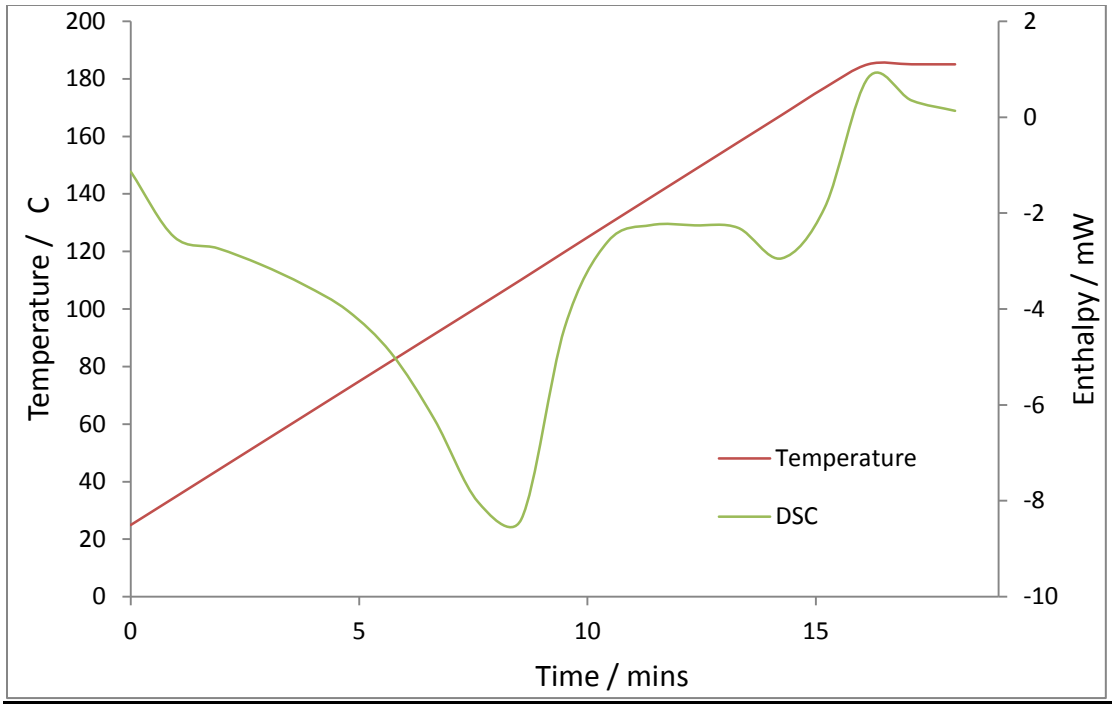

Figure 4.1.13.2 - Paracetamol and BCD, 1:9 formulated using microwave heating without the presence of water

Figure 4.1.13.2 displays paracetamol and BCD formulated using microwave heating. Two peaks are illustrated within this DSC trace, and the first has a peak temperature of 110°C which shows the dehydration of the cyclodextrin cavity. The second peak has a temperature of 170°C which is the melt of the drug.

4.1.14 Paracetamol and 2HPBCD, 1:1 and 1:9

Paracetamol was formulated with 2HPBCD in the 1:1 and 1:9 ratios using microwave or conventional heating without the presence of water.

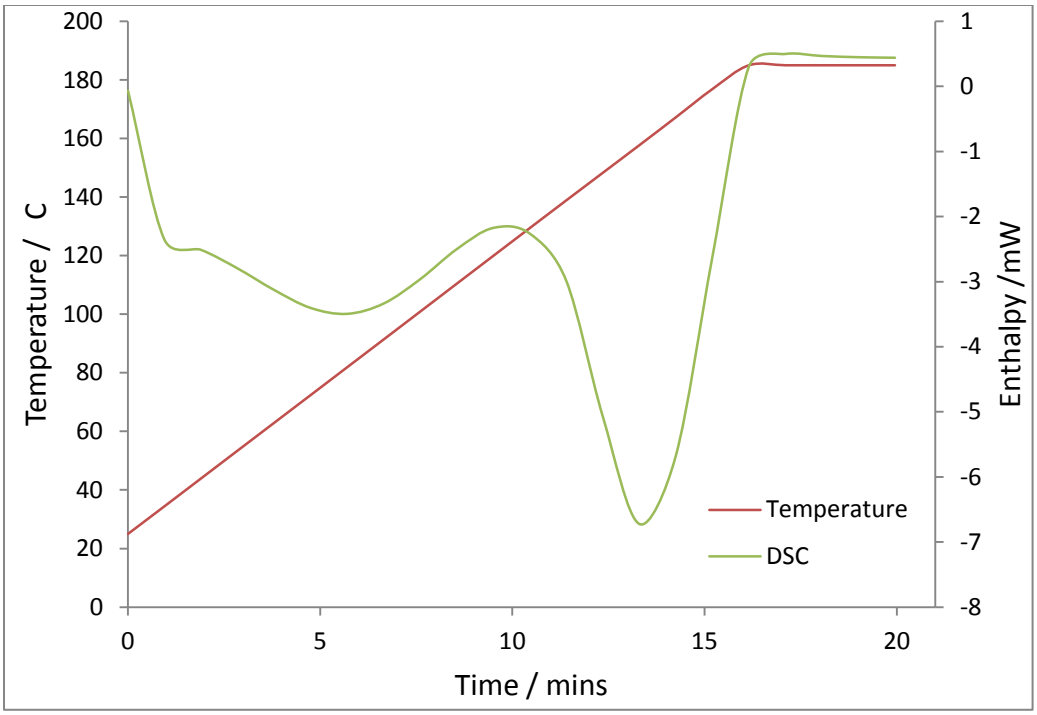

Figure 4.1.14.1 – Microwave formulated paracetamol and 2HPBCD, 1:1 without water present in the formulation process

Figure 4.1.14.1 illustrates paracetamol and 2HPBCD, and it can be seen that two peaks are present and the first peak which is for the release of water from the 2HPBCD cavity has a peak temperature of 85°C and the second peak which is the melt of paracetamol has a peak temperature of 165°C. It is evident that there is a reduction in the melting of the drug and also the expulsion of water from the cavity.

After analysis of the conventionally heated paracetamol and 2HPBCD, 1:1 it was noticed that the same results were achieved regardless of heating method, which shows no significant difference between the heating methods.

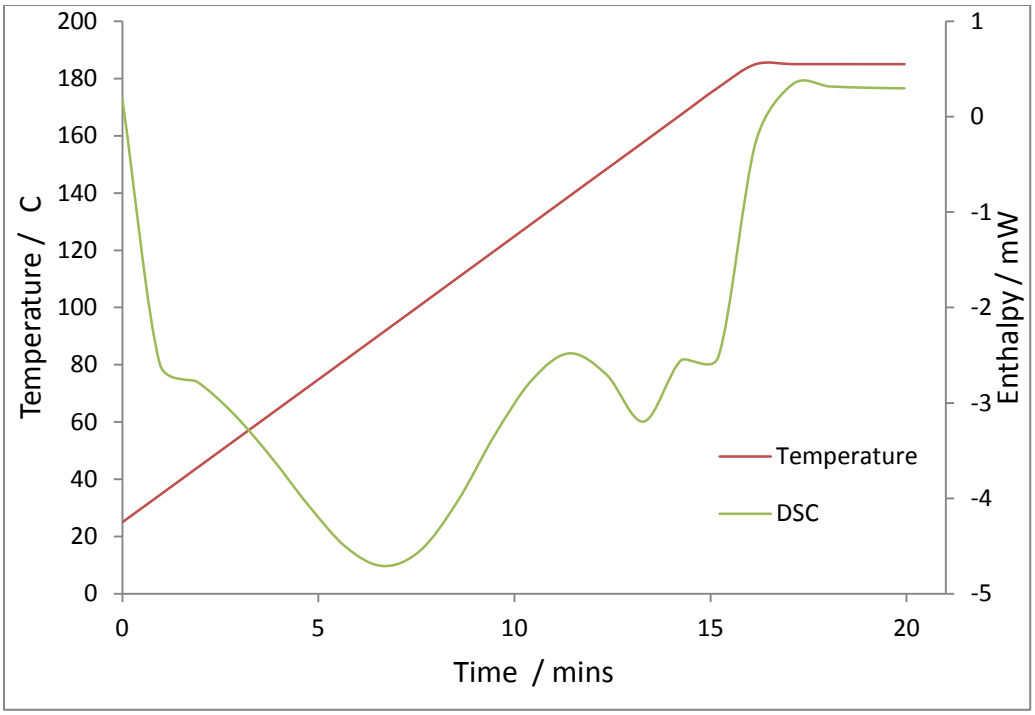

Figure 4.1.14.2 – Microwave formulated paracetamol and 2HPBCD, 1:9 without water present in the formulation process

Figure 4.1.14.2 is for microwave formulated paracetamol and 2HPBCD, 1:9 and again there are two peaks present. The first peak is at 85°C and the second peak is for paracetamol and this has a temperature of 165°C. This result was also seen for the conventional formulated paracetamol and 2HPBCD, displaying that no difference exists between the two heating methods.

4.1.15 Paracetamol and PVP, 1:1 and 1:9

Paracetamol was formulated with PVP in the 1:1 and 1:9 ratios, using microwaves and conventional heating without the presence of water. After analysis of the different formulations, it became evident that the same results were obtained as previously seen with the other paracetamol formulations. There was a peak around 100°C symbolising the release of any trapped water from the polymer chain and a peak around 170°C corresponding to the melting point of the drug. Consequently because of this the DSC results were not illustrated.

After DSC was employed to determine if any differences occurred between formulations on a molecular level, it was important to see if any differences can be seen visually and therefore on a physical level. SEM was used to investigate the physical properties of each of the different formulations.

14.2 Scanning Electron Microscope (SEM)

The scanning electron microscope was used to determine if any structural differences could be seen between the different formulations. First the pure compounds were analysed at three different magnifications (X33, X85 and X300) to gain a representative image of the samples. Each formulation prepared, i.e. with or without the presence of water and using the two different heating methods was analysed. Figures 4.2.1 - 4.2.8 illustrate the pure compounds and these were used for comparison with the formulations.

4.2.1 Comparison of pure drug and excipients

Figure 4.2.1 -SEM image for pure ibuprofen, magnification x300

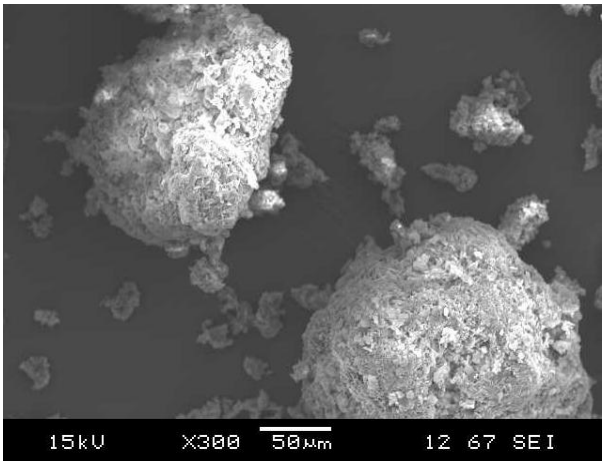

Figure 4.2.2 – SEM image for pure ketoprofen, magnification x300

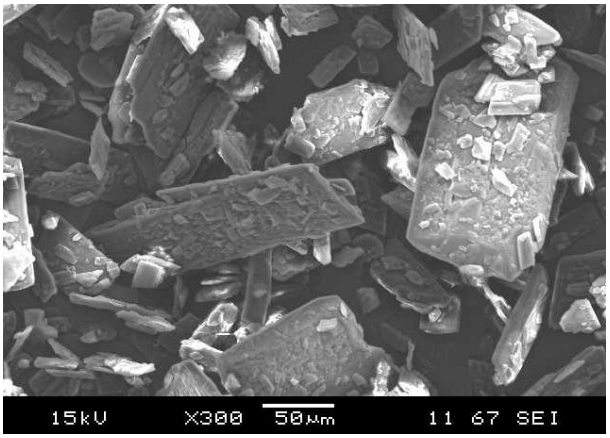

Figure 4.2.3 – SEM image for pure flurbiprofen, magnification x300

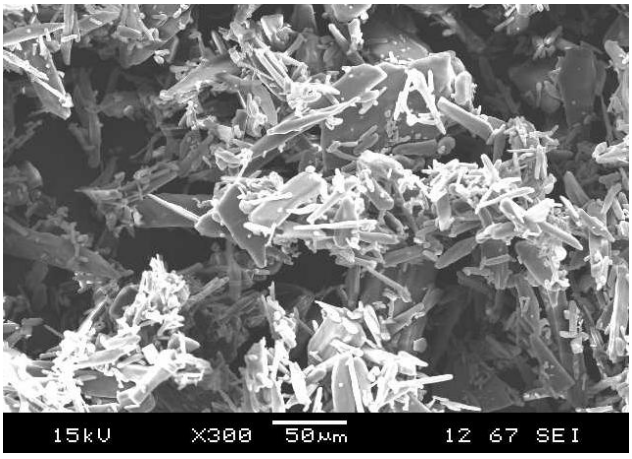

Figure 4.2.4 – SEM image for pure paracetamol, magnification x300

Figures 4.2.1 - 4.2.4 display the SEM images for the four pure drugs. Figure 4.2.1 illustrates pure ibuprofen. From the image it is possible to conclude that the drug has a regular elongated particle shape. Figure 4.2.2 is for ketoprofen and from the image it is possible to conclude that the drug has a spherical particle shape. Figure 4.2.3 is for flurbiprofen, and for this particular drug the particle shape is rectangular, and the final image, Figure 4.2.4, is for paracetamol and the particles appear to be needle-like in shape.

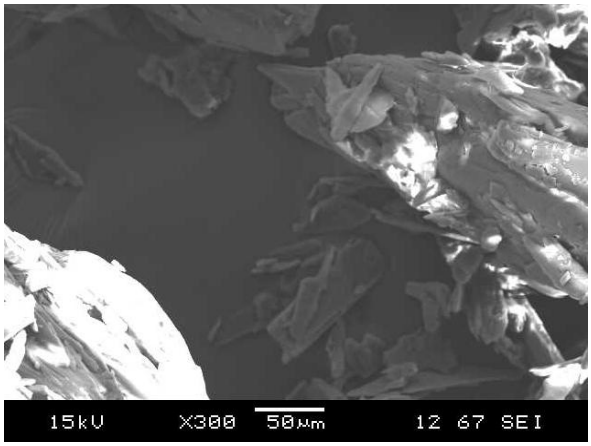

Figure 4.2.5 - SEM image for pure stearic acid (SA), magnification x300

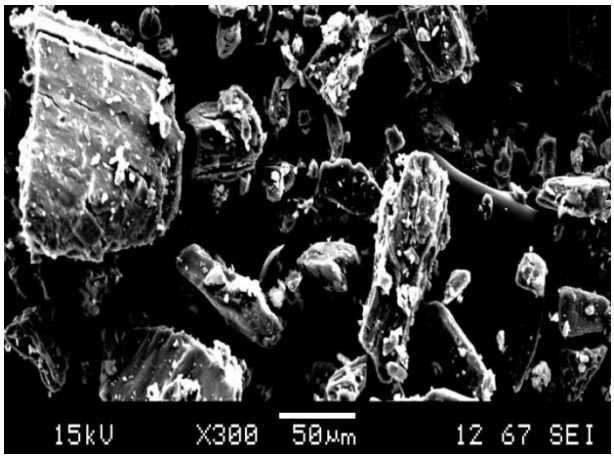

Figure 4.2.6 - SEM image for pure β-cyclodextrin (BCD), magnification x300

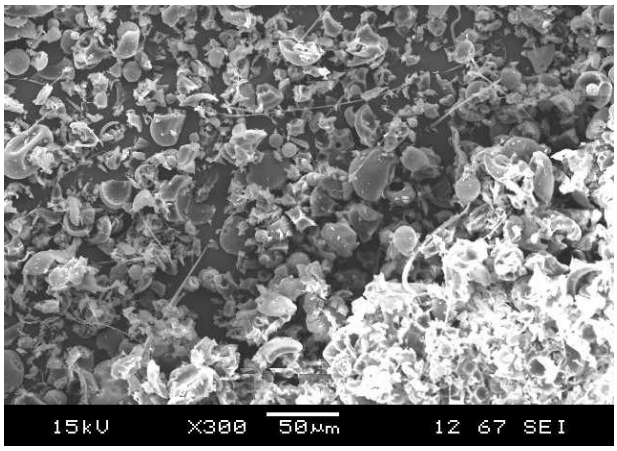

Figure 4.2.7 – SEM image for pure hydroxypropyl-β-cyclodextrin (2HPBCD), magnification x300

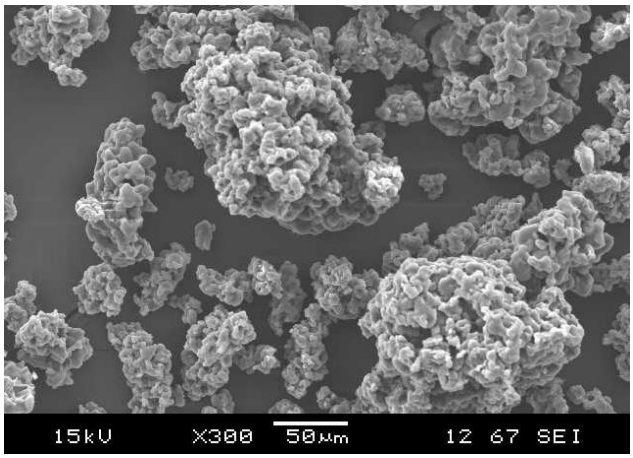

Figure 4.2.8 – SEM image for pure polyvinylpyrrolidone (PVP), magnification x300

Figure 4.2.5 is the SEM image for stearic acid, and it is evident from the image that no definable shape appears with this excipient, there only appears to be small and large particles that are random in shape. This is also the case for BCD, illustrated in Figure 4.2.6. Figure 4.2.7 illustrates 2HPBCD, which appears to have spherical shaped particles. Figure 4.2.8 displays the SEM image for PVP which appears to include particles that are random in size but also have a rough texture.

4.2.2 Comparison of the different formulations

Ibuprofen was the first drug to be investigated with the four different excipients. Figures 4.2.2.1 to 4.2.2.3 illustrates a few examples of the different ibuprofen formulations, and Table 4.2.2.1 summarises all the results obtained from the SEM for this particular drug.

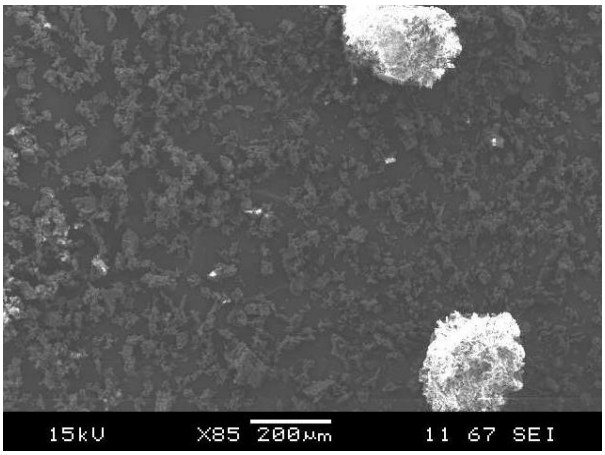

Figure 4.2.2.1 - Microwave formulated ibuprofen and BCD, 1:1 ratio, with water present during formulation, magnification x85

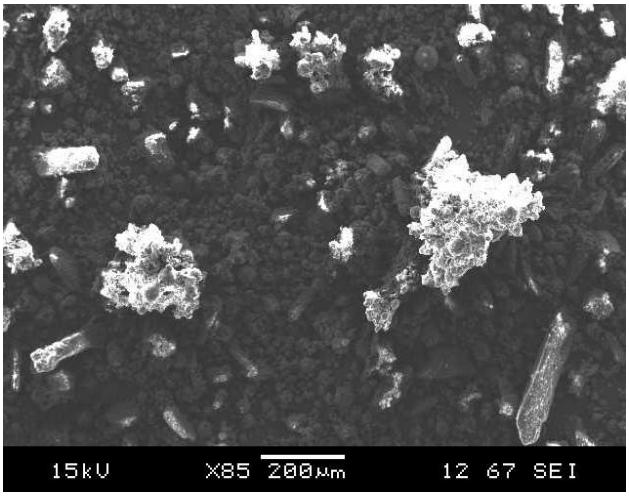

Figure 4.2.2.2 - Microwave formulated ibuprofen and 2HPBCD 1:1 ratio, without water present during formulation, magnification x85

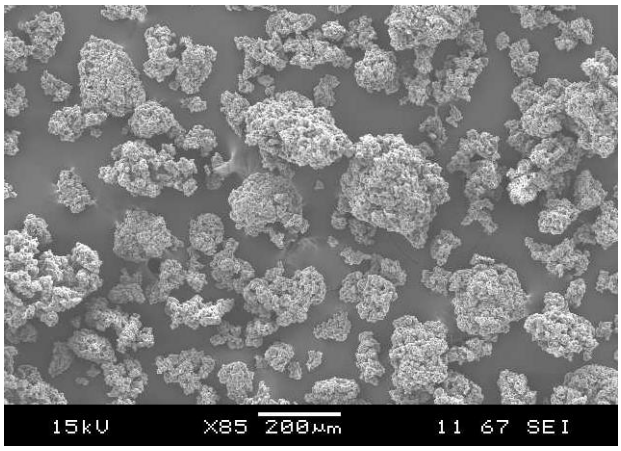

Figure 4.2.2.3 - Microwave formulated ibuprofen and PVP 1:9 ratio, without water present during formulation, magnification x85

Formulation	Heating Method	Water Present	Description	Comment
Ibuprofen and SA	MW	Yes	Small particles, with a regular shape and size	No pure drug appears to be in the formulated product,
1:3	MW	No	Larger, irregular particle shape and size	Formulation process changed appearance for with and without water
Ibuprofen and SA	CN	Yes	The same was also witnessed for the	Same witnessed for conventional as for the microwave
	CN	No	conventionally formulated as with the MW formulation	formulations
Ibuprofen and BCD	MW	Yes		
1:1	MW	No		
Ibuprofen and BCD	CN	Yes	In all cases, when water is present there is a clear reduction	
	CN	No	in particle size. The particles appear to be uniform in shape.	Formulation with water contains smaller particles with no evidence
	MW	Yes	This is the case regardless of the heating method and the	of pure drug. However when water wasn't present possibility of needle-like
1:9	MW	No	chosen ratio of drug to excipient.	particles remaining which could be ibuprofen.
Ibuprofen and BCD	CN	Yes		
	CN	No		
Ibuprofen and 2HPBCD	MW	No	No comparison can be made to formulations prepared with water. There appears to be no	MW formulation appeared to contain particles from the pure drug, where the formulation prepared using conventional heating doeant
1:1			significant difference between	appear to contain any drug particles.
Ibuprofen and 2HPBCD	CN	No	the choice of heating methods.	Both formulations look significant different to the pure compounds
	MW	No		Same results obtained for this ratio and formulation as the 1:9
1:9			This result was also obtained for the 1:9 ratio	Difference between heating methods appears to exist
Ibuprofen and 2HPBCD	CN	No		
Ibuprofen and PVP	MW	Yes		
1:1	MW	No		
Ibuprofen and PVP	CN	Yes	Larger, irregular particle shape and size when water was present	Water causes polymer to swell, therefore larger particles should be witnessed when
	CN	No	during formulation. Polymer swells Smaller particles. Not usually	compared to formulation prepared without water This is usually not the case, with the formulations
	MW	Yes	witnessed.	prepared with water illustrating smaller
1:9	MW	No		particle size.
Ibuprofen and PVP	CN	Yes		
	CN	No		

Table 4.2.2.1 – Summary of SEM results obtained for the different ibuprofen formulations.

After all the different ibuprofen formulations were analysed using SEM, the different ketoprofen formulations were also investigated. Figures 4.2.2.4 to Figure 4.2.2.7 illustrate a few examples of the SEM micrographs obtained for the different ketoprofen formulations, and Table 4.2.2.2 is an overall summary of all the results obtained with SEM.

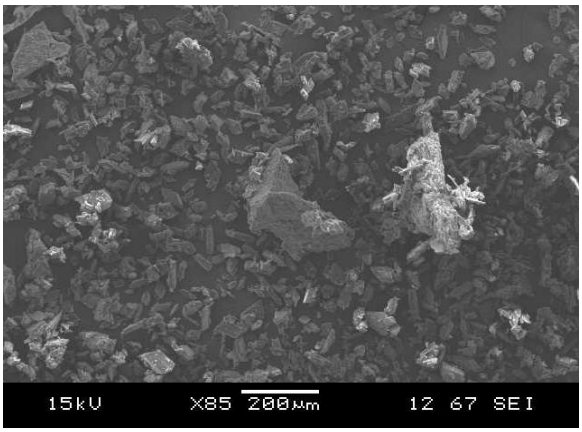

Figure 4.2.2.4 - Microwave formulated ketoprofen and BCD 1:1 ratio, with water present during formulation, magnification x85

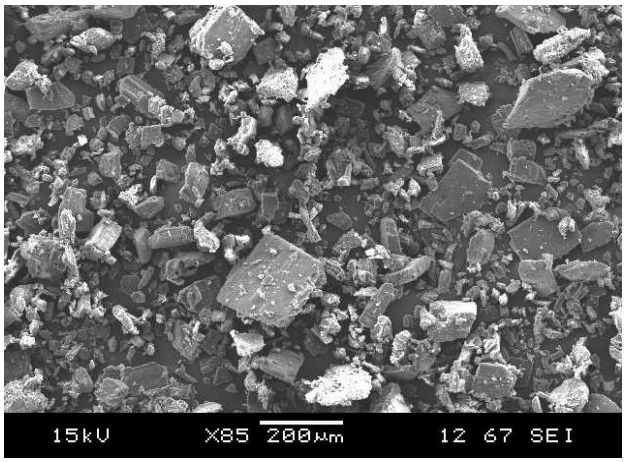

Figure 4.2.2.5 - Microwave formulated ketoprofen and BCD 1:9 ratio, without water present during formulation, magnification x85

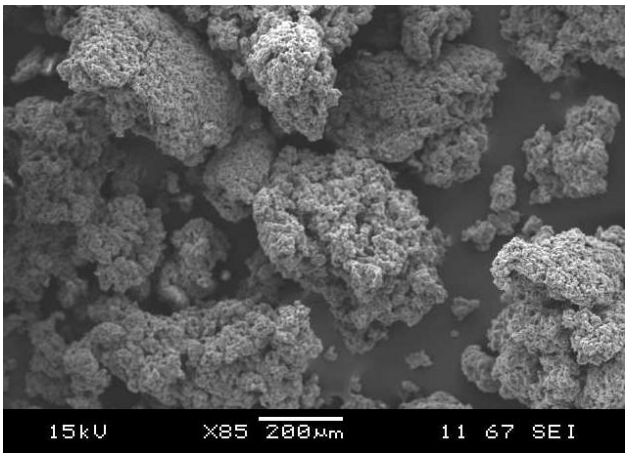

Figure 4.2.2.6 - Microwave formulated ketoprofen and PVP 1:1 ratio, with water present during formulation, magnification x85

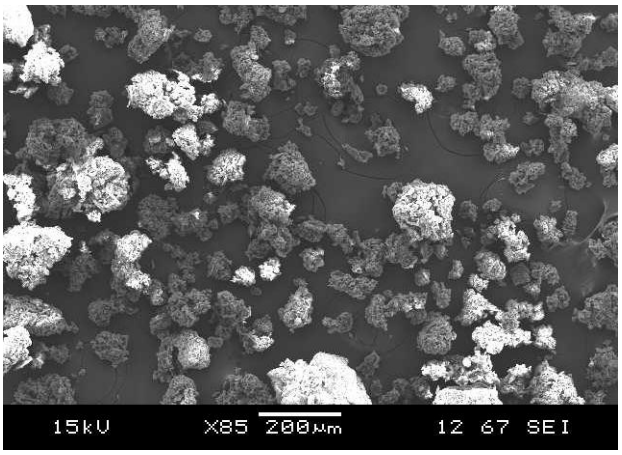

Figure 4.2.2.7 - Microwave formulated ketoprofen and PVP 1:1 ratio, without water present during formulation, magnification x85

Formulation	Heating Method	Water Present	Description	Comment
Ketoprofen and SA	MW	Yes	Small particles, with a regular shape and size	No pure drug appears to be in the formulated product,
1:3	MW	No	Larger, irregular particle shape and size	Formulation process changed appearance for with and without water
Ketoprofen and SA	CN	Yes	The same was also witnessed for the	Same witnessed for conventional as for the microwave
	CN	No	conventionally formulated as with the MW formulation	formulations
Ketoprofen and BCD	MW	Yes		
1:1	MW	No		The choice of heating method appears to make no significant difference
Ketoprofen and BCD	CN	Yes	In all cases, when water is present during formulation	to the appearance of the formulations. However the presence of water does affect
	CN	No	the particle size and shape appears smaller and more	the particle size and shape. With smaller particles present after formulation with
	MW	Yes	uniform. This result was obtained for both the heating	water
1:9	MW	No	methods and the two different ratios	
Ketoprofen and BCD	CN	Yes		
	CN	No		
Ketoprofen and 2HPBCD	MW	No	No comparison can be made to formulations prepared with water. There appears to be no	The formulation method appears to have significantly changed the appearance
1:1			significant difference between	of the drug and excipient after formulation.
Ketoprofen and 2HPBCD	CN	No	the choice of heating methods.	The choice of heating method appears to make no significant difference
	MW	No	This result was also obtained for the	to the appearance of the formulations
1:9			1:9 ratio	This result was also obtained for the 1:9 ratio
Ketoprofen and 2HPBCD	CN	No		
Ketoprofen and PVP	MW	Yes		
1:1	MW	No		
Ketoprofen and PVP	CN	Yes	Larger, irregular particle shape and size when water was present	Water causes polymer to swell, therefore larger particles should be witnessed when
	CN	No	during formulation. Polymer swells Smaller particles. Not usually	compared to formulation prepared without water This is usually not the case, with the formulations
	MW	Yes	witnessed.	prepared with water illustrating smaller
1:9	MW	No		particle size.
Ketoprofen and PVP	CN	Yes		
	CN	No		

Table 4.2.2.2 – Summary of SEM results obtained for the different ketoprofen formulations.

Flurbiprofen was the next drug investigated using SEM, Figure 4.2.2.8 and Figure 4.2.2.9 are a few examples of the SEM micrographs obtained. Table 4.2.2.3 summarises all the results obtained for this drug and the two different excipients.

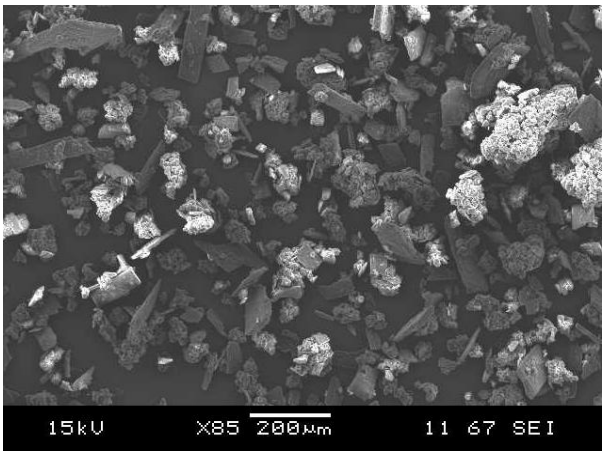

Figure 4.2.2.8 - Microwave formulated flurbiprofen and PVP 1:1, without water present during formulation, magnification x85

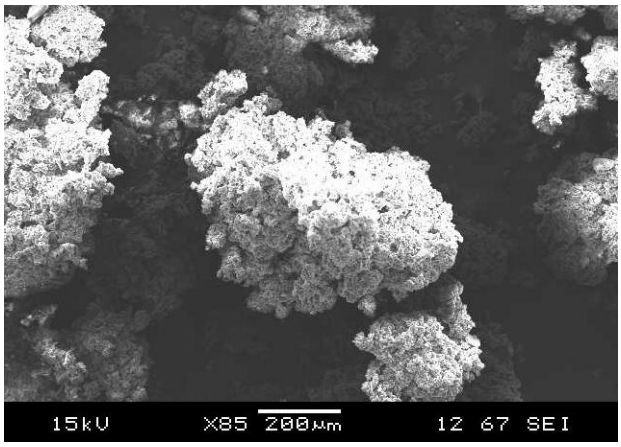

Figure 4.2.2.9 - Microwave formulated flurbiprofen and PVP 1:9, with water present during formulation, magnification x85

Formulation	Heating Method	Water Present	Description	Comment
Flurbiprofen and SA	MW	Yes	Small particles, with a regular shape and size	No pure drug appears to be in the formulated product,
1:3	MW	No	Larger, irregular particle shape and size	Formulation process changed appearance for with and without water
Flurbiprofen and SA	CN	Yes	The same was also witnessed for the	Same witnessed for conventional as for the microwave
	CN	No	conventionally formulated as with the MW formulation	formulations
Flurbiprofen and PVP	MW	Yes		
1:1	MW	No		
Flurbiprofen and PVP	CN	Yes	Larger, irregular particle shape and size when water was present	Water causes polymer to swell, therefore larger particles should be witnessed when
	CN	No	during formulation. Polymer swells	compared to formulation prepared without water
	MW	Yes	Smaller particles. Not usually witnessed.	This is usually not the case, with the formulations prepared with water illustrating smaller
1:9	MW	No		particle size.
Flurbiprofen and PVP	CN	Yes		
	CN	No		

Table 4.2.2.3 – Summary of SEM results obtained for the different flurbiprofen formulations.

The last drug analysed using SEM was paracetamol with the four different excipients. Figure 4.2.2.10 to Figure 4.2.2.12 display a few examples of these formulations and Table 4.2.2.4 summarises all the results obtained from the SEM for this drug.

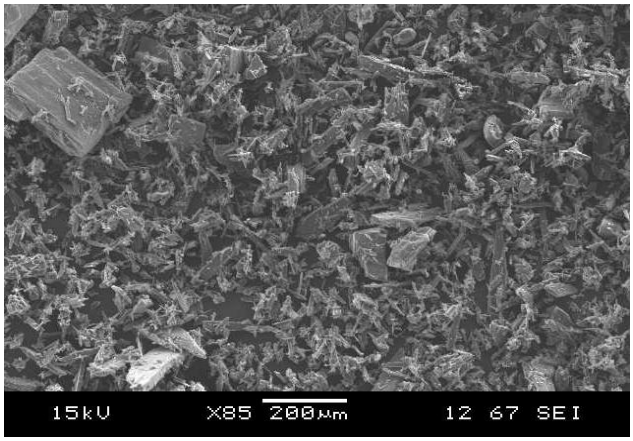

Figure 4.2.2.10 - Conventionally formulated paracetamol and BCD 1:1 ratio, without water present during formulation, magnification x85

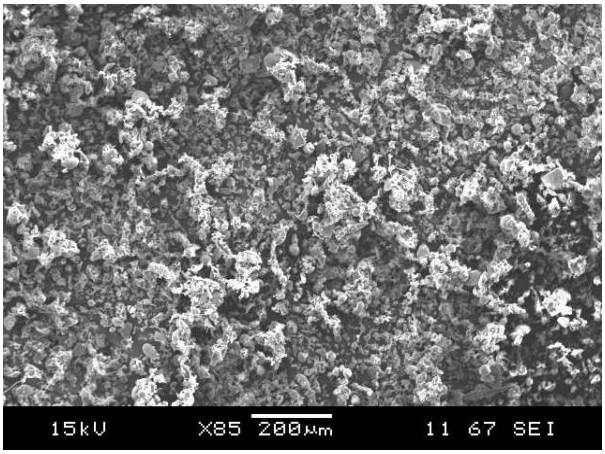

Figure 4.2.2.11 - Microwave formulated paracetamol and 2HPBCD 1:9 ratio, without water present during formulation, magnification x85

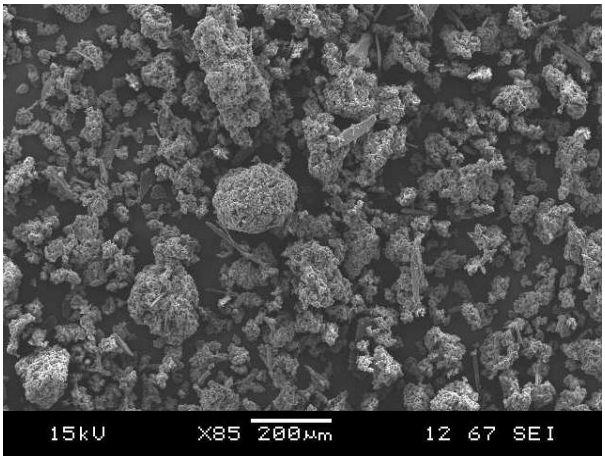

Figure 4.2.2.12 - Microwave formulated paracetamol and PVP 1:9 ratio, without water present during formulation, magnification x85

Formulation	Heating Method	Water Present	Description	Comment
Paracetamol and SA 1:3 Paracetamol and SA	MW	No	Both formulations illustrate large and irregular shaped particles	No comparison can be made between with and without water. There appears to be no significant difference between the heating methods.
	CN	No		
Paracetamol and BCD 1:1 Paracetamol and BCD	MW	No	All formulations illustrate small particles, with no particular shape. This is consistent between heating methods and different formulations	No comparison can be made between with and without water. There appears to be no significant difference between the heating methods.
	CN	No		
1:9 Paracetamol and BCD	MW	No		
	CN	No		
Paracetamol and 2HPBCD 1:1 Paracetamol and 2HPBCD	MW	No	All formulations consist of large and small particles, with no particular shape or size. This is consistent over the two heating methods and different ratios.	No comparison can be made between with and without water. There appears to be no significant difference between the heating methods.
	CN	No		
1:9 Paracetamol and 2HPBCD	MW	No		
	CN	No		
Paracetamol and PVP 1:1 Paracetamol and PVP	MW	No	All formulations consist of large and small particles, with no particular shape or size. This is consistent over the two heating methods and different ratios.	No comparison can be made between with and without water. There appears to be no significant difference between the heating methods.
	CN	No		
1:9 Paracetamol and PVP	MW	No		
	CN	No		

Table 4.2.2.4 – Summary of SEM results obtained for the different paracetamol formulations.

4.2.3 SEM summary

From all the results obtained, it appears that little or no significant difference exists between the two different heating methods. However, in cases where water was present during formulation the particle size seemed to be reduced. This was seen throughout the analysis until PVP was used as the excipient and when water was present. Here, the formulation with water illustrated a larger particle size and this may be because of the polymer swelling when exposed to the water in the formulation method.

All the different formulations were analysed and compared using DSC and SEM. It was noted from the DSC that the formulation method did affect the thermal behaviour of the drug and excipient and these differences were seen visually by using the SEM. Despite the usefulness of DSC and SEM, these techniques do not determine the stability of the drug once it has undergone the heating process, an instrument that will allow this to be calculated is the thermal activity monitor (TAM). Out of all the drugs that were formulated with the different excipients, ibuprofen was the only one that melted at the chosen formulation temperature. It was therefore important to ensure that this didn't affect the stability of the drug once formulated.

4.3 Thermal Activity Monitor (TAM)

A thermal activity monitor (TAM) was used to investigate the stability of different formulations at 30°C for a period of four days. The TAM has two sample cells so each formulation was analysed in duplicate.

4.3.1 Pure ibuprofen

Three separate experiments were performed to determine the stability of ibuprofen. These included:

A) Under 0% humidity
B) Under 51% humidity ($(Mg(NO_3)_2$)
C) Dissolved in buffer (pH8)

In all cases, there appears to be 0μW/g of heat flow. This indicated that no thermal processes occurred over the four day period under any conditions used. Consequently it can be said ibuprofen was stable under all conditions, and an example can be seen in Figure 4.3.1.1

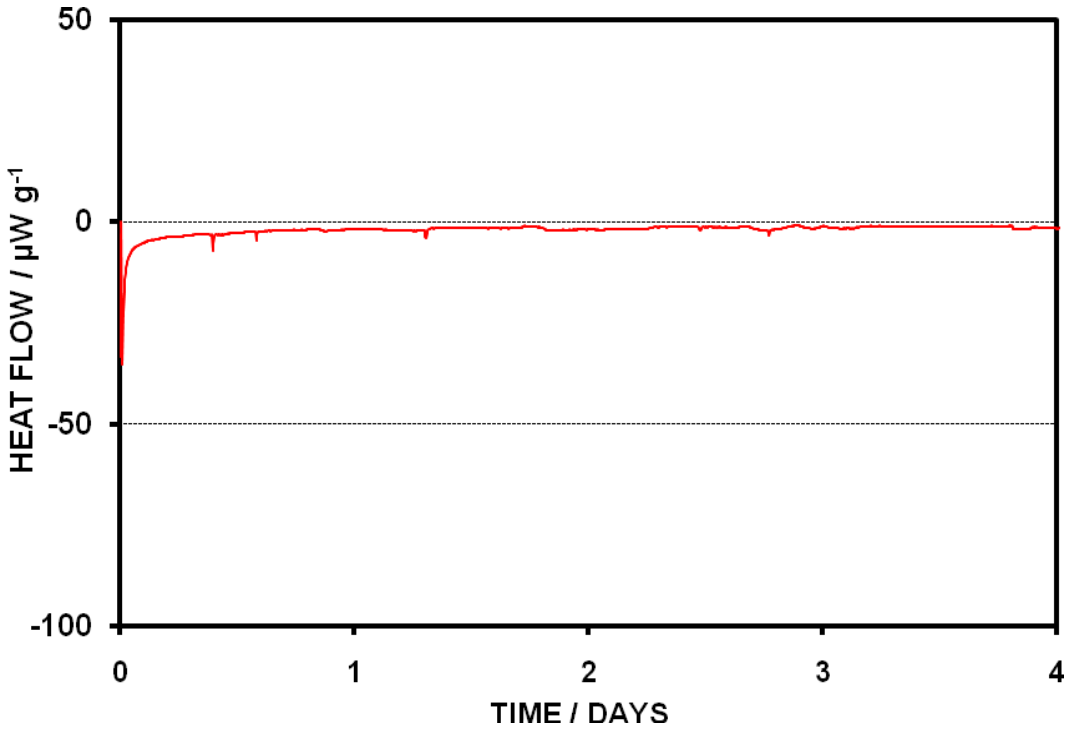

Figure 4.3.1 - Pure Ibuprofen, held at 30°C, 0% relative humidity

After pure ibuprofen was investigated, each of the different formulations was analysed using TAM over a four day period. In all cases an output of 0μW/g was evident for all the different formulations indicating no thermal processes occurred, consequently all the formulations appeared stable after the formulation process. Two examples are illustrated in Figure 4.3.2 and Figure 4.3.3.

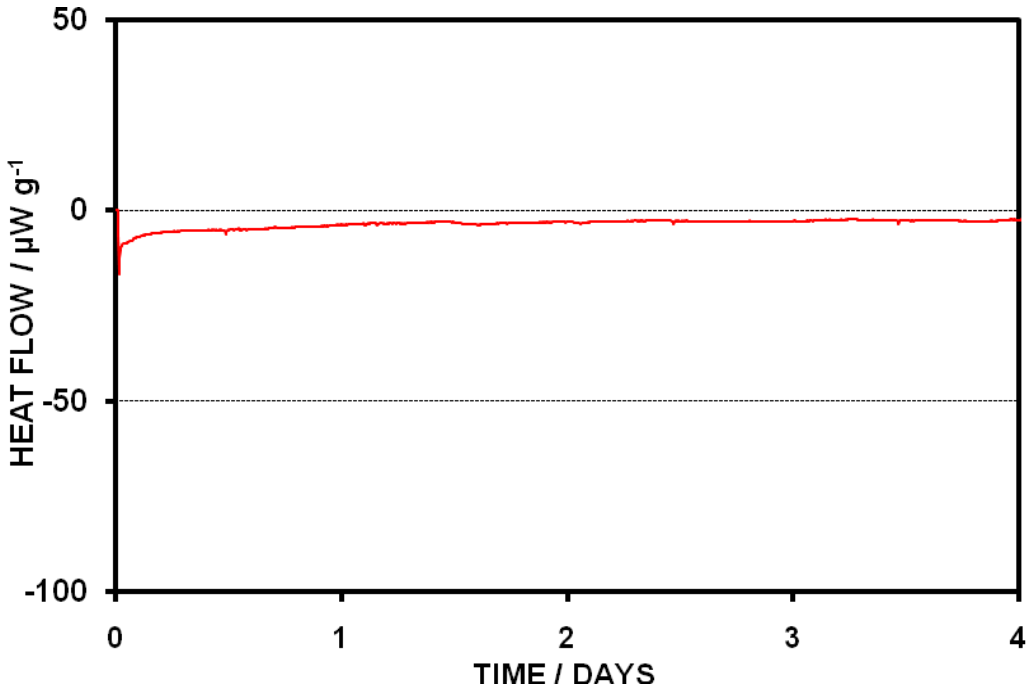

Figure 4.3.2 Ibuprofen with SA, held at 30°C, 0% relative humidity, formulated using the microwave method with water present during formulation

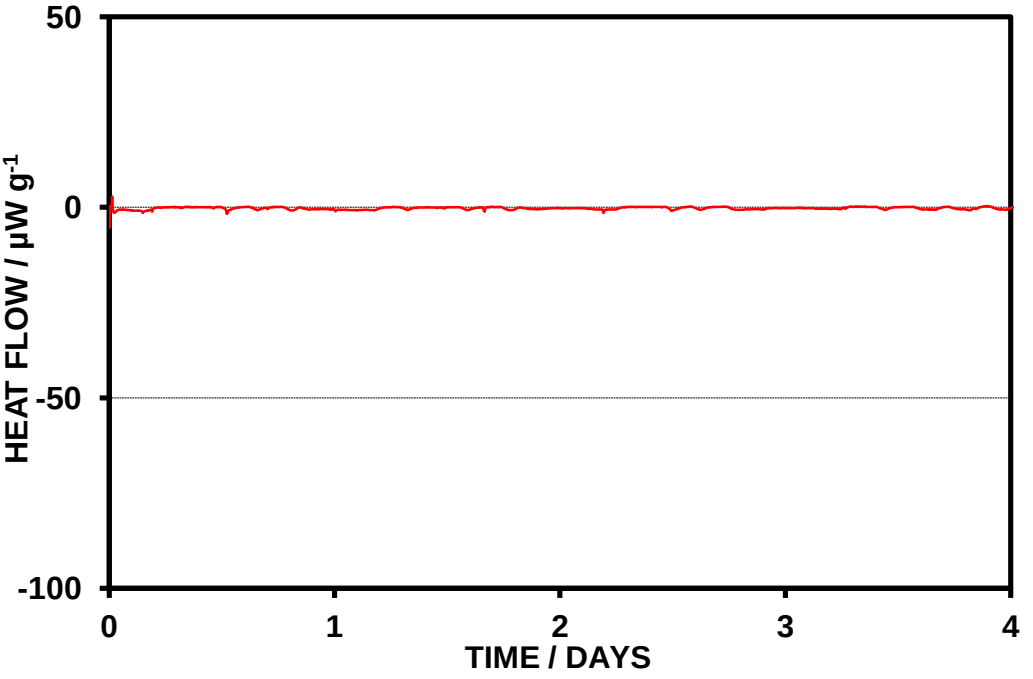

Figure 4.3.3 - Ibuprofen with BCD, 1:1 ratio, held at 30°C, 0% relative humidity, formulated using the conventional method with water present during formulation

In total there were four drugs and four different excipients formulated. However other than ibuprofen, the other three drugs (ketoprofen, flurbiprofen, and paracetamol) did not melt at the formulation temperature (85°C). Consequently ibuprofen was studied in detail, with the other three drugs to be carried on in the future work programme.

However after analysis of a few formulations for the other three drugs, the same results seen for ibuprofen were also witnessed for ketoprofen, flurbiprofen and paracetamol. Figure 4.3.4 – Figure 4.3.6 illustrate a few examples of the graphs obtained from the TAM, in all cases 0μw/g heat flow can be seen and therefore no thermal processes occurred over the four days.

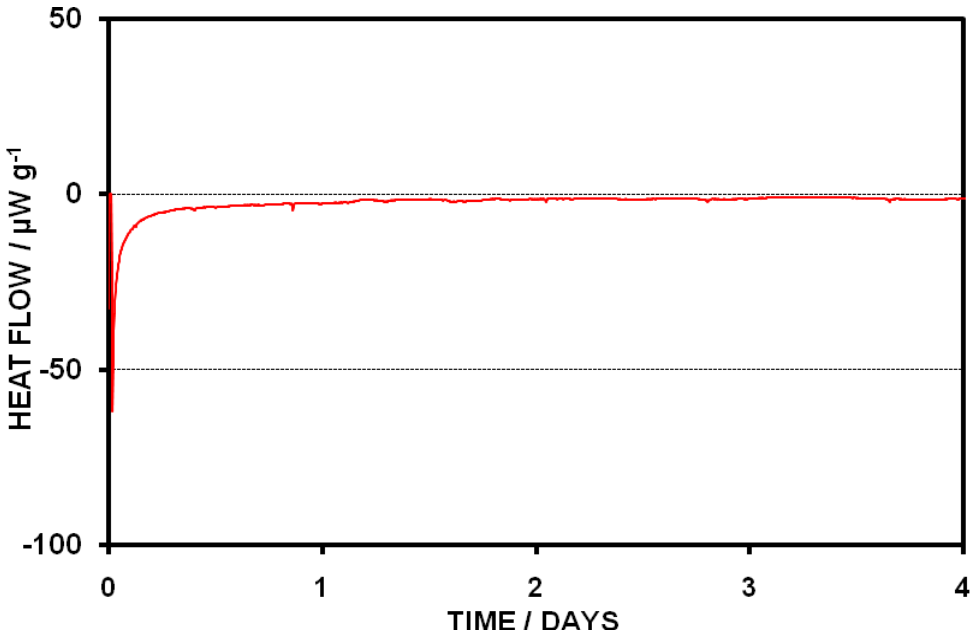

Figure 4.3.4 - Ketoprofen with PVP, 1:1 ratio, held at 30°C, 0% relative humidity, formulated using the microwave method with water present during formulation

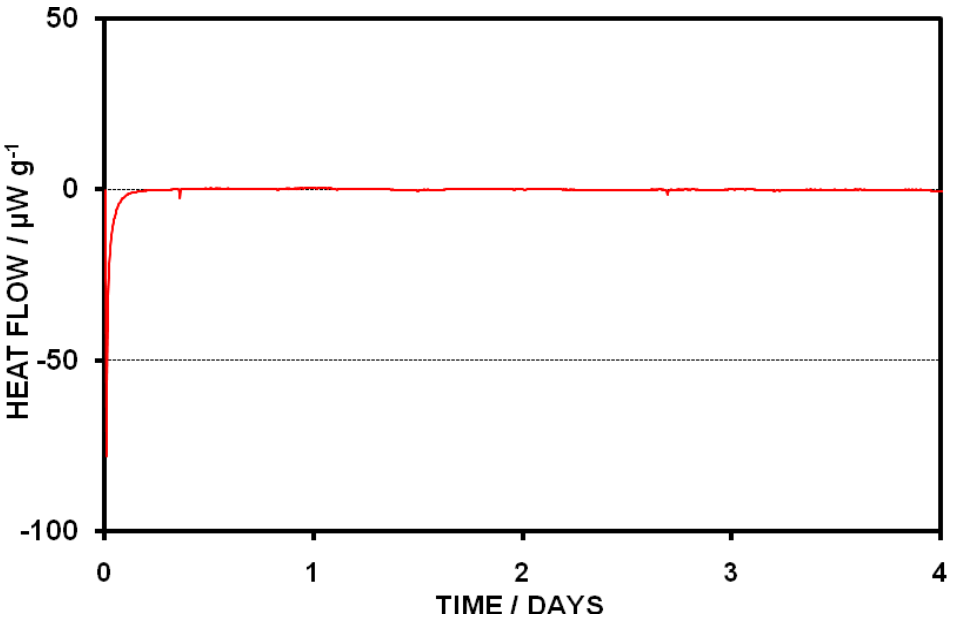

Figure 4.3.5 - Flurbiprofen with PVP, 1:1 ratio, held at 30°C, 0% relative humidity, formulated using the microwave method without water present during formulation

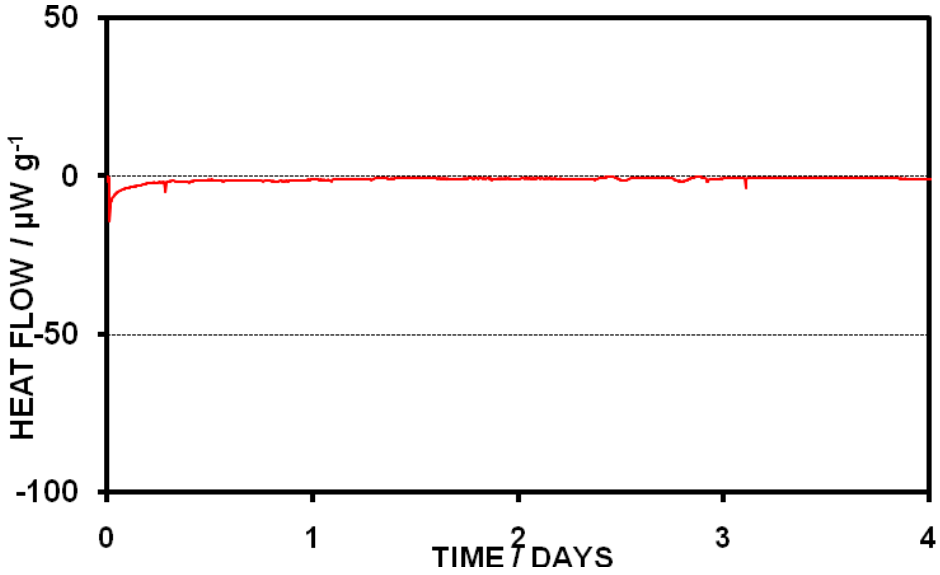

Figure 4.3.6 - Paracetamol with BCD, 1:1 ratio, held at 30°C, 0% relative humidity, formulated using the microwave method without water present during formulation

From all the results illustrated, the output signal is zero for all the ibuprofen formulations and for the few examples illustrated for ketoprofen, flurbiprofen and paracetamol. It can be said that the formulation process and the presence of water has made no difference to the stability of the drug. It is difficult to determine if all the formulations show the same results for ketoprofen, flurbiprofen and paracetamol but because of time restrictions these drugs could not be studied further. Therefore these formulations can be continued and analysed within a programme of future work. However to hypothesise, from the results previously seen it is likely that the other formulations will again show no adverse effects, i.e. show a signal output on or around zero and consequently will be stable within the four different excipients.

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Chapter 5

Drug Release

Chapter 5 – Drug Release: Dissolution Analysis

5.1 Introduction

Dissolution analysis is an important analytical technique in the pharmaceutical industry. It provides drug release profiles which can then be used to determine any differences between any two or more products under consideration[1-4]. A detailed discussion on the theoretical aspects of the analytical technique itself can be found in Chapter One.

The percentage of drug release was measured over four hours, however only the first ninety minutes will be illustrated as this period is where the majority of the observed differences occurred.

Each graph presented in this section indicates which heating method was used, microwave heating (MW) or conventional heating (CN), and identifies the presence (with), or the absence (without), of water where appropriate. Each curve is the average of three repeat runs with error bars equal to one standard deviation. Where differences between the dissolution profiles were observed the initial rate of dissolution was calculated by dividing the slope by the horizontal distance between any two points (rate of change).

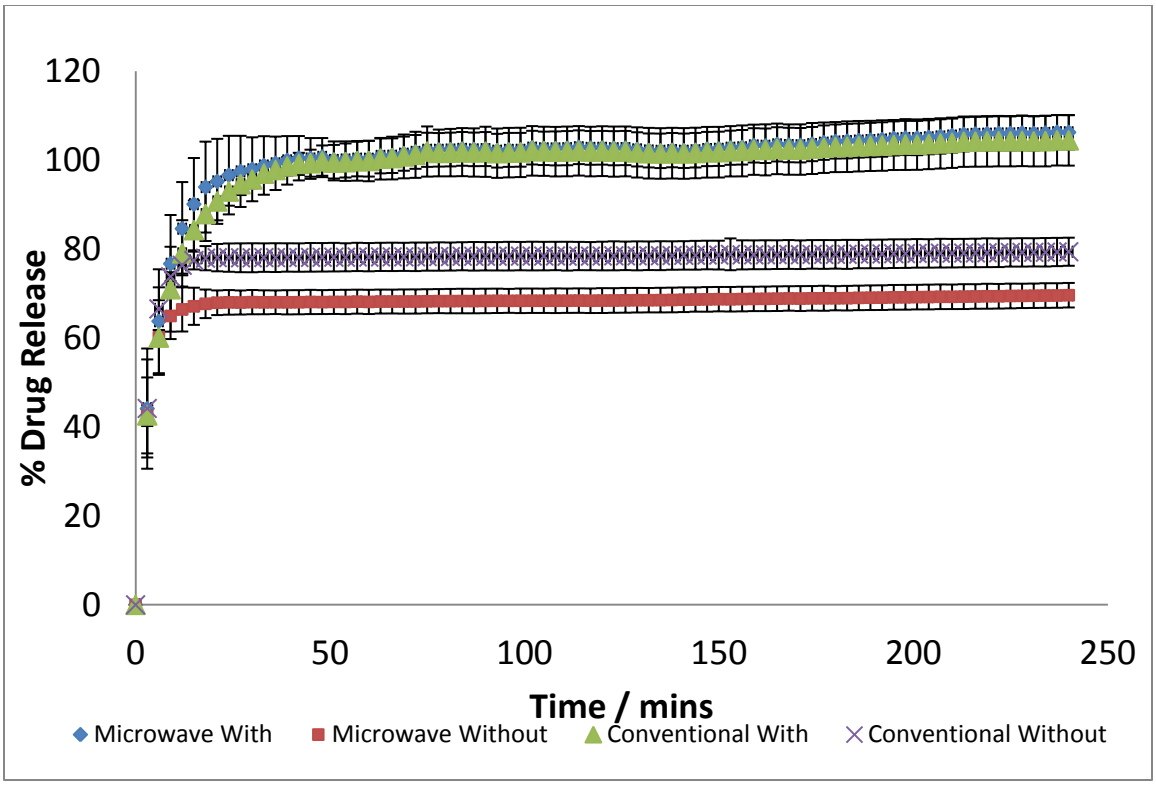

Figure 5.1.1 –A drug release profile for Ibuprofen and BCD, 1:1 ratio, displaying the full four hours of data

5.2 Ibuprofen, Ketoprofen and Flurbiprofen Drug Release in Water

Previous research has suggested that microwaves can increase the solubility and rate of drug release of certain drugs[5-10], that are classified within the BCS Class Two, without the necessity of increasing the pH of the dissolution media.

To further investigate these findings, all the formulations that were prepared using microwave or conventional heating were analysed using dissolution analysis with a media of water. The two different heating methods were also compared to determine if microwave heating produced any differences in dissolution when compared with conventional heating.

The first formulations analysed were ibuprofen with the four different excipients. In all cases there was an improvement in the dissolution of the drug once formulated with the various excipients. Another observed trend was that the microwave formulations seemed to improve the extent of dissolution of ibuprofen when compared with formulations prepared using conventional heating (Figures 5.2.1 and 5.2.2 are

examples of ibuprofen with two of the excipients), although the difference is relatively small.

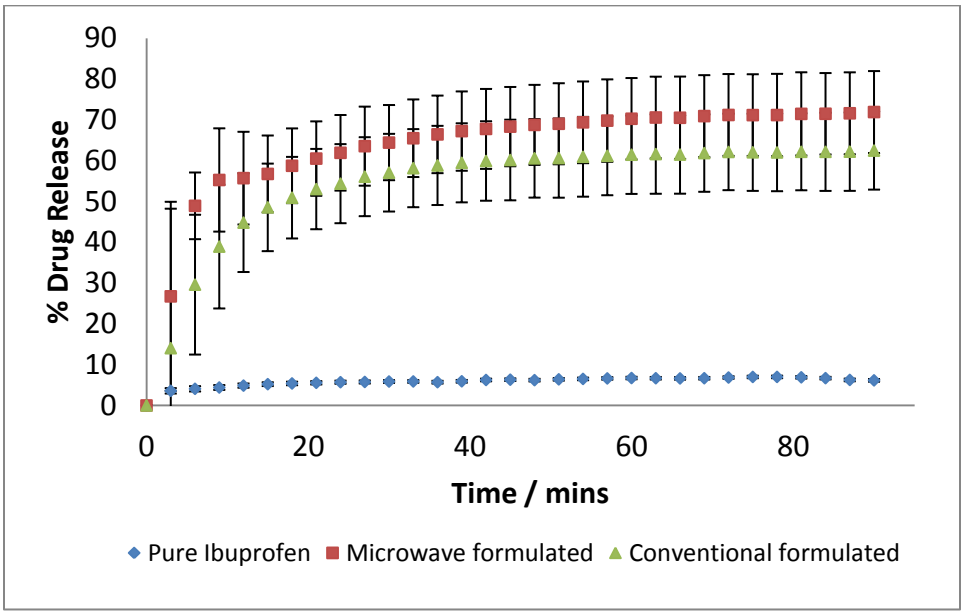

Figure 5.2.1 – A drug release profile for Ibuprofen and BCD, 1:9 ratio, highlighting the improved release in the presence of the excipient

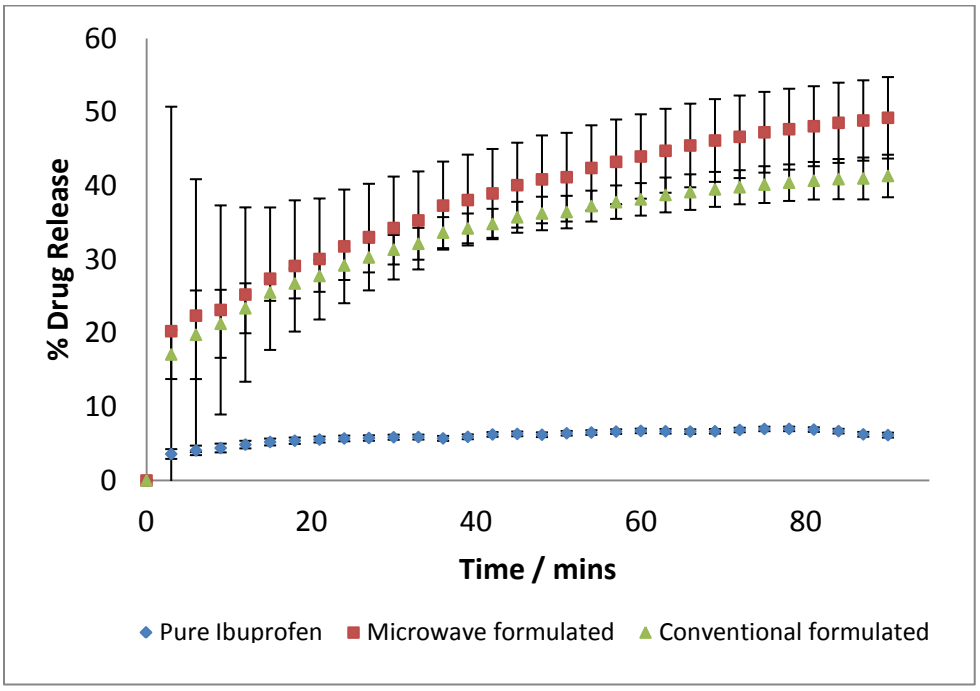

Figure 5.2.2 – A drug release profile for Ibuprofen and 2HPBCD 1:9 ratio highlighting the improved release in the presence of the excipient

Figure 5.2.1 and Figure 5.2.2 are examples of ibuprofen formulations. Formulating ibuprofen with the different excipients seems to increase the extent of the dissolution for the drug. Figure 5.2.1 is for ibuprofen with BCD in a 9:1 ratio, the maximum amount of pure drug released over the ninety minute time period is 6% (±1%), and when this is compared with formulated ibuprofen with BCD, 1:9 ratio an increase up to 60-70% (±10%) is seen. This shows an approximate 10-12 fold increase in the extent of dissolution after the formulation process. Along with this increase, the release profile for ibuprofen formulated using microwave heating appears to improve the dissolution of the drug to a greater extent than conventional heating. The first five minutes of analysis shows little difference between the two heating methods but after this time period the % drug release profiles separate and visually appear to be different. However, when the percentage error is calculated a 10% error can be associated with the majority of the measurements. This consequently makes it difficult to determine if there are significant differences between the release profiles and therefore the two heating methods.

Figure 5.2.2 displayes ibuprofen with a second excipient, 2HPBCD. When the dissolution for the pure drug was compared with the dissolution of the formulation an improvement is again evident. The release profile for the pure drug shows only 6% (±1%) of the drug in solution compared with 40-49% (±5%) for the formulated product. This illustrates an approximate 7-8-fold increase in the dissolution. There is also a slight difference between the release profiles for microwave and conventional heating with the microwave formulation releasing a higher percentage of the drug over the ninety minute time period. For the first thirty minutes, both profiles appear to release the same amount of ibuprofen (35% ± 3%) After this time period, the two release profiles begin to separate with the microwave heating releasing over 45% (± 7%) of the drug compared with 39-40%(± 2%) for conventional heating.

Both profiles show how pure ibuprofen behaves in water, only 6-7% of the drug dissolves and this illustrates how limiting the rate of dissolution is which will ultimately limit bioavailability. The two examples illustrated demonstrate that by adding an excipient and heating ibuprofen a great improvement in the degree of drug release can be obtained. For all the formulations that were prepared, an improvement in the extent of ibuprofen released was obtained. In addition, microwave heating tends to show a

greater improvement in the extent of drug release of ibuprofen when compared with conventional heating.

The highest increase in drug release for ibuprofen was observed when formulated with BCD in a 1:9 ratio (Figure 5.2.1), with the next significant increase 2HPBCD (Figure 5.2.2). The SA and PVP formulations provided an increase in the extent of drug release but not as significant as the two formulations illustrated.

A similar pattern of improved dissolution after formulation was also observed with ketoprofen. Figure 5.2.3 is an example of ketoprofen with PVP, 1:9, Figure 5.2.4 shows ketoprofen formulated with SA, 1:3.

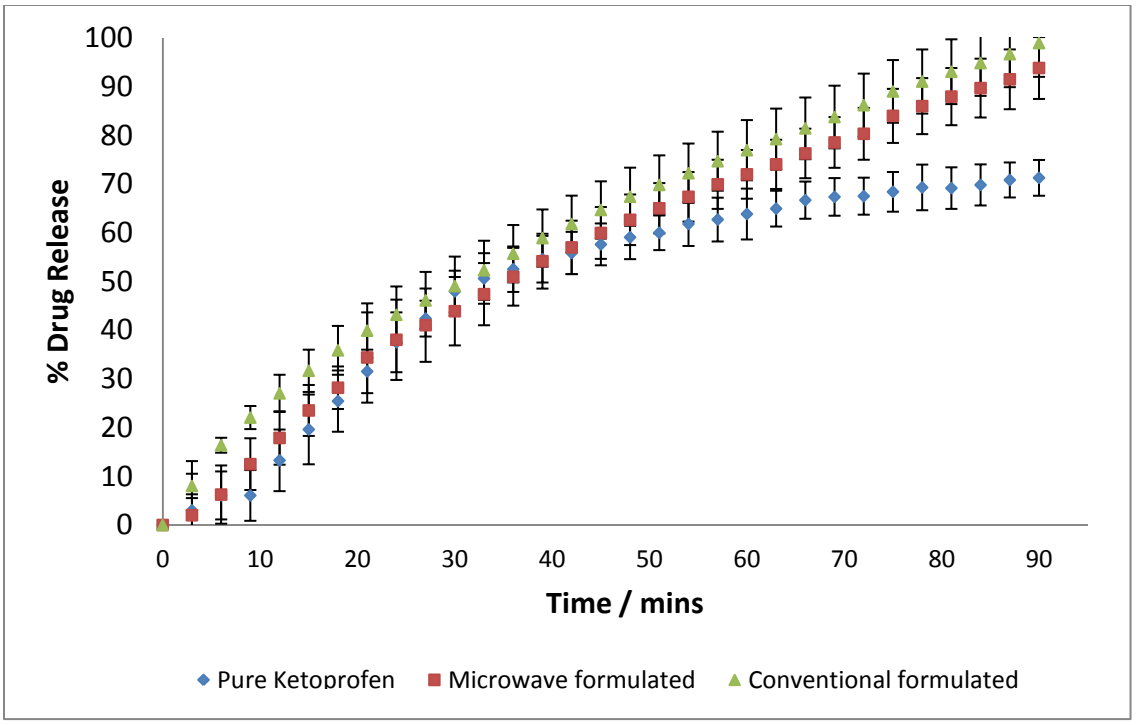

Figure 5.2.3 – A drug release profile for ketopofen and PVP, ratio 1:9 using both microwave and conventional heating methods compared with ketoprofen alone

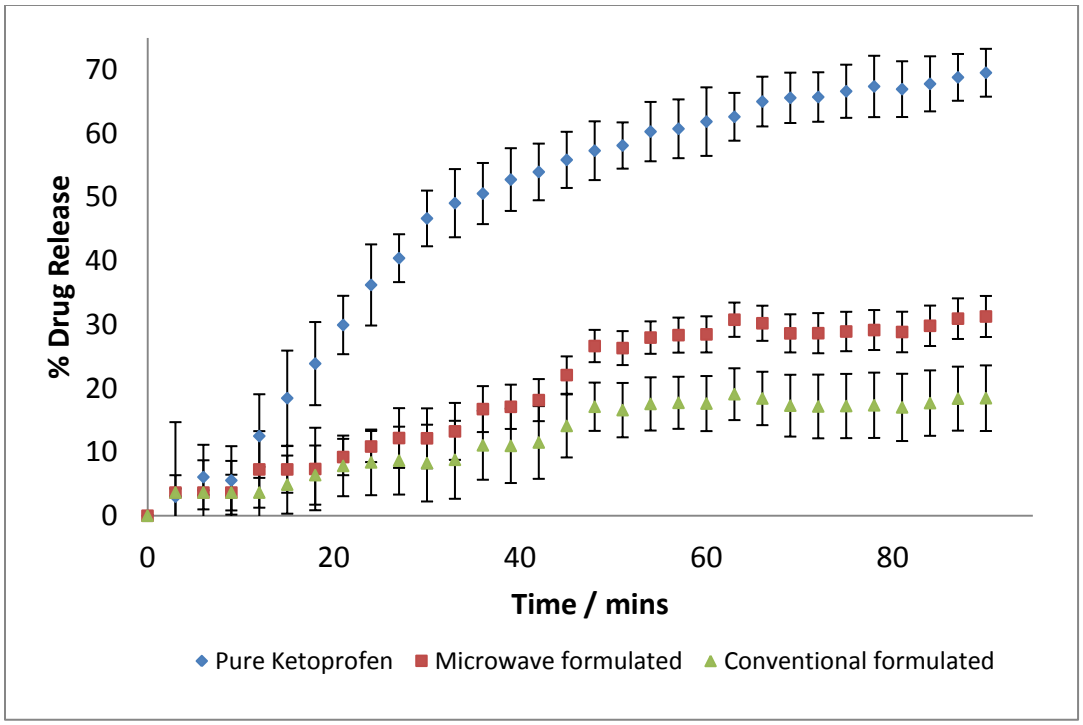

Figure 5.2.4 – A drug release profile for ketopofen and SA, ratio 1:3 using both microwave and conventional heating methods compared with ketoprofen alone

Figure 5.2.3 is an example of ketoprofen formulated with PVP in a 1:9 ratio using microwaves and conventional heating. From analysis of the dissolution curves, it appears that a slight increase in the release of the drug occurred over the ninety minutes. However, when the percentage error was calculated a 10% error can be associated with the measurements. This consequently makes it difficult to determine any significant differences, but over the last twenty minutes of the dissolution the percentage drug release continues to increase for the formulated drug. This may help to illustrate that after formulation there is an improvement in the dissolution for ketoprofen. There also appears to be little or no difference between the two heating methods with both releasing over 90% (±7%) of ketoprofen towards the end of the ninety minutes time period.

Figure 5.2.4 illustrates ketoprofen and SA formulated using microwaves and conventional heating. It is evident from the release profiles that adding the excipient SA to ketoprofen has decreased the release of the drug. This result shows an approximate 2-fold decrease for the microwave formulation and a decrease of 4-fold for the

conventional formulation. It is probable the result has been obtained because SA is a waxy compound that doesn't dissolve in this solvent and unlike ibuprofen, ketoprofen doesn't melt at a similar temperature to SA. It is therefore likely that during the formulation process the SA coated the drug making it difficult for any dissolution media to penetrate into the matrix once formulated. Also, when the release profiles for both the heating methods were compared, it can be seen that the microwave formulation released a slight higher percentage of ketoprofen. After the ninety minutes period the microwave formulation attained a drug release of 31% (±3%) compared with 18% (±5%) using the conventional method. This result may have occurred because of the uniform heating that microwaves provide, resulting in a formulation that had the drug and excipient evenly mixed throughout the matrix.

From analysis of all the different formulations, it is evident that an improvement in the extent of release of ketoprofen occurred with the inclusion of excipients, other than SA. There is also little or no significant difference between the two heating methods other than in the ketoprofen and SA example illustrated (Figure 5.2.4). The highest increase in drug release was observed when the drug was formulated with PVP in a 1:9 ratio (Figure 5.2.3), with the lowest improvement in the release of ketoprofen when SA is present in the formulation, illustrated by Figure 5.2.4.

After ketoprofen was analysed, a third drug was investigated, namely fluribiprofen. Flurbiprofen was formulated with SA and PVP only. It was not formulated using BCD and HPBCD because of difficulties experienced when monitoring the drug release as a consequence of a possible shift in absorbance. Despite not investigating this drug with all four excipients, some trends were seen. These include an improvement in the release of flurbiprofen when PVP was added. Also when SA was added to flurbiprofen, a similar trend to that seen for ketoprofen and SA was observed (Figure 5.2.5).

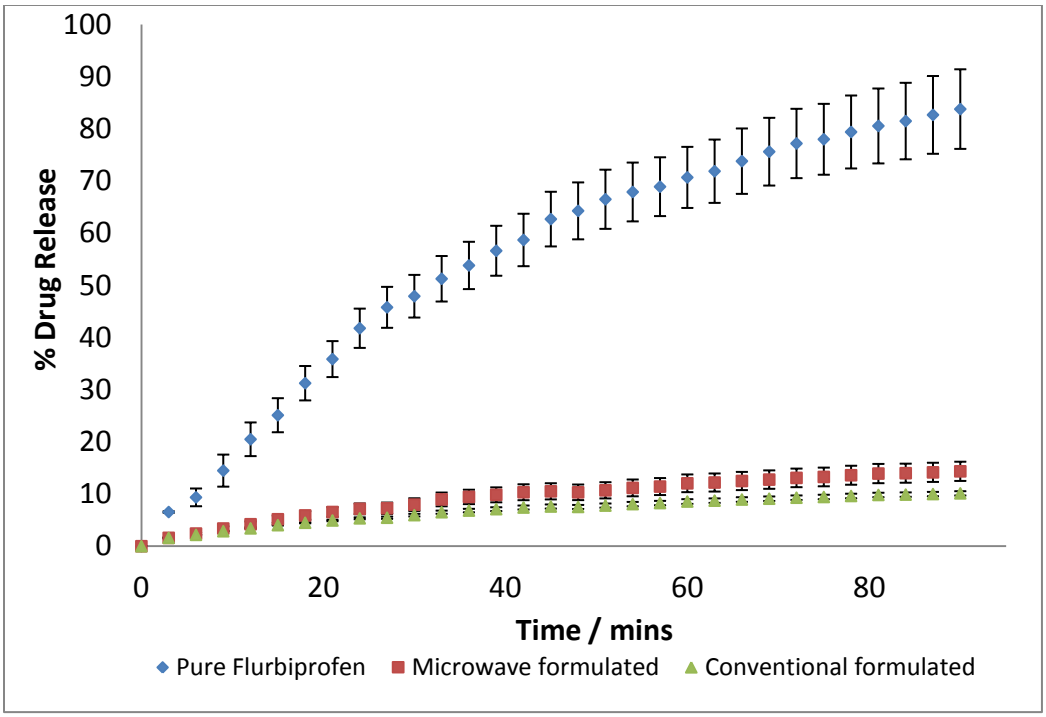

Figure 5.2.5 – A drug release profile for flurbiprofen and SA, ratio 1:3 using microwave heating and conventional heating compared with flurbiprofen alone

It is evident from Figure 5.2.5 that by adding SA to the drug a decrease in the percentage of drug released occurred. The maximum amount of drug in solution for the pure drug at the end of the ninety minutes time period is 84% (±9%), compared with 14% (±13%) for the microwave formulated flurbiprofen and 10% (±4%) for the conventional formulation. Both the formulations show between a 6-8-fold decrease in the release of flurbiprofen. As previously mentioned this was a result seen with ketoprofen and SA. As with ketoprofen, flurbiprofen doesn't melt at a similar temperature to SA during the heating process. Consequently, the un-melted drug is encapsulated by the SA as it melts and the resultant formulation has a waxy texture (insoluble). This would make it difficult for the dissolution media to penetrate into the matrix and release the drug.

The previous section shows the ‘dry melts’ of the drug and excipient can have a significant impact on the dissolution profiles and that, in some cases, microwave heating showed small but observable differences to conventional heating. The next section describes results of experiments investigating the effect of water on the formulation process.

5.3 Ibuprofen

5.3.1 The effect of the presence of water during formulation

It was decided to incorporate water into the formulation process to determine how the presence of a liquid affected the release profiles of a drug with poor aqueous solubility.

Ibuprofen was formulated with three different excipients (2HPBCD not formulated with water present) with the resultant formulations analysed to establish drug release profiles. A summary of all the results are illustrated at the end of this section in Table 5.3.1.8. Figures 5.3.1.1 to 5.3.1.7 are examples of some of the results obtained from the dissolution of ibuprofen with SA, BCD and PVP. Where significant differences occurred in the dissolution profiles, the rate was calculated to support the visual data seen on the presented graphs.

Figure 5.3.1.1 and Figure 5.3.1.2 are examples of where the presence of water during formulation did not significantly affect the release of the drug.

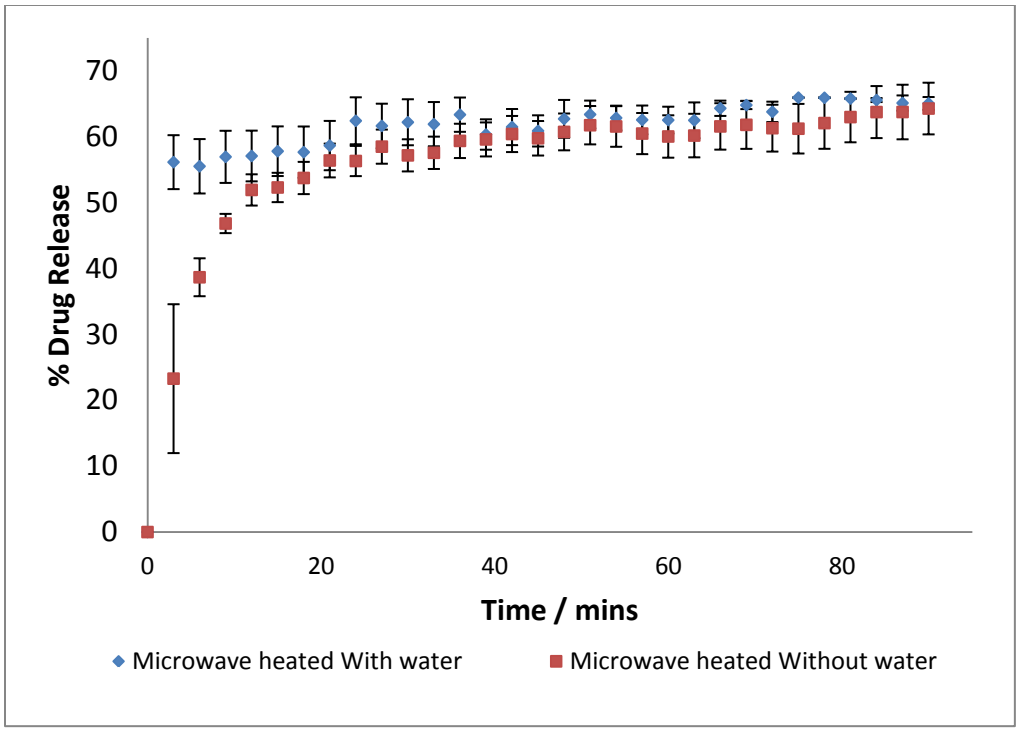

Figure 5.3.1.1 – A drug release profile for Ibuprofen and SA (ratio 1:3), formulated using microwave heating both with and without the presence of water during the formulation process

Figure 5.3.1.1 is an illustration of ibuprofen and SA formulated using microwave heating. After the first fifteen minutes, it is evident that the two profiles are the same. Over the ninety minutes both formulations are seen to release 70% (±5%) of the drug. Therefore it can be said that the presence of water in this particular example did not affect the release of ibuprofen from SA. However, the first fifteen minutes of the dissolution profile are different and consequently the rate was calculated to support this visual difference. After calculation of the rate it becomes evident that the formulation with water releases ibuprofen at a rate of 18.7% per minute compared with 7.8% per minute over a three minute time period. As a result, it can be said that the first fifteen minutes of the dissolution are different, with the formulation prepared with water present releasing the drug at a faster rate. From fifteen minutes onwards it can be seen that both rates become similar and the same amount of ibuprofen was released. Table 5.3.1.1 illustrates the rates for each formulation over a thirty minute time period.

Rate (% released per minute)		
Time(min)	With	Without
0-3	18.71	7.76
3-15	0.16	2.38
15-30	0.36	0.37

Table 5.3.1.1 – Rate of release of ibuprofen from SA when prepared with or without the presence of water during microwave formulation

Table 5.3.1.1 illustrates the difference between the formulations for the first fifteen minutes of the dissolution experiment, after this time period the rate becomes similar (0.36% for the formulation in the presence of water compared with 0.37% for formulation without water).

Figure 5.3.1.2 is another example of an ibuprofen formulation that was not affected by the presence of water. The example illustrated is for ibuprofen and PVP, 1:9 ratio and conventionally heated.

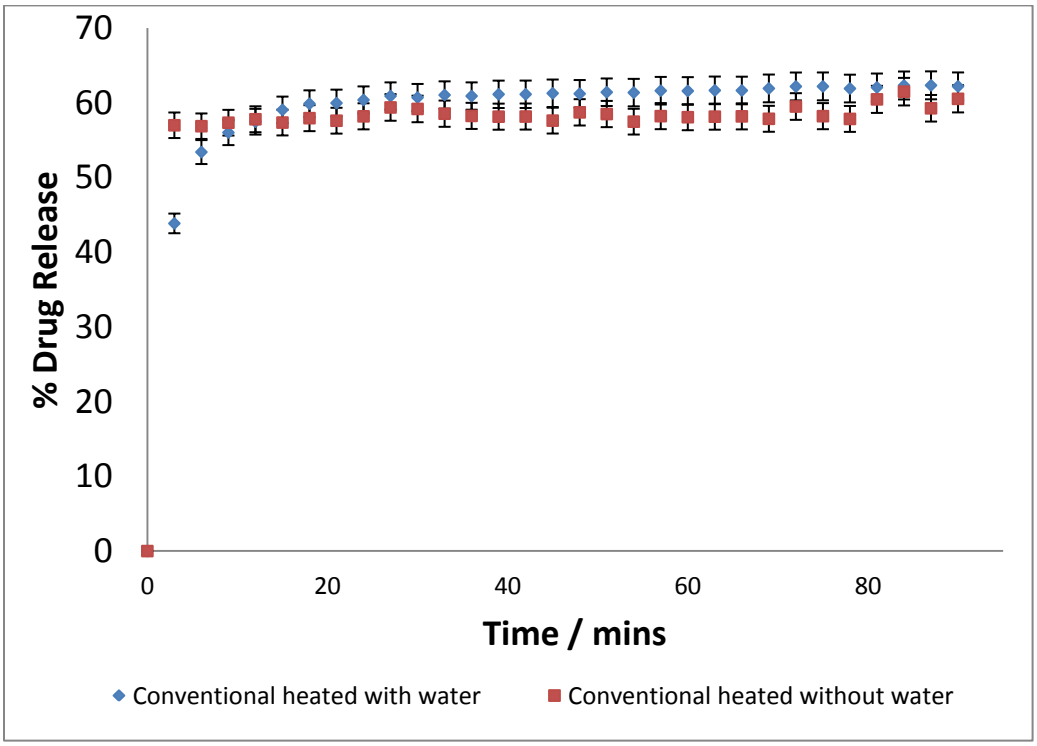

Figure 5.3.1.2 – A drug release profile for Ibuprofen and PVP (ratio 1:9), formulated using conventional heating both with and without the presence of water during the formulation process

Figure 5.3.1.2 displays no overall difference in total drug release with 60% of ibuprofen released over ninety minutes in both cases. However for the first three minutes there is a significant difference in the rate of release for ibuprofen. The formulation prepared without water present releases the drug at a rate of 19% per minute compared with 15% for the formulation prepared with water. After this time period the rate slows for both formulations. The calculated rate confirms what is visually seen in Figure 5.3.1.2, where a difference can be seen for the first fifteen minutes only, illustrated in Table 5.3.1.2.

Rate (% release per minute)		
Time (mins)	With	Without
0-3	14.62	19.00
3-15	1.15	0.06
15-30	0.11	0.13

Table 5.3.1.2 – Rate of release of ibuprofen from PVP, 1:9 when prepared with or without the presence of water during formulation

Figure 5.3.1.1 and Figure 5.3.1.2 illustrates the two formulations where the presence of water did not have an overall effect on the release of ibuprofen. However for the majority of the ibuprofen formulations prepared with or without water a significant difference occurred. From analysis of these formulations it becomes evident that when water was present in the formulation method a higher percentage of ibuprofen was released.

Figures 5.3.1.3 to Figure 5.3.1.5 illustrate a few examples of where the presence of water had affected ibuprofen release from the excipient.

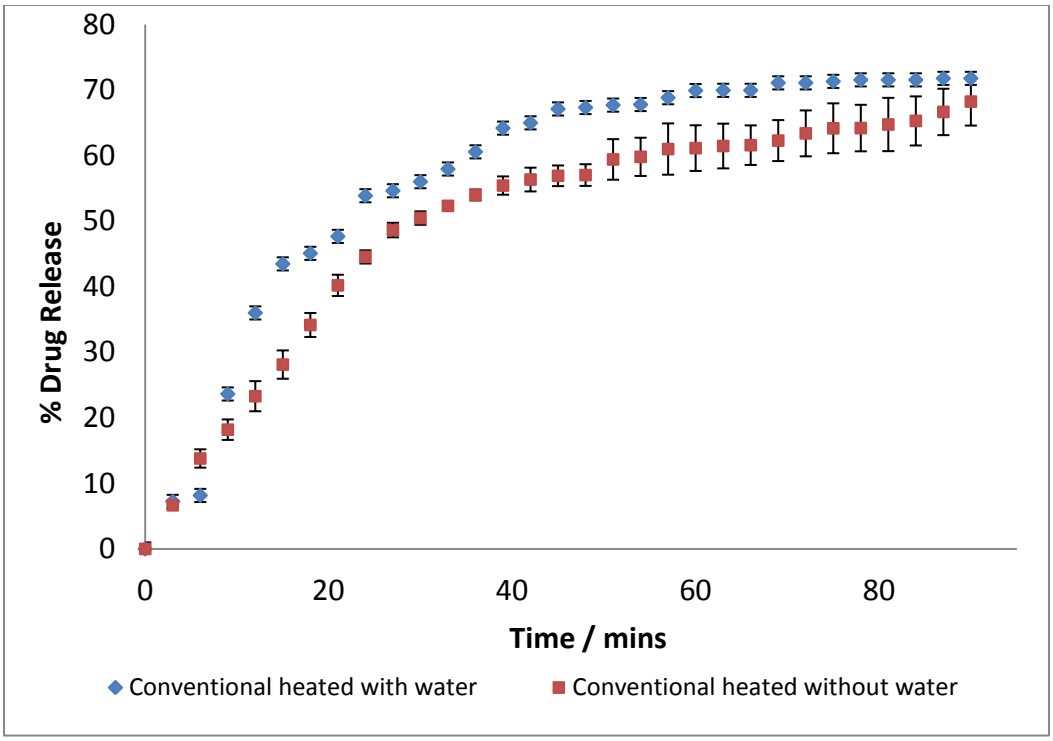

Figure 5.3.1.3 – A drug release profile for Ibuprofen and SA (ratio 1:3), formulated using conventional heating both with and without the presence of water during the formulation process

Figure 5.3.1.3 confirms that the presence of water facilitated a higher percentage of drug to be released, with 70-75% (±1%) of ibuprofen released after forty minutes. This is in comparison with 60% (±0.5%) released after forty minutes, which gives an overall 15% difference between the two formulations. The rate also agrees with this statement, i.e. the formulation with water present released ibuprofen at a faster rate than the formulation without water present (Table 5.3.1.3).

Rate (% release per minute)		
Time(Mins)	CN With	CN Without
0-3	2.42	2.22
3-15	3.34	1.75
15-30	0.93	1.52

Table 5.3.1.3 – Rate of release of ibuprofen from SA, when prepared with or without the presence of water during conventional formulating

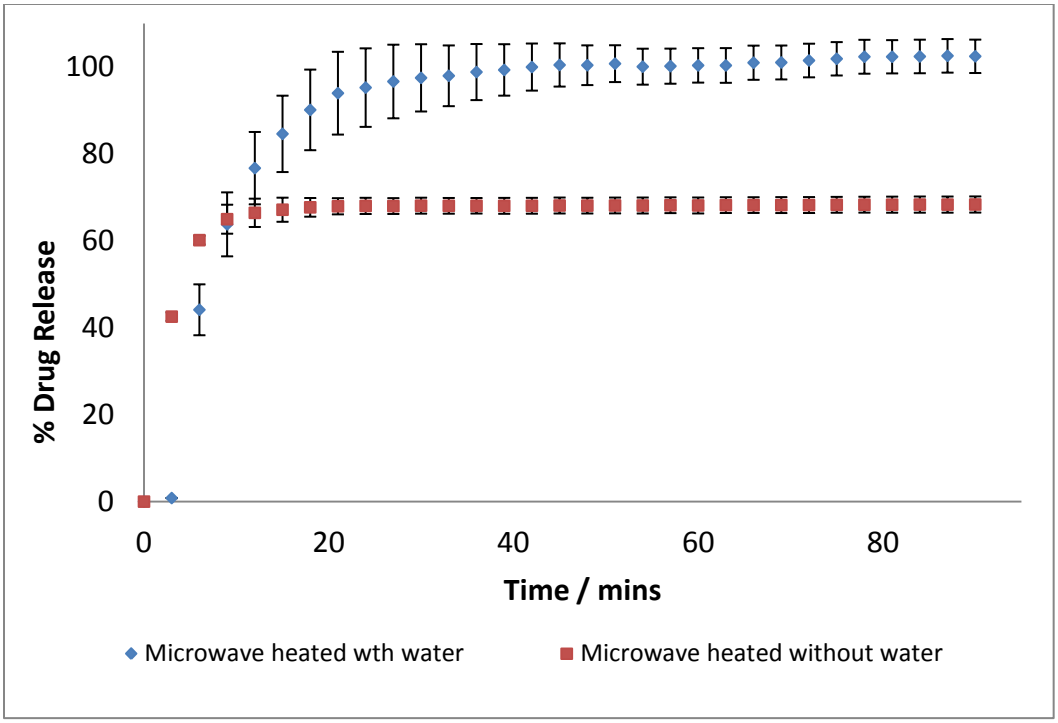

Figure 5.3.1.4 – A drug release profile for Ibuprofen and BCD (ratio 1:1), formulated using microwave heating both with and without the presence of water during the formulation process

Figure 5.3.1.4 shows that for ibuprofen and BCD 1:1 formulated with and without water there is a significant effect on the release of ibuprofen. In the presence of water more drug molecules are free to dissolve, with 85% (±9%) of the drug released in the first fifteen minutes. This is significantly different when compared with the formulations prepared without water where only 67% (±3%) of ibuprofen was released in a fifteen minute time period. When the rate was calculated for the different formulations, it became apparent that the formulation prepared with water released ibuprofen at a faster rate than the formulation prepared without water. It is also evident that the rate of release for both formulations also decreased as the dissolution progressed which can be seen in Figure 5.3.1.4.

Rate (% release per minute)		
Time(Mins)	MW With	MW Without
0-3	0.27	14.19
3-15	6.67	1.85
15-30	0.81	0.05

Table 5.3.1.4 – Rate of release of ibuprofen from BCD, when prepared with or without the presence of water during formulation

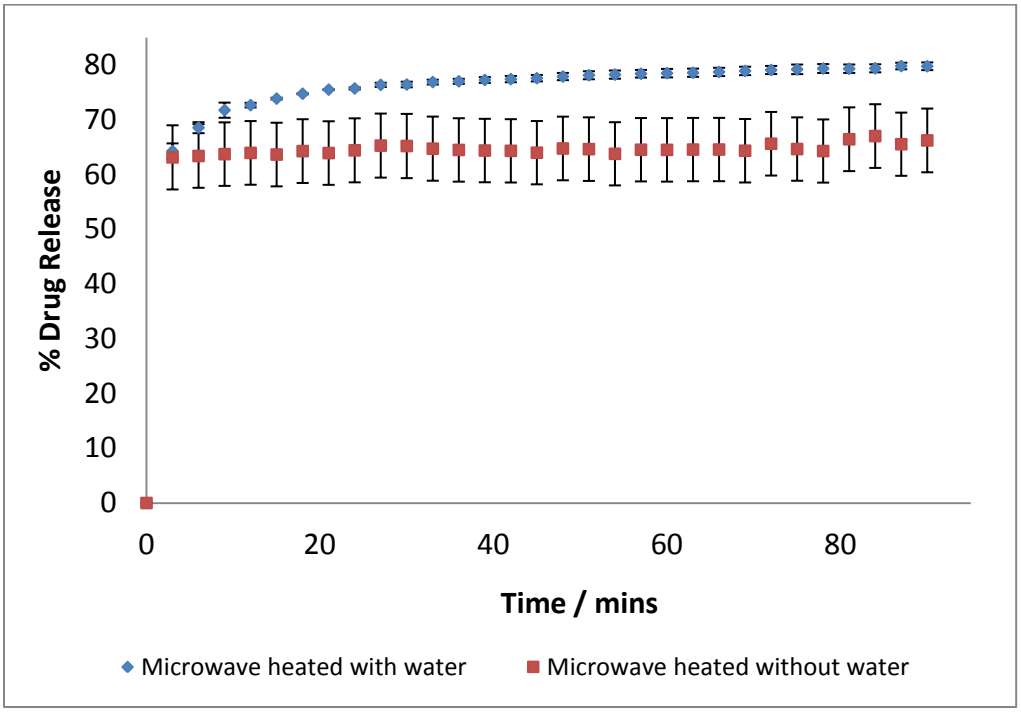

Figure 5.3.1.5– A drug release profile for Ibuprofen and PVP (ratio 1:9), formulated using microwave heating both with and without the presence of water during the formulation process

Figure 5.3.1.5 is another example of where the presence of water affected the release of ibuprofen. The release profile of ibuprofen formulated in the presence of water, displayed a higher amount of the drug going into solution. Over the ninety minutes, 80% (±1%) of the drug is free to dissolve compared with 66% (±6%) for the formulation without water. When the rate was calculated it can be seen that the formulation prepared without water initially released a higher percentage of ibuprofen. However after three minute, the rate dropped and the formulation prepared with water begins to

release more of the drug and this continued for the rest of the dissolution, seen in Table 5.3.1.5.

Rate (% release per minute)		
Time(Mins)	MW With	MW Without
0-3	21.42	21.03
3-15	0.78	0.05
15-30	0.17	0.11

Table 5.3.1.5 – Rate of release of ibuprofen from PVP, when prepared with or without the presence of water during formulation

In the majority of cases, a higher release of ibuprofen from the different excipients was observed when water had been present in the formulation process. This may occur for the following reasons: Water may aid the mixing process of the drug and excipient when drug or both are molten, and as a result a homogenous formulation occurs. This would improve dissolution because all drug molecules will be surrounded by the excipient improving overall solubility. Secondly, because of the presence of water, this may interfere with the interaction between the drug and excipient and as a result, a loosely bound complex was formed.

Alongside this hypothesis, another possible factor for ibuprofen and BCD (1:1) without water present can be considered. A decrease in the rate of dissolution was apparent and this could be occurring because the drug and excipient were in the same ratio (1:1) and consequently close to the saturation point of the excipient[11-12].

In the case of ibuprofen and SA, the difference in the release profiles may have occurred because of a loosely packed matrix. SA is a waxy fatty acid and when this excipient was formulated without water, there was no water to interfere with the interaction and full encapsulation occurs. This then made it difficult for the dissolution medium to penetrate into the formulation and slowed the release down (this is evident from all release profiles of ibuprofen and SA).

For ibuprofen and PVP, again the presence of water during formulation allowed more of the drug to be released over the time period. PVP has cross-linked chains and this gives it a pocket like structure which swells when exposed to moisture[13-14]. This may therefore cause an enlargement of these pockets allowing ibuprofen to fit better onto the structure, removing the drug from the water and improving dissolution. It is also

clear from the dissolution graphs that in most cases, ibuprofen was not released to a maximum of 100% when formulated with SA and PVP. A possible explanation for these results is because SA and PVP are insoluble in the chosen buffer and may have retained a certain percentage of the drug. It was previously mentioned that in the majority of cases when water is present in the formulation method, a higher percentage of the drug was released. However the following formulation (ibuprofen and BCD, 1:9) does not fit this trend.

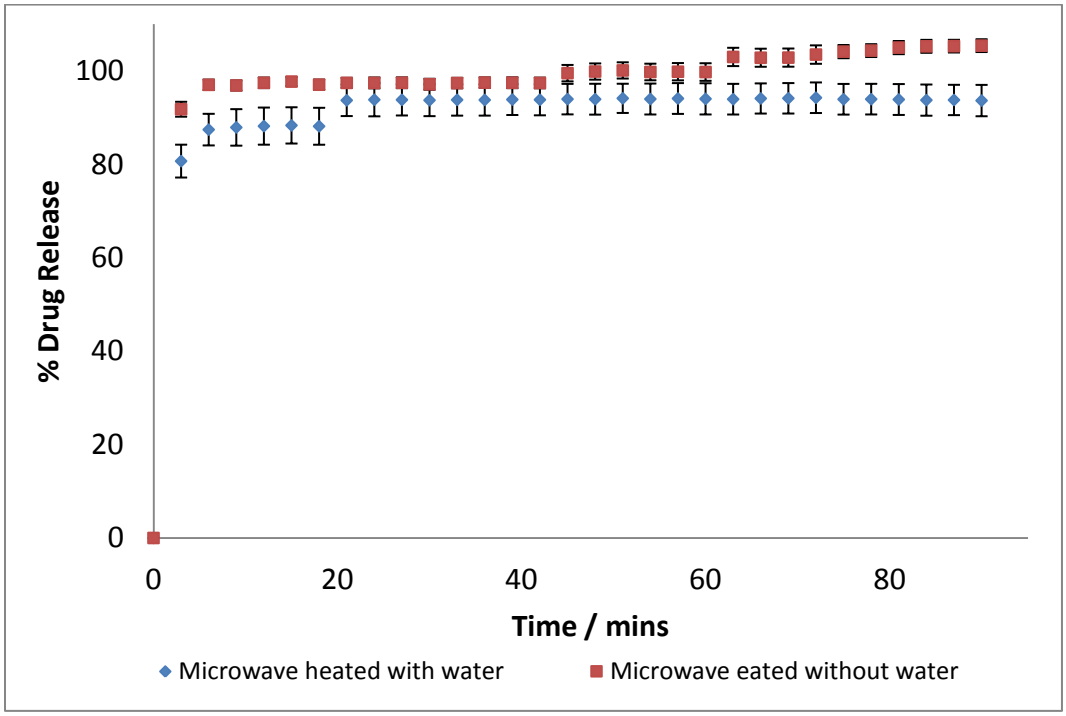

Figure 5.3.1.6 – A drug release profile for Ibuprofen and BCD (ratio 1:9), formulated using microwave heating both with and without the presence of water during the formulation process

Figure 5.3.1.6 displays ibuprofen and BCD (1:9) formulated using microwave heating. It can be seen that the presence of water has made no significant difference to the overall percentage drug release. The first twenty minutes of the dissolution profile indicates the formulation without water released a higher percentage of the drug (97% ±1% compared with 94% ±3%), and this is also reflected in the rate, Table 5.3.1.6. This was a result not previously seen with any other ibuprofen formulation, the usual trend

illustrated that when water was present a higher drug release was seen. However after this time period it was evident that there was no significant difference between the two.

Rate (% release per minute)		
Time(Mins)	MW With	MW Without
0-3	26.89	30.59
3-15	0.53	0.41
15-30	0.42	-0.02

Table 5.3.1.6 – Rate of release of ibuprofen from BCD, when prepared with or without the presence of water during formulation

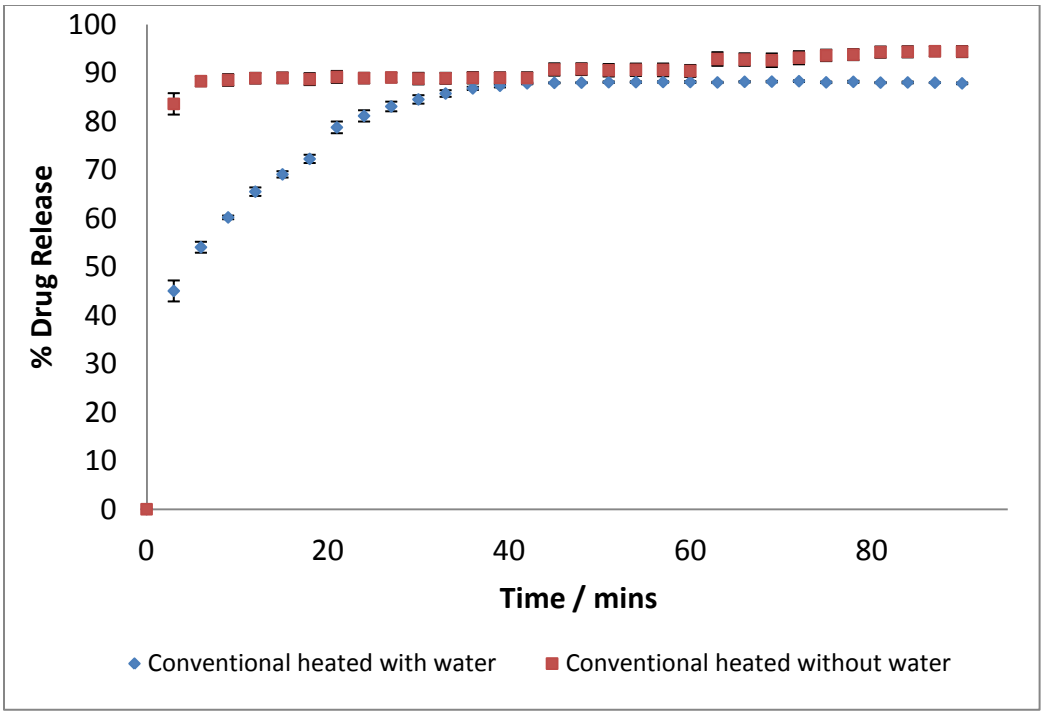

Figure 5.3.1.7 – A drug release profile for Ibuprofen and BCD (ratio 1:9), formulated using conventional heating both with and without the presence of water during the formulation process

Figure 5.3.1.7 illustrates conventionally formulated ibuprofen and BCD both with and without the presence of water during formulation. For this particular formulation when water was not present a higher proportion of the drug was initially released. This difference is seen within twenty minutes from the start of the dissolution. For formulations with water 79% (±1%) of the drug was released compared with 89% (±1%).

This difference is also illustrated by the rate of release of the drug (Table 5.3.1.7). Within the first three minutes ibuprofen was released from the formulation without water at 27.9% per minute with the majority of the drug released in this time period. The rate decreased after this, and this is also seen in Figure 5.3.1.7.

Rate (% release per minute)		
Time(Mins)	CN With	CN Without
0-3	15.01	27.87
3-15	1.99	0.38
15-30	1.07	0.00

Table 5.3.1.7 – Rate of release of ibuprofen from BCD, when prepared with or without the presence of water during formulation

Table 5.3.1.8 illustrates all the results obtained for ibuprofen and the four different excipients. In some cases no differences occurred, which is illustrated by the statement of ‘no difference’ in the table. When formulation with water resulted in a higher percentage drug release this is illustrated by the statement ‘with’ in the table, and conversely, when formulation without water resulted in a higher release it is identified as ‘without’. For ibuprofen and 2HPBCD no comparison could be made between formulations prepared with and without water, as this was only prepared without water, and this is consequently illustrated by the statement ‘N/A’.

Drug/Excipient	Microwave Heating	Conventional Heating
	Difference for formulations With/Without water	Difference for formulations With/Without water
Ibuprofen/SA 1:3	No Difference	With
Ibuprofen/BCD 1:1	With	With
Ibuprofen/BCD 1:9	Without	Without
Ibuprofen/PVP 1:1	With	No Difference
Ibuprofen/PVP 1:9	With	With
Ibuprofen/2HPBCD 1:1	N/A	N/A
Ibuprofen/2HPBCD 1:9	N/A	N/A

Table 5.3.1.8 –A summary to indicate conditions that created the greatest drug release for ibuprofen with the four different excipients formulated with and without the presence of water over a ninety minute time period.

5.3.2 The influence of microwave heating compared with conventional heating on subsequent drug release

Microwaves provide a quicker and more uniform technique of heating which could allow an advanced method for formulation of drugs and excipients. Consequently if a direct change over to microwave heating can be achieved without causing a reduction in drug release and bioavailability this would be advantageous to the pharmaceutical industry. In this section ibuprofen and the four different excipients were compared and analysed to determine if there were any differences between the two heating methods.

From all the results obtained, it appeared that the majority of formulations gave a higher percentage drug release when formulated using microwave heating. However there are some exceptions to this and the following graphs (Figure 5.3.2.1-5.3.2.4) illustrate this. A summary of all the results can be seen at the end of this section (Table 5.3.2.9).

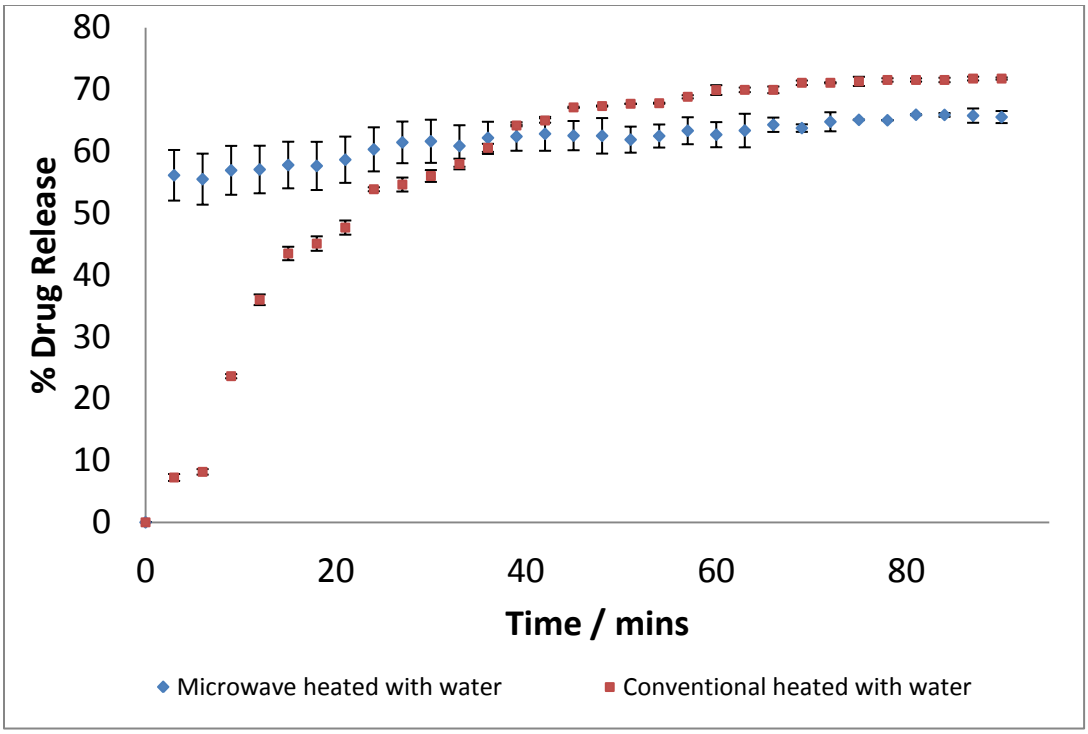

Figure 5.3.2.1 – A drug release profile for Ibuprofen and SA (ratio 1:3), formulated using microwave heating and conventional heating, in both cases with water present as a solvent

Figure 5.3.2.1 displays ibuprofen and SA, 1:3 ratio and from this graph it can be seen that the conventional heating method gave a controlled and higher percentage release. In the first twenty minutes 60% (±4%) of the drug was released when microwave is the chosen heating method compared with 50% (±1%) for conventional heating. However, after the first twenty minutes it is evident that the formulation prepared using conventional heating begins to release the drug to a greater extent. This occurred until a total of 72% (±0.2%) was released from the conventional formulation compared with 66% (±1%). From calculation of the rate, this was also evident, Table 5.3.2.1. For the first three minutes the microwave formulation released ibuprofen at a rate of 19% per minute, compared with 2% per second. This then dramatically decreased for the microwave formulation as the conventional formulation continues to increase and release a higher percentage of the drug.

Rate (% release per minute)		
Time (Mins)	Microwave Heating	Conventional Heating
0-3	18.71	2.42
3-15	0.16	3.34
15-30	0.31	0.93

Table 5.3.2.1 – Rate of release of ibuprofen from SA, microwave heating compared with conventional heating

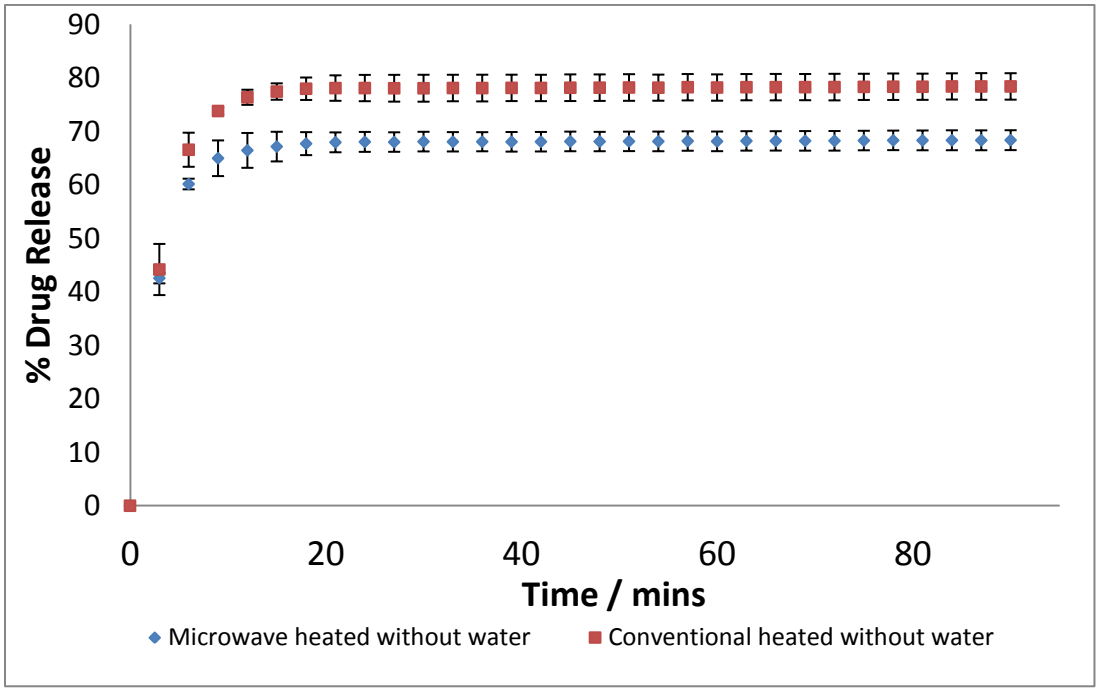

Figure 5.3.2.2 - A drug release profile for Ibuprofen and BCD (ratio 1:1), formulated using microwave heating and conventional heating, in both cases without water present as a solvent

Figure 5.3.2.2 illustrates a formulation where conventional heating achieved a higher percentage of the drug released compared with microwave heating. The initial release was similar but after a ten minute period, a separation in the release profiles becomes evident, with 78% (±2%) of the drug released from the conventional formulation over ninety minutes compared with 68% (±2%) for the microwave formulation. These results are also reflected in the rate, the initial three minutes of the dissolution show a similar rate for both formulations with 44% (±1%) of ibuprofen released (Table 5.3.2.2). After

this time period a decrease in the rate was seen (again for both formulations) but the rate of release for ibuprofen from the conventional formulations remained higher and consequently more of the drug was released.

Rate (% release per minute)		
Time (Mins)	Microwave Heating	Conventional Heating
0-3	14.19	14.72
3-15	1.85	2.55
15-30	0.05	0.03

Table 5.3.2.2 – Rate of release of ibuprofen from BCD 1:1, microwave heating compared with conventional heating

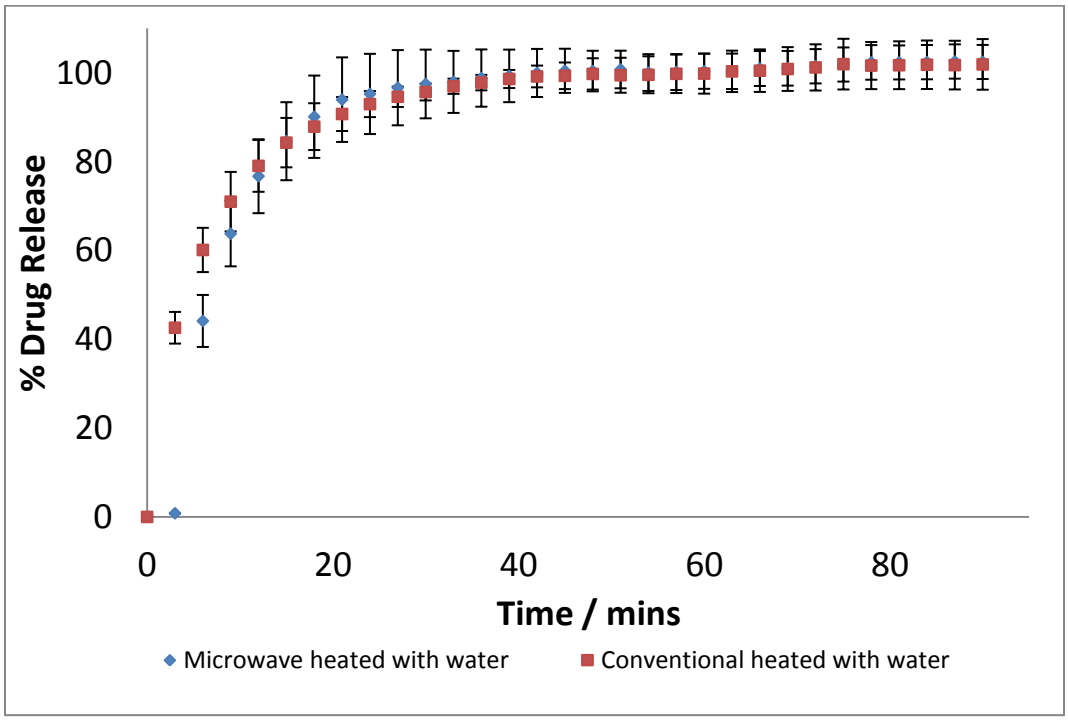

Figure 5.3.2.3 – A drug release profile for Ibuprofen and BCD (ratio 1:1), formulated using microwave heating and conventional heating, in both cases with water present as a solvent

Figure 5.3.2.3 displays no significant difference between microwave and conventional heating. In both cases 100% (±4%) of ibuprofen was released over the ninety minutes. When the rate of release was calculated it was noted at the beginning of the experiment, the formulation prepared using microwave heating released the drug at a higher rate. However this rate decreased and at the end of the experiment both formulations have a similar rate of release and as a result the same amount of the drug was released.

Rate (% release per minute)		
Time (Mins)	Microwave heating	Conventional heating
0-3	0.27	14.20
3-15	6.67	3.41
15-30	0.81	0.76

Table 5.3.2.3 – Rate of release of ibuprofen from BCD 1:1, microwave heating compared with conventional heating

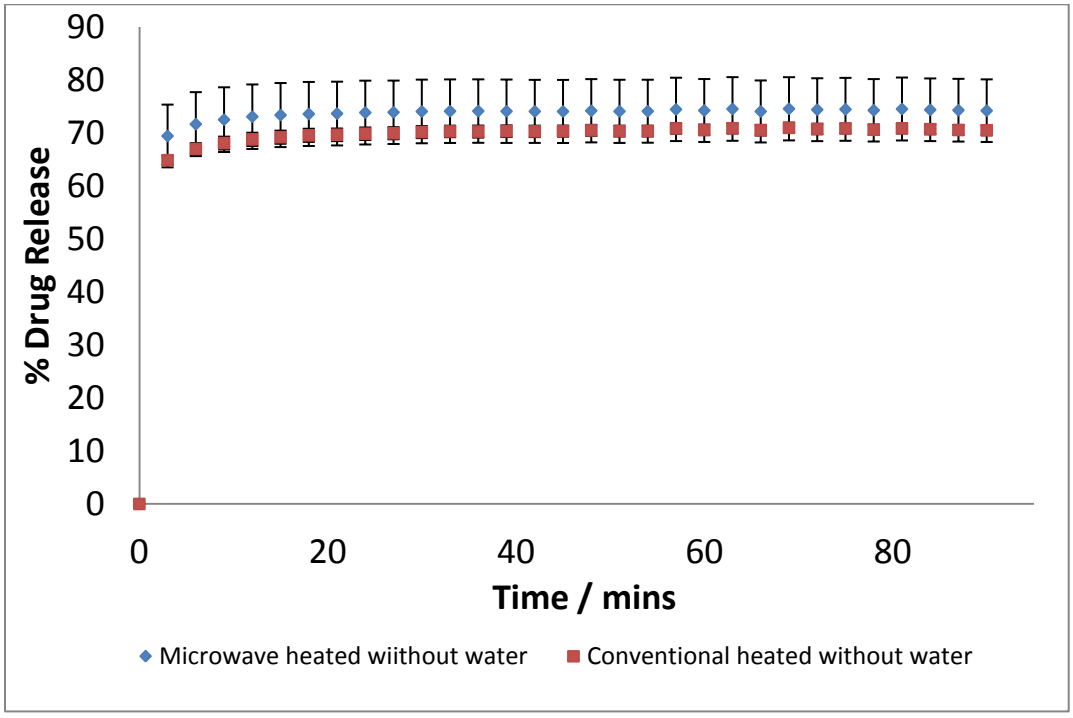

Figure 5.3.2.4 – A drug release profile for Ibuprofen and PVP (ratio 1:1), formulated using microwave heating and conventional heating, in both cases without water present as a solvent

Figure 5.3.2.4 illustrates no significant difference in the release of the drug from either heating methods. A higher release of ibuprofen from PVP was seen for the microwave formulation in the initial three minutes (69% ±6% compared with 65% ±1%). However after this time period, both formulations released approximately the same amount of the drug.

Rate (% release per minute)		
Time (Mins)	Microwave Heating	Conventional Heating
0-3	23.15	21.62
3-15	0.31	0.35
15-30	0.04	0.06

Table 5.3.2.4 – Rate of release of ibuprofen from PVP 1:1, microwave heating compared with conventional heating

For other ibuprofen based formulations, microwave heating appeared to show a higher percentage drug release when compared with conventional heating. Figures 5.3.2.5 to 5.3.2.9 illustrate a few examples of where this applies.

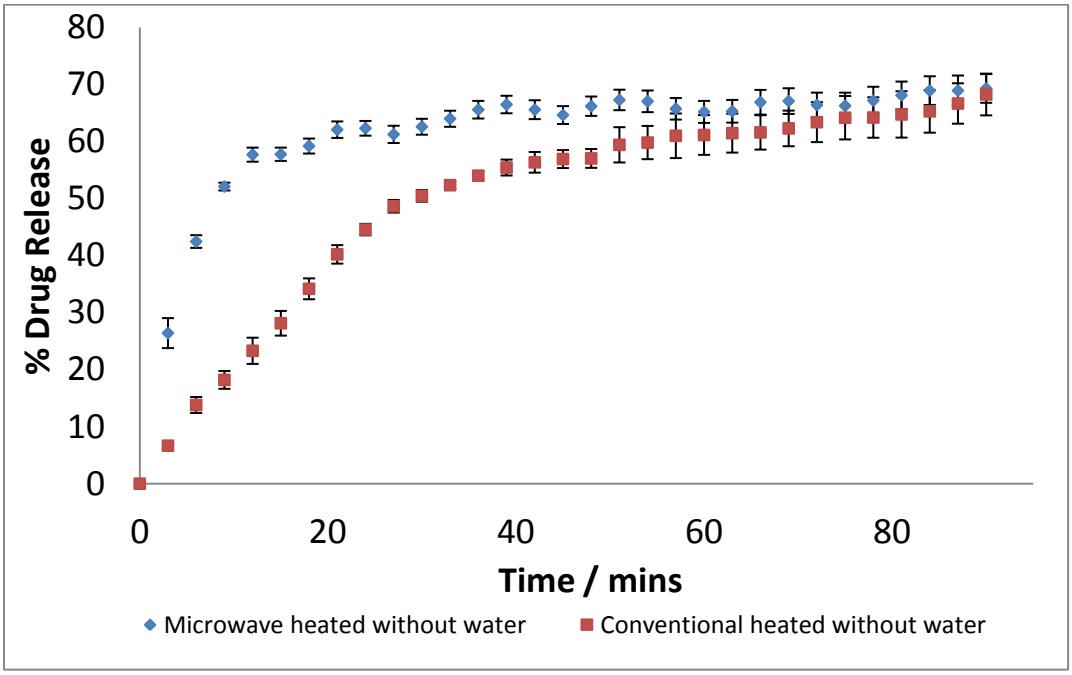

Figure 5.3.2.5 - A drug release profile for Ibuprofen and SA, formulated using microwave heating and conventional heating, in both cases without water present as a solvent

Figure 5.3.2.5 illustrates ibuprofen and SA formulated using microwave and conventional heating. It is evident from the dissolution profile that when this particular formulation was heated using microwaves, a higher percentage drug release occurred initially but after the ninety minutes both formulations released the same amount of the drug. After fifty minutes, the microwave formulation released 67% (±2%) and the conventional formulation released 59% (±3%). After ninety minutes, both formulations were seen to release approximately 70% of the drug (MW 69% ±2%, CN 68% ±4%). This result can also be seen in the rate of release, Table 5.3.2.5.

Rate (% release per minute)		
Time (Mins)	Microwave Heating	Conventional Heating
0-3	8.80	2.22
3-15	2.60	1.75
15-30	0.29	1.52

Table 5.3.2.5 – Rate of release of ibuprofen from SA, microwave heating compared with conventional heating

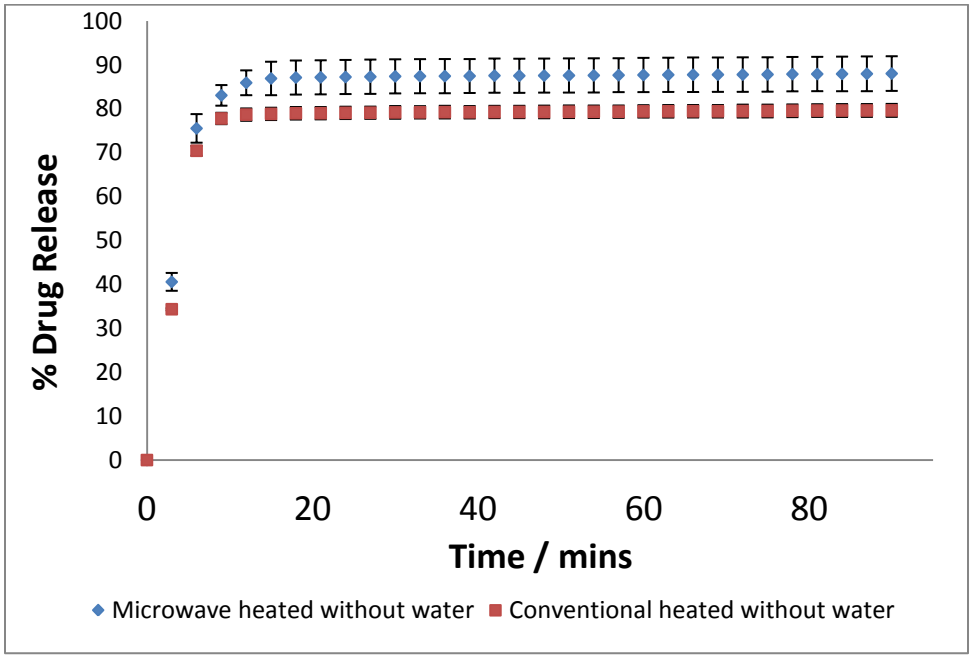

Figure 5.3.2.6 – A drug release profile for Ibuprofen and HPBCD, formulated using microwave heating and conventional heating, in both cases without water present as a solvent

Figure 5.3.2.6 illustrates that for ibuprofen and 2HPBCD, microwave heating released 90% (±4%) of the drug over the ninety minute period compared with 80% (±1%) for conventional heating. Upon calculation of the rate of release, Table 5.3.2.6 it can be seen that the microwave formulation releases the drug at a faster rate when compared with conventional heating. Consequently more of the drug is released from the microwave formulation over the time period.

Rate (% release per minute)		
Time (Mins)	Microwave Heating	Conventional Heating
0-3	13.53	11.45
3-15	3.43	3.24
15-30	0.03	0.02

Table 5.3.2.6 – Rate of release of ibuprofen from HPBCD, microwave heating compared with conventional heating

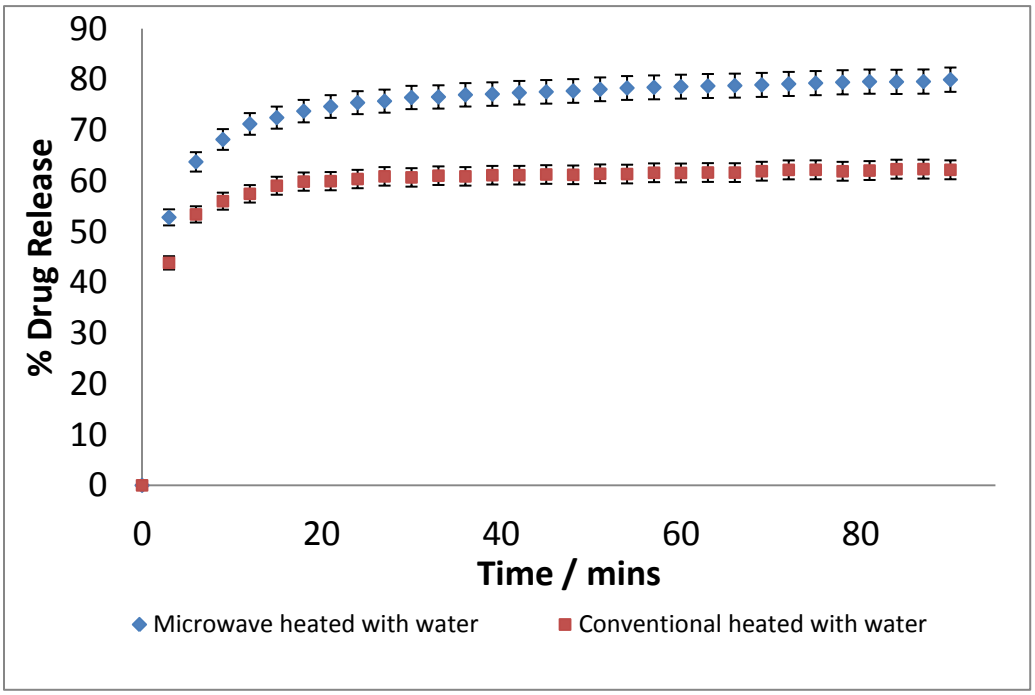

Figure 5.3.2.7 – A drug release profile for Ibuprofen and PVP (ratio 1:9), formulated using microwave heating and conventional heating, in both cases with water present as a solvent

From Figure 5.3.2.7 it can be seen that with the formulation using microwave heating more of the drug was released over the ninety minutes time period. It can be seen that 80% (±1%) of ibuprofen was released from the microwave heated formulation compared with 62% (±2%) for conventional heating. The difference between the two formulations is also evident from the calculated rate of release, Table 5.3.2.7.

Rate (% release per minute)		
Time (Mins)	Microwave Heating	Conventional Heating
0-3	21.42	14.62
3-15	0.78	1.15
15-30	0.17	0.11

Table 5.3.2.7 – Rate of release of ibuprofen from PVP, microwave heating compared with conventional heating

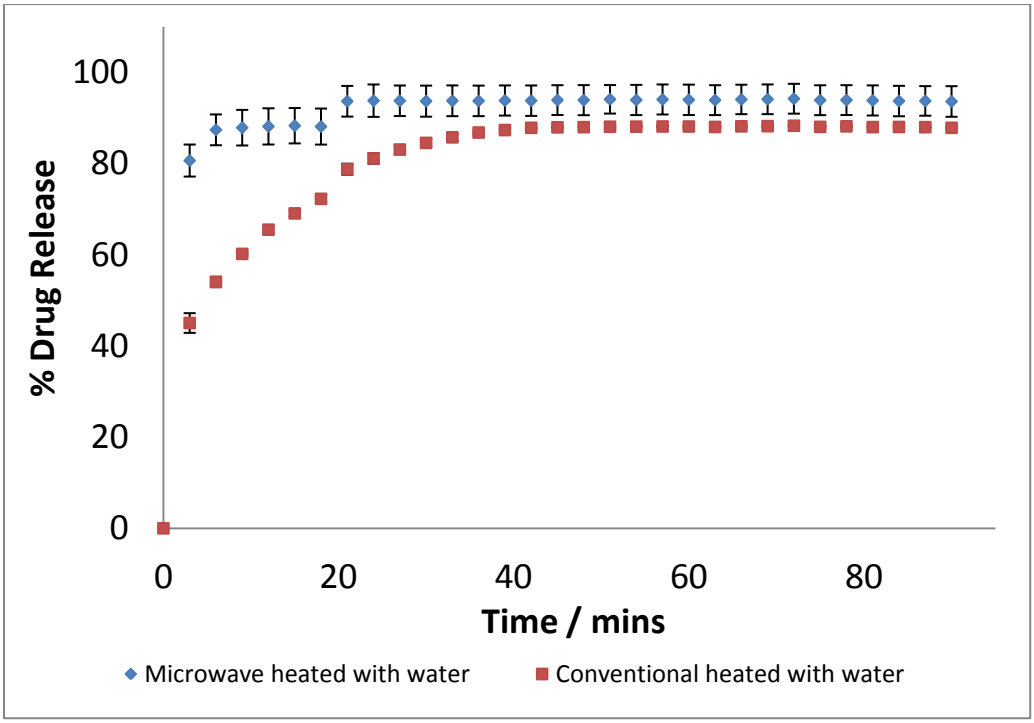

Figure 5.3.2.8 – A drug release profile for Ibuprofen and BCD (ratio 1:9), formulated using microwave heating and conventional heating, in both cases with water present as a solvent

From Figure 5.3.2.8 it can be seen that microwave heating not only released more of the drug over the time period, but the maximum amount was achieved at a faster rate. For the microwave heated formulation in the first twenty minutes 90% (±3%) of the drug was released compared with 79% (±1%). However, towards the end of the analysis, the profiles began to level with the microwave formulation releasing 94% (±3%) compared with 79% (±1%) for conventional. This finding is also reflected in the rate of release of ibuprofen, Table 5.3.2.8.

Rate (% release per minute)		
Time (Mins)	Microwave Heating	Conventional Heating
0-3	26.89	15.01
3-15	0.53	1.99
15-30	0.42	1.07

Table 5.3.2.8 – Rate of release of ibuprofen from PVP, microwave heating compared with conventional heating

To determine why these differences occurred, the way the two different methods heat the formulations must be considered. Firstly conventional heating is a slower method of heating which works over a temperature gradient, and may illustrate uneven heating (Section 1.5.1 Conventional heating). Microwave heating is rapid and by directly interacting with the drug and excipient molecules (causing them to flip in alignment with the wave of energy, generating heat) no temperature gradient may be observed (Section 1.5.2 microwave heating). As a result a more homogenous formulation may be evident, and consequently illustrate an improved dissolution.

Table 5.3.2.9 illustrates all the results obtained for ibuprofen and the four different excipients prepared using microwave and conventional heating. In some cases no differences occurred, which is illustrated by the statement of ‘no difference’ in the table. When microwave heating showed a higher percentage drug release this is illustrated by the statement ‘MW’ in the table. When conventional heating illustrated a higher percentage drug release this is indicated by the statement ‘CN’ in the table.

Drug/Excipient	With water Differences between MW/CN	Without water Differences between MW/CN
Ibuprofen/SA 1:3	CN	MW
Ibuprofen/BCD 1:1	No Difference	CN
Ibuprofen/BCD 1:9	MW	MW
Ibuprofen/PVP 1:1	MW	No Difference
Ibuprofen/PVP 1:9	MW	MW
Ibuprofen/2HPBCD 1:1	N/A	MW
Ibuprofen/2HPBCD 1:9	N/A	MW

Table 5.3.2.9 –A summary to indicate conditions that created the greatest drug release for ibuprofen and the different excipients analysed for differences between microwave and conventional heating over a ninety minute time period.

5.3.3 Excipients

Formulation method parameters, such as the heating method and presence of solvent, are not the only factors that affect drug release, excipient selection can also play a vital role. In particular, it was found that the excipient which released the greatest amount of ibuprofen (formulated in the presence of water) was BCD in the 1:1 ratio using both heating methods. Whilst the excipient that released the smallest amount of ibuprofen (formulated using conventional heating in the presence of water) was PVP in the 1:9 ratio.

When water was not used in the formulation process, the excipient that released the greatest amount of ibuprofen was BCD in the 1:9 ratio (formulated using both heating methods). The excipient that slowed the release of ibuprofen most dramatically was 2HPBCD in the 1:9 ratio (formulated using conventional heating).

In summary, based on these results, if formulating ibuprofen to enhance drug release it would be advisable to use BCD either with or without water present using either heating method.

In contrast, if formulating ibuprofen to retard drug release it would be advisable to formulate conventionally using PVP, when water is present, or HPBCD, when water is not present as a solvent.

5.3.4 Summary

To summerise; when water was present during the formulation method a higher percentage of ibuprofen was released. It is difficult to determine the reasons this occurred as a number of factors may be contributing to the observed results.

In the majority of cases when ibuprofen was formulated using microwave heating a higher percentage of drug release was witnessed.

With respect to excipient choice, when formulating ibuprofen to enhance the drug release it is advisable to formulate using BCD. If however the drug release needs to be delayed then PVP (1:9) or HPBCD should be used.

5.4 Ketoprofen

5.4.1 The effect of water on the release profile of ketoprofen

Formulations of ketoprofen were prepared with or without the presence of water during the formulation process to determine if the presence of a liquid affected the release profiles of the drug.

Ketoprofen was formulated with three different excipients (2HPBCD not formulated in the presence of water) with the resultant formulations analysed to establish drug release profiles. A summary of all the results are illustrated at the end of this section in Table 5.4.1.6. Figures 5.4.1.1 to 5.4.1.5 are examples of some of the results obtained for the dissolution of ketoprofen with SA, BCD and PVP. Figure 5.4.1.1 and Figure 5.4.1.2 are examples of where the presence of water has significantly affected the release of the drug.

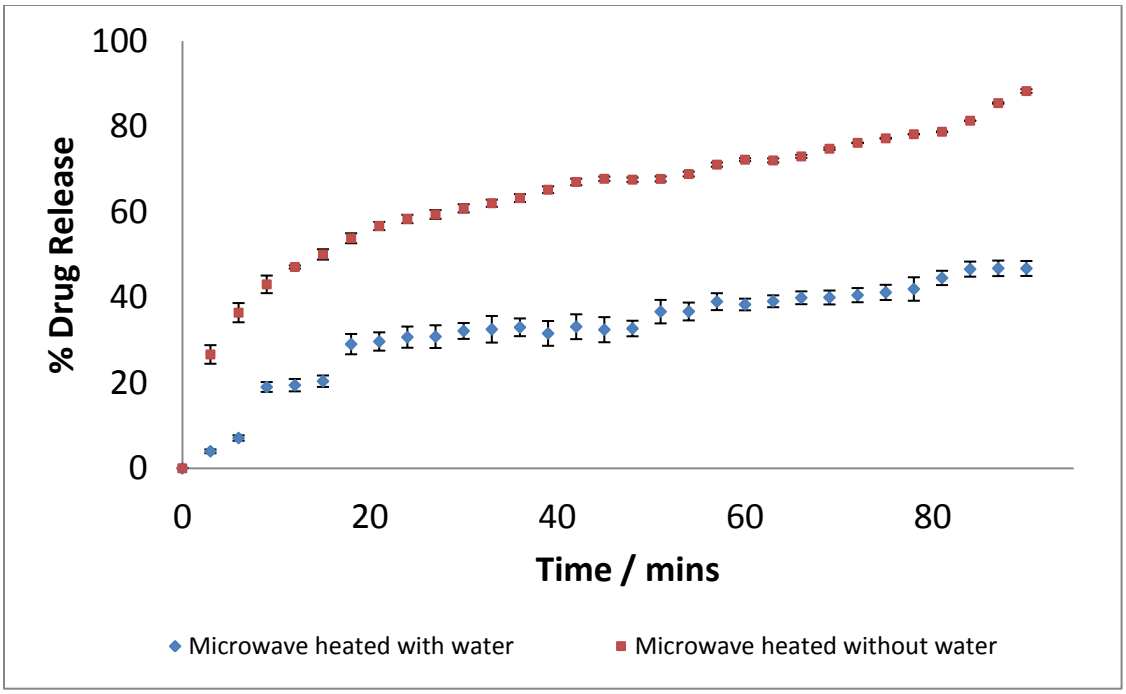

Figure 5.4.1.1 – A drug release profile for ketoprofen and SA (ratio 1:3), formulated using microwave heating both with and without the presence of water during the formulation process

Figure 5.4.1.1 is an illustration of ketoprofen and SA formulated using microwave heating. It can be seen from the graph that the presence of water has decreased the release of the drug. After fifteen minutes the formulation prepared with water only released 20% (±1%) compared with 50% (±1%). After the ninety minutes the formulation prepared with water released 47% (±2%) compared with 88% (±1%).

The result visually seen in Figure 5.4.1.1 is also reflected in the rate, Table 5.4.1.1.

Rate (% release per minute)		
Time (Mins)	MW With	MW Without
0-3	1.33	8.88
3-15	1.51	1.92
15-30	0.62	0.69

Table 5.4.1.1 Rate of release of ketoprofen from SA, when prepared with or without the presence of water during microwave formulation

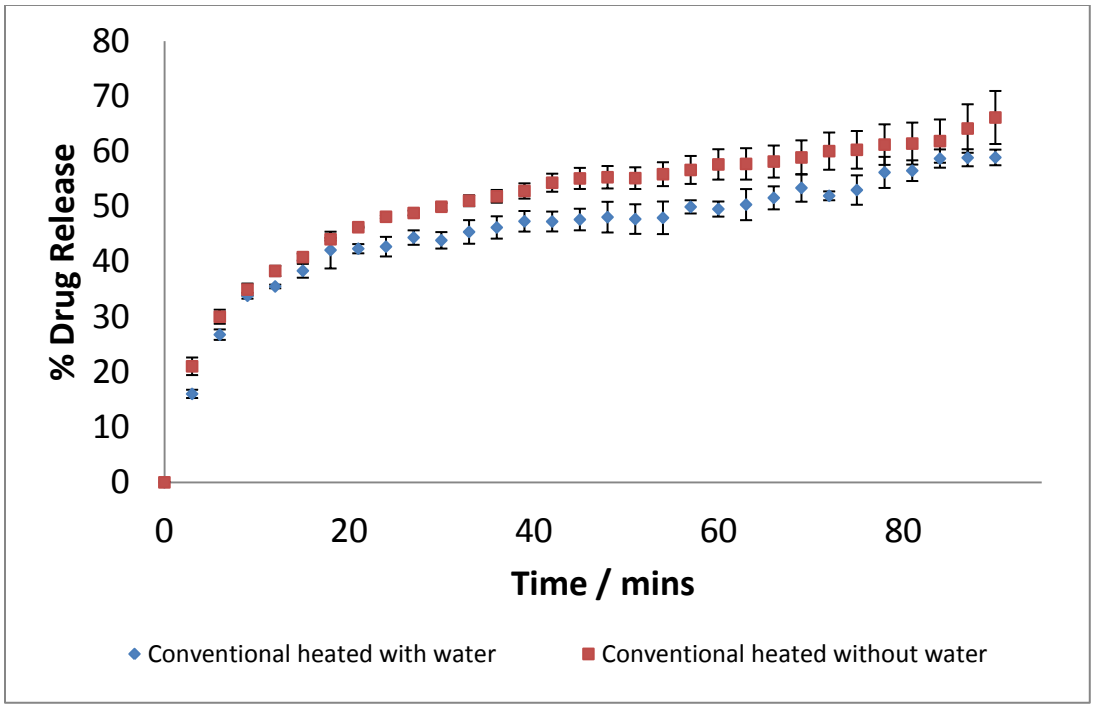

Figure 5.4.1.2 – A drug release profile for ketoprofen and SA (ratio 1:3), formulated using conventional heating both with and without the presence of water during the formulation process

Figure 5.4.1.2 displays that the formulation prepared without water has released a higher percentage of the drug. The formulation prepared without water released 41% (±1%) compared with 38 (±1%), and after the ninety minutes 66% (±5%) of the drug was released from the formulation prepared without water compared with 59% (±1%). The results obtained in Figure 5.4.1.2 are also illustrated by the rate, Table 5.4.1.2. For the first fifteen minutes of the dissolution the formulation without water released ketoprofen at a faster rate, which would explain why more of the drug is detected in solution from the formulation prepared without water.

Rate (% release per minute)		
Time (Mins)	CN With	CN Without
0-3	5.35	7.01
3-15	1.78	1.60
15-30	0.33	0.59

Table 5.4.1.2 Rate of release of ketoprofen from SA, when prepared with or without the presence of water during conventional formulation

Figure 5.4.1.3 illustrates ketoprofen formulation with BCD (ratio 1:9) and this is an example of where the presence of water hasn't greatly affected the release of the drug.

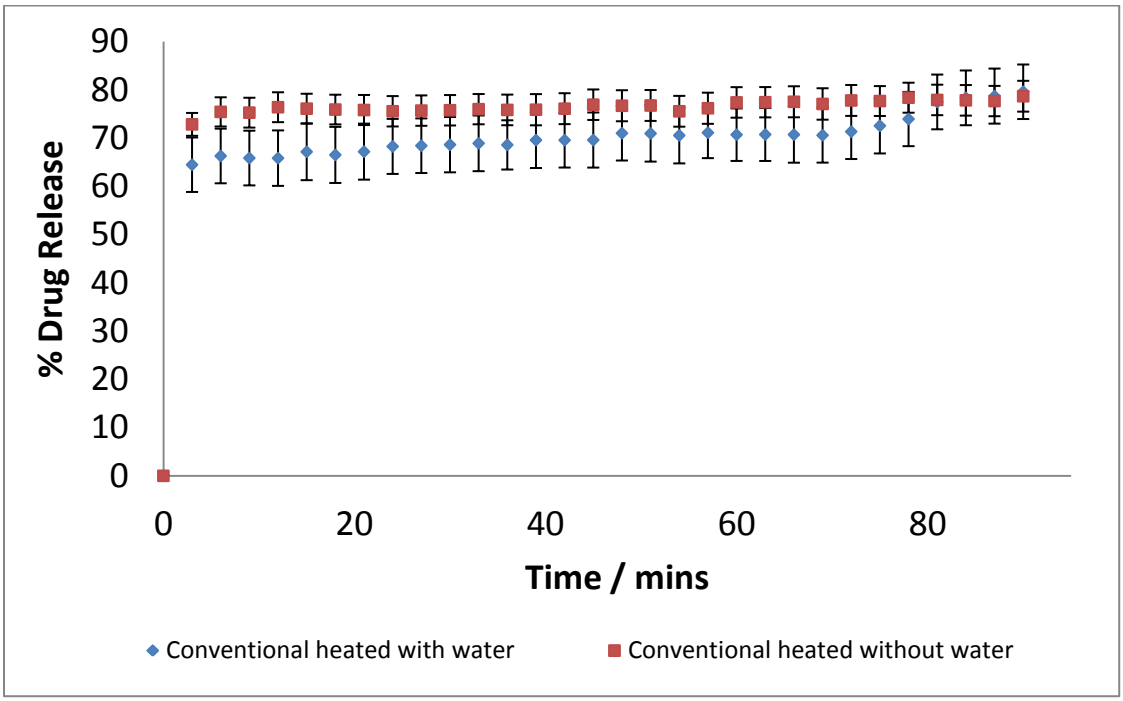

Figure 5.4.1.3 – A drug release profile for ketoprofen and BCD (ratio 1:9), formulated using conventional heating both with and without the presence of water during the formulation process

Figure 5.4.1.3 shows a small initial difference between the two profiles. For the first fifteen minutes 67% (±6%) of the drug is released from the formulation prepared with the presence of water, compared with 76% (±3%). From this result it is evident that a difference occurred, however with the associated error it is difficult to be 100% certain.

Also after this initial time period, the release profiles become very similar, with 80% (±6%) compared with 79% (±3%) of the drug released in total. This is also seen when the rate is calculated, Table 5.4.1.3.

Rate (% release per minute)		
Time (Mins)	CN With	CN Without
0-3	21.49	24.28
3-15	0.16	0.25
15-30	0.14	-0.02

Table 5.4.1.3 Rate of release of ketoprofen from BCD, 1:9 when prepared with or without the presence of water during conventional formulation

Figures 5.4.1.3 to 5.4.1.5 illustrate formulations where water shows a higher percentage drug release.

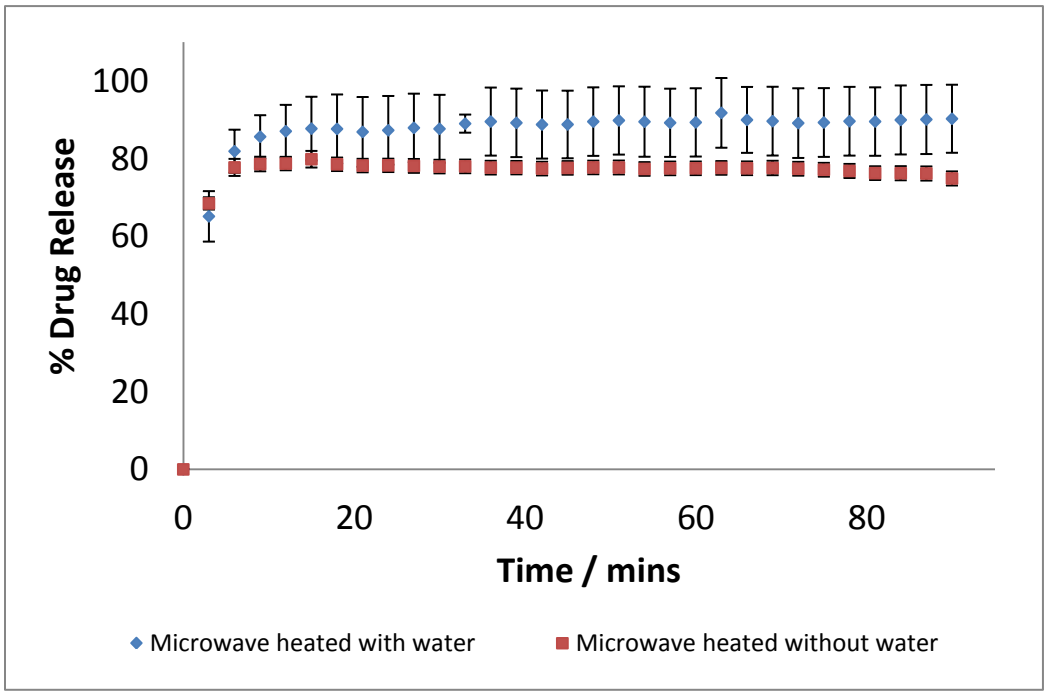

Figure 5.4.1.4 – A drug release profile for ketoprofen and BCD (ratio 1:1), formulated using microwave heating both with and without the presence of water during the formulation process

Figure 5.4.1.3 illustrates the release profile for ketoprofen and BCD, (ratio 1:1). It is evident that the presence of water has increased the percentage drug release. For the formulation prepared with water a drug release of 88% (±8%) is seen, and this is compared with 80% (±2%) for the formulation prepared without water. From these results it is evident that the initial part of the dissolution is similar, however, after this time period a separation between the release profiles occurs. After the ninety minutes a drug release of 90% (±9%) is seen for the formulation with water which is compared with 75% (±2%). This result is also demonstrated in the rate, Table 5.4.1.4.

Rate (% release per minute)		
Time (Mins)	MW With	MW Without
0-3	21.72	22.83
3-15	1.68	0.79
15-30	0.01	-0.10

Table 5.4.1.4 Rate of release of ketoprofen from BCD, 1:1 when prepared with or without the presence of water during microwave formulation

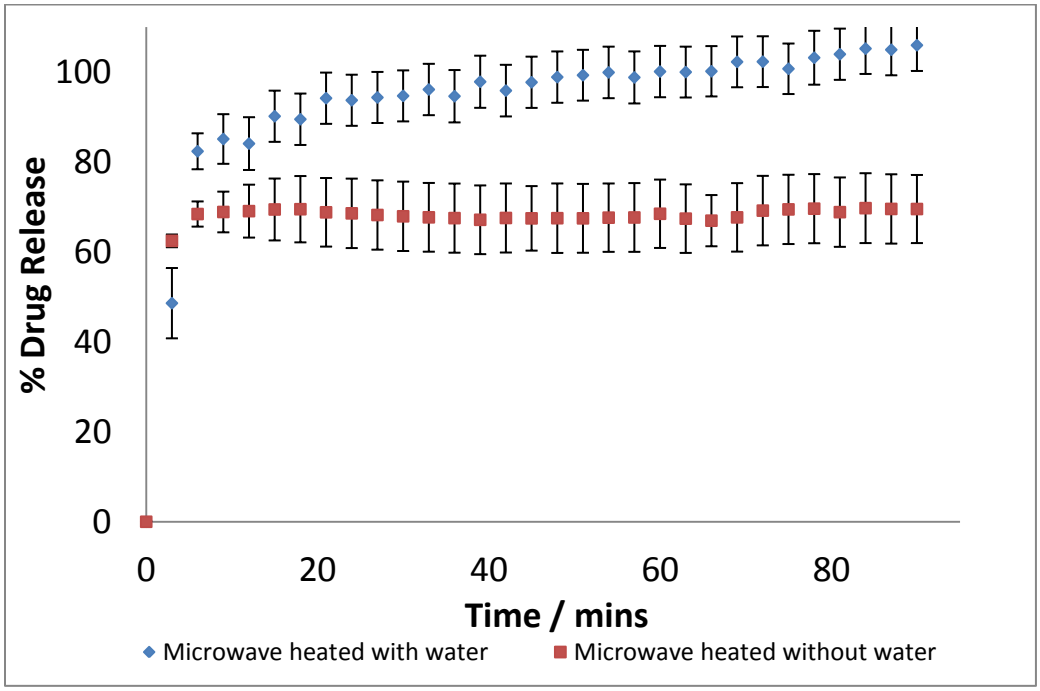

Figure 5.4.1.5 – A drug release profile for ketoprofen and BCD (ratio 1:9), formulated using microwave heating both with and without the presence of water during the formulation process

Figure 5.4.1.5 displays ketoprofen and BCD 1:1 ratio formulated using microwave heating. It can be seen from the release profiles that the presence of water has had a significant effect to the way the drug is released. After the first fifteen minutes of the dissolution 90% (±6%) of ketoprofen is released which is compared with 69% (±7%), and after the ninety minutes 100% (±6%) of ketoprofen is released when water is present, compared with 70% (±7%). The difference in the release profiles was also illustrated in the rate calculation, Table 5.4.1.5. For the initial three minutes of the dissolution the formulation prepared without water present illustrates a faster drug release, 20.83% per minute compared with 16.2%. However after this time period both rates drop but the formulation prepared with water has a higher rate of release which continues over thirty minutes and consequently more ketoprofen is released.

Rate (% release per minute)		
Time (Mins)	MW With	MW Without
0-3	16.21	20.83
3-15	2.83	0.49
15-30	0.35	-0.11

Table 5.4.1.5 Rate of release of ketoprofen from BCD, 1:9 when prepared with or without the presence of water during microwave formulation

The above results illustrate the different formulations and how the presence of water during formulation has affected the percentage drug release. Some formulations (SA and BCD 1:1) illustrate that when water is present during the formulation process, a decrease in the percentage drug release is demonstrated. However in the majority of cases, when water is present during the formulation process a higher percentage drug release is apparent.

Table 5.4.1.6 illustrates all the results obtained for ketoprofen and the four different excipients. In some cases no differences occurred, which is illustrated by the statement of 'no difference' in the table. When formulation with water resulted in a higher percentage drug release this is illustrated by the statement 'with' in the table, and conversely, when formulation without water resulted in a higher percentage drug release it is identified as 'without'. For ketoprofen and 2HPBCD no comparison could be made between formulations prepared with and without water, as this was only prepared without water, and this is consequently illustrated by the statement 'N/A'.

Drug/Excipient	**MW**	**CN**
	With/Without	**With/Without**
Ketoprofen/SA 1:3	Without	No Difference
Ketoprofen/BCD 1:1	With	With
Ketoprofen/BCD 1:9	With	No Difference
Ketoprofen/PVP 1:1	With	With
Ketoprofen/PVP 1:9	With	With
Ketoprofen/2HPBCD 1:1	N/A	N/A
Ketoprofen/2HPBCD 1:9	N/A	N/A

Table 5.4.1.6- A summary to indicate conditions that created the greatest drug release for ketoprofen with the four different excipients formulated with and without the presence of water over a ninety minute time period

5.4.2 The influence of microwave heating compared with conventional heating on subsequent drug release

Formulation methods using microwave and conventional heating were compared for ketoprofen to determine if the method choice influenced drug release. In the majority of cases no difference between the heating methods was apparent, however some formulations do show a difference and these are illustrated by Figures 5.4.2.1 to 5.4.2.3. A summary of all results obtained can be seen at the end of this section in Table 5.4.2.7.

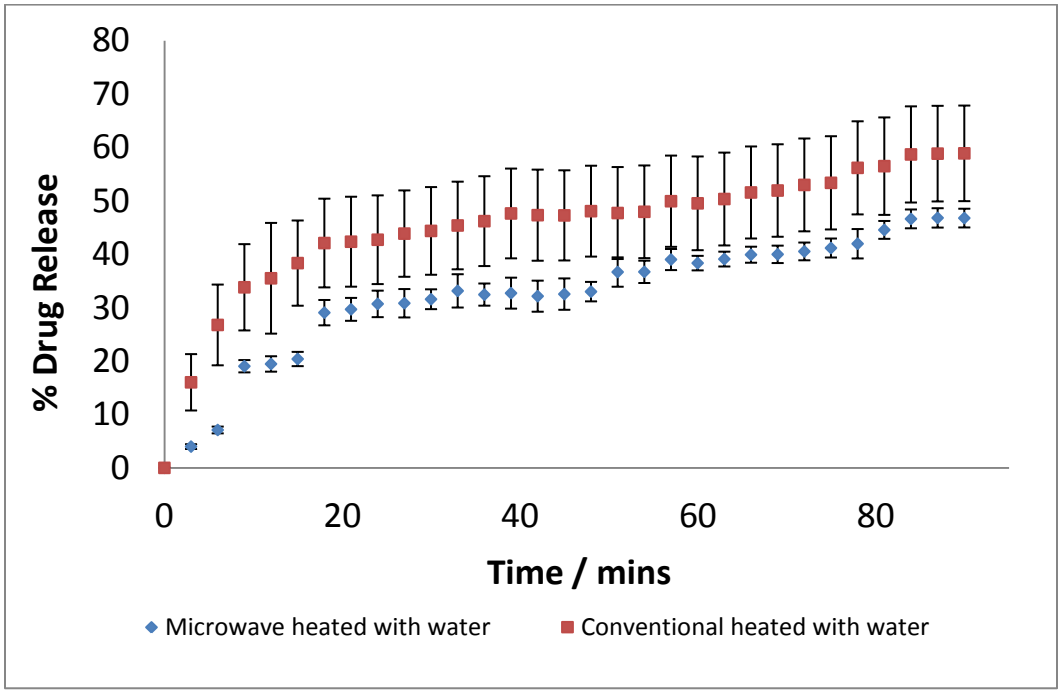

Figure 5.4.2.1 – A drug release profile for ketoprofen and SA (ratio 1:3), formulated using microwaves and conventional heating, in both cases with water present as a solvent

Figure 5.4.2.1 is for ketoprofen and SA and from the graph it can be seen that the conventional method showed a higher percentage drug release. For the first fifteen minutes 20% (±1%) of ketoprofen was released for the formulation prepared using microwave heating, however for the conventional formulation 38% (±8%) of the drug was released within this time. After ninety minutes the microwave formulation released

47% (±2%) compared with 59% (±9%). This is also reflected in the rate of release, Table 5.4.2.1.

Rate (% release per minute)		
Time (Mins)	Microwave heating	Conventional Heating
0-3	1.33	5.34
3-15	1.51	1.78
15-30	0.59	0.34

Table 5.4.2.1- Rate of release of ketoprofen from SA, microwave heating compared with conventional heating

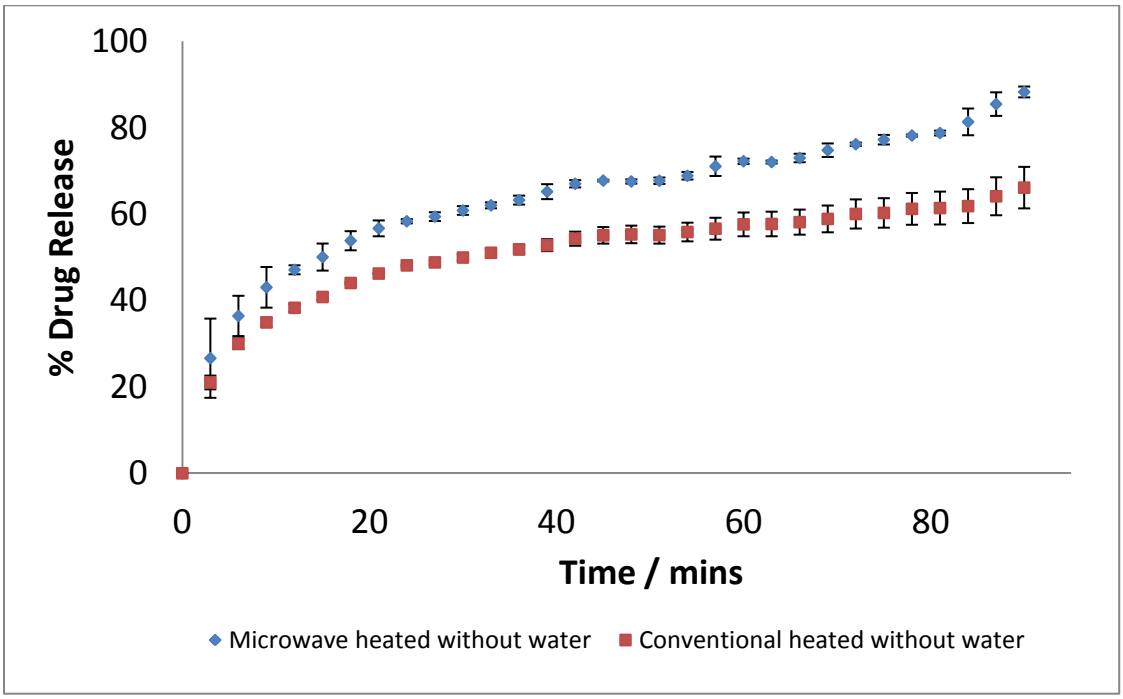

Figure 5.4.2.2 – A drug release profile for ketoprofen and SA (ratio 1:3), formulated using microwaves and conventional heating, in both cases without water present as a solvent

Figure 5.4.2.2 illustrates a formulation where microwave heating achieved a higher percentage drug release when compared with conventional heating. For the first fifteen minutes 50% (±3%) of ketoprofen was released from the formulation prepared using microwave heating compared with 41% (±1%) for the conventional formulation. After ninety minutes 88% (±1%) of the drug was released for the microwave formulation, and

only 66% (±5%) of ketoprofen was released for the conventional method. This result is also demonstrated in the rate, with the microwave formulation showing a faster rate of release of ketoprofen illustrated in Table 5.4.2.2.

Rate (% release per minute)		
Time (Mins)	Microwave Heating	Conventional Heating
0-3	8.88	7.01
3-15	1.92	1.60
15-30	0.69	0.59

Table 5.4.2.2- Rate of release of ketoprofen from SA, microwave heating compared with conventional heating

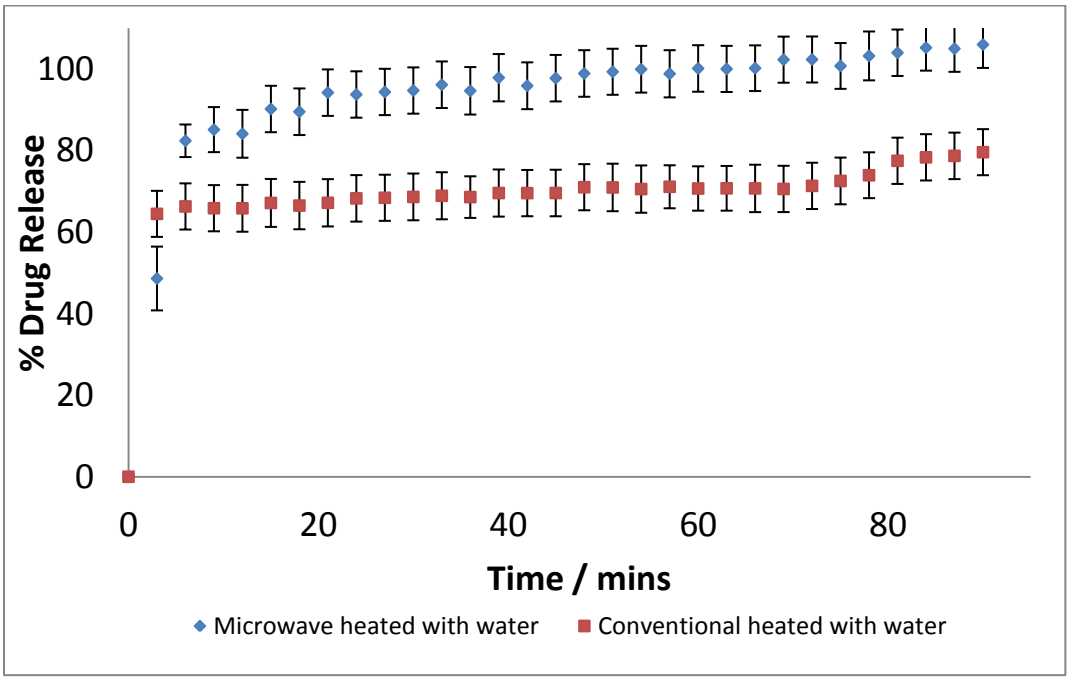

Figure 5.4.2.3 – A drug release profile for ketoprofen and BCD (ratio 1:9), formulated using microwaves and conventional heating, in both cases with water present as a solvent

Figure 5.4.2.3 illustrates ketoprofen and BCD, 1:9 and it can be seen from the two release profiles that the formulation prepared using microwaves released a higher percentage of the drug. After fifteen minutes 90% (±6%) of the drug is released from the formulation prepared using microwave heating which is in comparison with 67% (±6%).

After ninety minutes over 100% (±6%) of ketoprofen is released from the microwave formulation compared with 80% (±6%), this is also illustrated in the rate, Table 5.4.2.3.

Rate (% release per minute)		
Time (Mins)	Microwave Heating	Conventional Heating
0-3	16.21	21.49
3-15	2.83	0.16
15-30	0.35	0.14

Table 5.4.2.3- Rate of release of ketoprofen from BCD 1:9, microwave heating compared with conventional heating

The previous graphs have illustrated where the choice of heating method has made a significant difference to the release of ketoprofen. However in the majority of cases the choice of heating method doesn't have an overall affect on the release of ketoprofen. A few examples are illustrated in Figures 5.4.2.4 – 5.4.2.6.

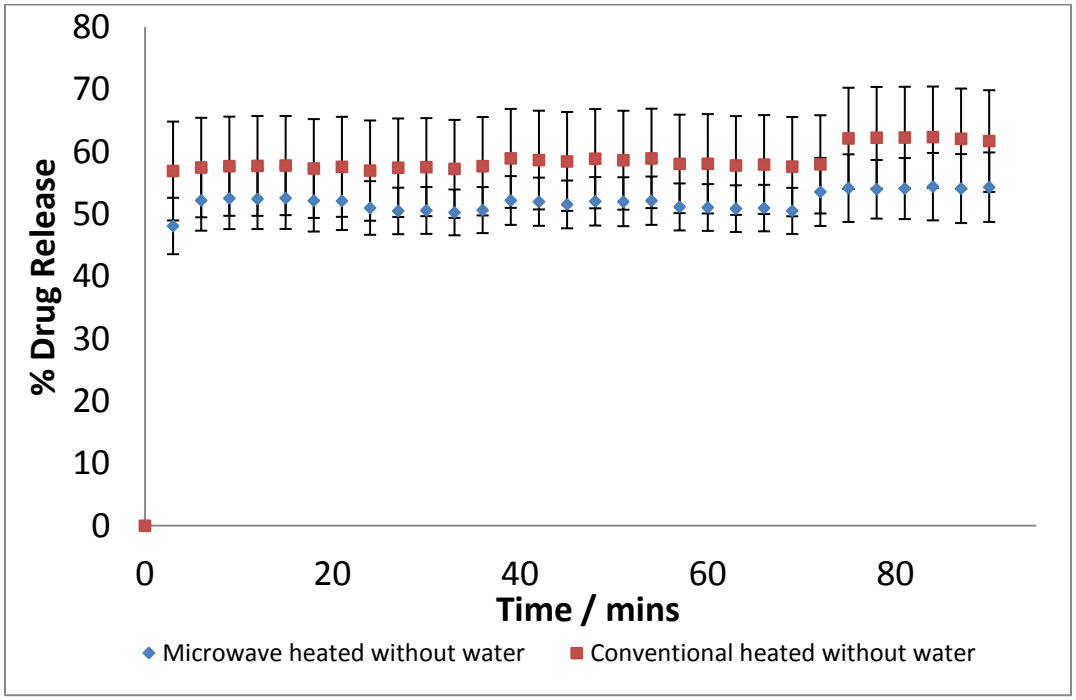

Figure 5.4.2.4 – A drug release profile for ketoprofen and 2HPBCD (ratio 1:9), formulated using microwaves and conventional heating, in both cases without water present as a solvent

Figure 5.4.2.4 displays the release profiles for ketoprofen and 2HPBCD formulated using microwaves and conventional heating. After the experimental error was calculated it can be said that no significant difference occurred between the two heating methods. However, after analysis of the percentage drug release, it may be possible to speculate that a slight difference does exist. For the first fifteen minutes 53% (±5%) of ketoprofen was released from the microwave formulation which is compared with 58% (±8%). After the ninety minutes 54% (±6%) of the drug was released from the microwave formulation compared with 62% (±8%). However because of the error associated with these results it is difficult to be completely sure whether a significant difference does occur. Upon calculation of the rate, a difference can be seen between the two heating methods, but again the experimental error makes it difficult to be definitive.

Rate (% release per minute)		
Time (Mins)	Microwave Heating	Conventional Heating
0-3	16.04	18.98
3-15	0.31	0.07
15-30	-0.15	-0.01

Table 5.4.2.4- Rate of release of ketoprofen from 2HPBCD 1:9, microwave heating compared with conventional heating

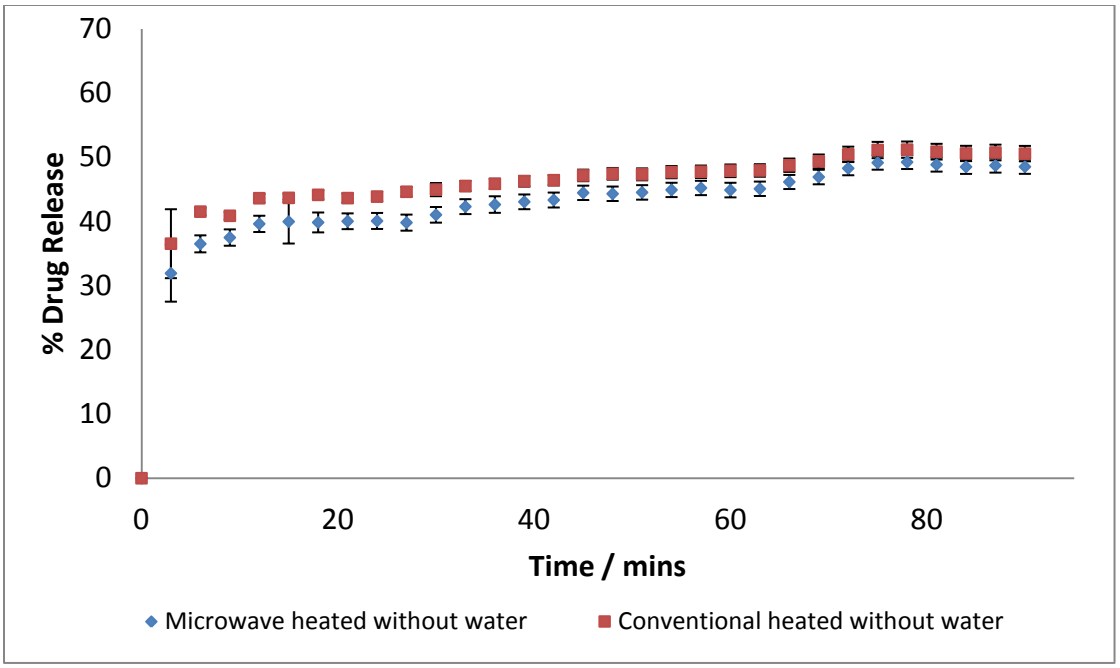

Figure 5.4.2.5 – A drug release profile for ketoprofen and PVP (ratio 1:9), formulated using microwaves and conventional heating, in both cases without water present as a solvent

Figure 5.4.2.5 demonstrates that the choice of heating method for this particular formulation doesn't affect the way the drug is released. For the first fifteen minutes of the dissolution a slight difference is observed with the microwave formulation releasing 40% (±3%) compared with 44% (±1%). However after this time period both the formulations released approximately 50% (49% ±1% microwave formulation, 51% ±1% conventional formulation) over the ninety minutes. The result demonstrated above is also seen in the rate calculation, Table 5.4.2.5. The conventional formulation released the drug at a faster rate within the first three minutes, with 12.2% per minute released compared with 10.6% per minute for microwave formulation. However after this time period, both rates decrease and a similar amount of drug release can be seen.

Rate (% release per minute)		
Time (Mins)	MW Without	CN Without
0-3	10.64	12.18
3-15	0.64	0.55
15-30	0.05	0.08

Table 5.4.2.5- Rate of release of ketoprofen from PVP 1:9, microwave heating compared with conventional heating

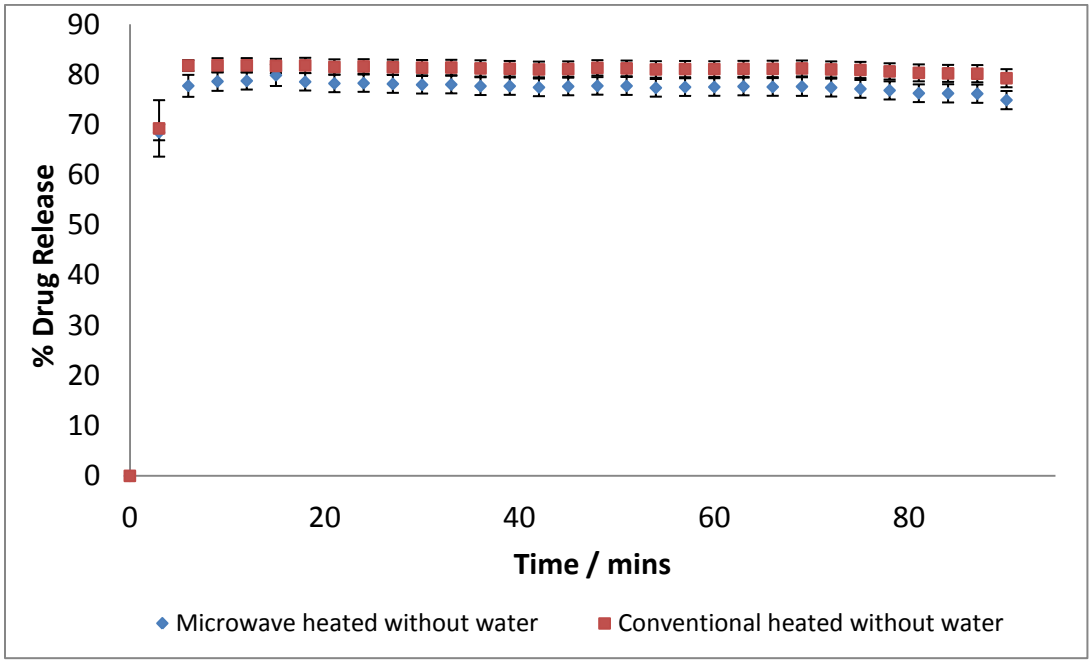

Figure 5.4.2.6– A drug release profile for ketoprofen and BCD (ratio 1:1), formulated using microwaves and conventional heating, in both cases without water present as a solvent

Figure 5.4.2.6 illustrates another example of where the choice of heating method has made no significant difference to the release of ketoprofen. For the first fifteen minutes of the dissolution 80% (±2%) of ketoprofen was released from the microwave formulation compared with 82% (±1%) for the conventional formulation. After the ninety minutes 80% (±2%) of ketoprofen was released from the microwave formulation compared with 82% (±2%) for the conventional formulation, this shows a slight

difference between the two formulations but nothing significant. Upon calculation of the rate it can also been seen that both formulations release ketoprofen at the same rate.

Rate (% release per minute)		
Time (Mins)	MW Without	CN Without
0-3	22.83	23.09
3-15	0.79	0.83
15-30	-0.10	-0.03

Table 5.4.2.6- Rate of release of ketoprofen from BCD 1:1, microwave heating compared with conventional heating

All the formulations illustrated in this section are examples of ketoprofen with the four different excipients. It can be seen that in the majority of cases the choice of heating method doesn't affect the way ketoprofen is released. However there are a few exceptions which are also illustrated. Table 5.4.2.7 summarises all the different ketoprofen formulations prepared using microwaves or conventional heating. In some cases no differences occurred, which is illustrated by the statement of 'no difference' in the table. When microwave heating showed a higher percentage drug release this is illustrated by the statement 'MW' in the table. When conventional heating released a higher percentage of the drug this is illustrated by 'CN' in the table. For ketoprofen and 2HPBCD only the formulation prepared without water present could be analysed for any differences between the two heating methods, consequently N/A is seen for this formulation prepared with water present during formulation.

Drug/Excipient	With MW/CN	Without MW/CN
Ibuprofen/SA 1:3	CN	MW
Ibuprofen/BCD 1:1	MW	No Difference
Ibuprofen/BCD 1:9	MW	No Difference
Ibuprofen/PVP 1:1	No Difference	No Difference
Ibuprofen/PVP 1:9	MW	No Difference
Ibuprofen/2HPBCD 1:1	N/A	No Difference
Ibuprofen/2HPBCD 1:9	N/A	No Difference

Table 5.4.2.7- A summary to indicate conditions that created the greatest drug release for ketoprofen and the excipients analysed for differences between microwave and conventional heating

5.4.3 Excipients

The formulation method, such as the heating method and the presence of solvent, are not the only factors that affect drug release, excipient selection can also play a vital role.

In particular, it was found that the excipient that released the greatest amount of ketoprofen (formulated in the presence of water) was BCD in the 1:9 ratio using microwave heating. While the excipient that released the smallest amount of ketoprofen was PVP in the 1:9 ratio (formulated using both heating methods in the presence of water).

When water was not present in the formulation process, the excipient that released the greatest amount of ketoprofen was 2HPBCD (formulated using microwaves and conventional heating), and the excipient that slowed the release most dramatically was SA (formulated using conventional heating).

In summary, based on these results, if formulating ketoprofen to enhance drug release it would be advisable to formulate using BCD 1:9, with the presence of water and using microwave heating. When water is not present during the formulation

process, it would be advisable to formulate using 2HPBCD (formulated with microwaves or conventional heating) to enhance drug release.

In contrast, if formulating ketoprofen to retard drug release it would be advisable to formulate using conventionally heated PVP in the 1:9 ratio (formulated in the presence of water). When water is not present during the formulation process, it would be advisable to formulate using SA (formulated using microwaves and conventional heating).

5.4.4 Summary

To summarise, when water was present during the formulation method, a higher percentage of ketoprofen was released. It is difficult to determine the reasons why this occurred, as a number of factors may be contributing to the observed results. When the two different heating methods were compared, it was noted that no significant difference was seen in the majority of cases. However there were some exceptions to that result.

With respect to the excipient choice, when formulating ketoprofen to enhance drug release it is advisable to formulate using BCD or 2HPBCD. If however the drug release needs to be delayed then PVP (1:9) or SA should be used.

5.5 Flurbiprofen

After an investigation into flurbiprofen and the different excipients began, it became evident that a problem was occurring with the absorbance for the drug in formulations based on BCD and 2HPBCD. Upon comparison of the Beer-Lambert plot for pure flurbiprofen it was noted that the formulations were illustrating a higher absorbance and consequently a possible shift may have occurred[15]. As a result it was difficult to measure and report the percentage drug release, a trend only witnessed with flurbiprofen and the two excipients. It is difficult to determine why this has occurred and only in this case. However a possibility, is that flurbiprofen has fluorine group attached which the other drugs do not possess. This therefore may be affecting the way the drug and excipients interact. Consequently, flurbiprofen was formulated with SA and PVP only and the results are illustrated below.

5.5.1 The effect of water on the release profile of flurbiprofen

It was decided to incorporate water into the formulation process to determine how the presence of a liquid affected the release profiles of a drug with poor aqueous solubility. Flurbiprofen was formulated with two excipients with the resultant formulations analysed to establish drug release profiles. A summary of all results are illustrated at the end of this section in Table 5.5.1.6. Figures 5.5.1.1 to 5.5.1.5 are examples of some of the results obtained from the dissolution of flurbiprofen with SA and PVP.

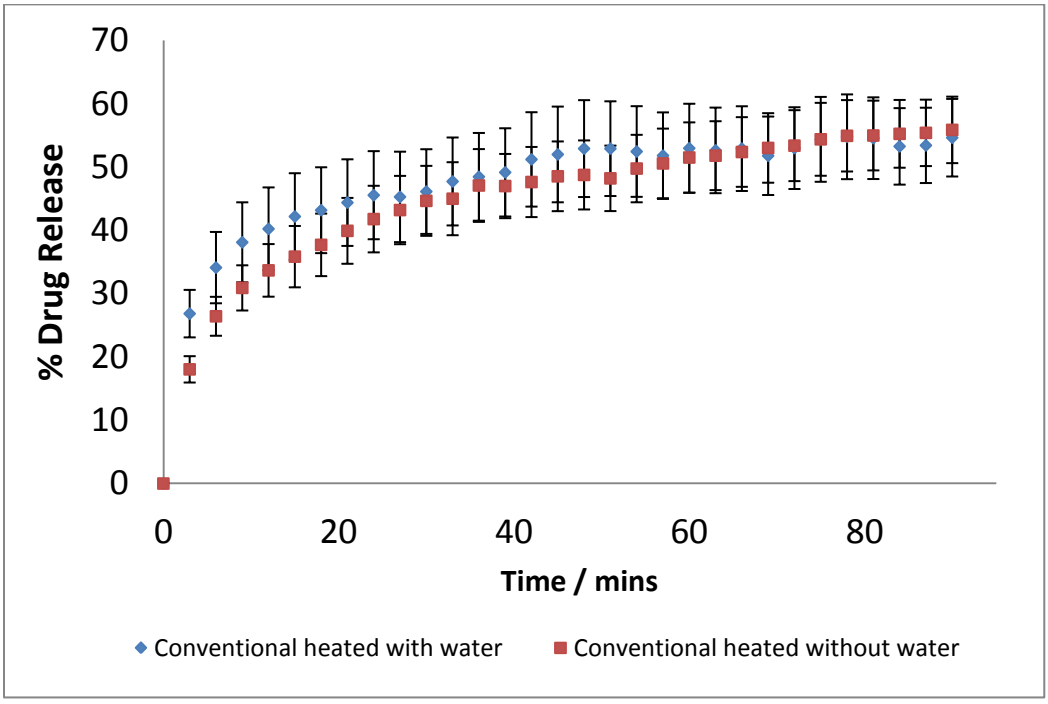

Figure 5.5.1.1 – A drug release profile for flurbiprofen and SA (ratio 1:3), formulated using conventional heating both with and without the presence of water during the formulation process

Figure 5.5.1.1 displays the release profile for flurbiprofen formulated with SA using conventional heating with and without the presence of water. It is apparent from the graph that there is no significant difference between the two formulations, therefore it can be said that the presence of water has made no difference to the release of flurbiprofen from SA. For the first fifteen minutes of the dissolution the formulation prepared with water released 42% (±7%) compared with 36% (±5%), this shows a possible difference during the early stages of the dissolution. However after the ninety

minutes 55% (±6%) of flurbiprofen was released from the formulation prepared with water compared with 56% (±5%) for the formulation prepared without water. This trend is also shown when the rate was calculated, Table 5.5.1.1. It can be seen that the formulation prepared with water releases flurbiprofen at a slightly higher rate of 8.95% per minute compared with 6.01% per minute for the formulation prepared without water.

Rate (% release per minute)		
Time (Mins)	CN With	CN Without
0-3	8.95	6.01
3-15	1.23	1.43
15-30	0.26	0.59

Table 5.5.1.1 Rate of release of flurbiprofen from SA when prepared with or without the presence of water during formulation

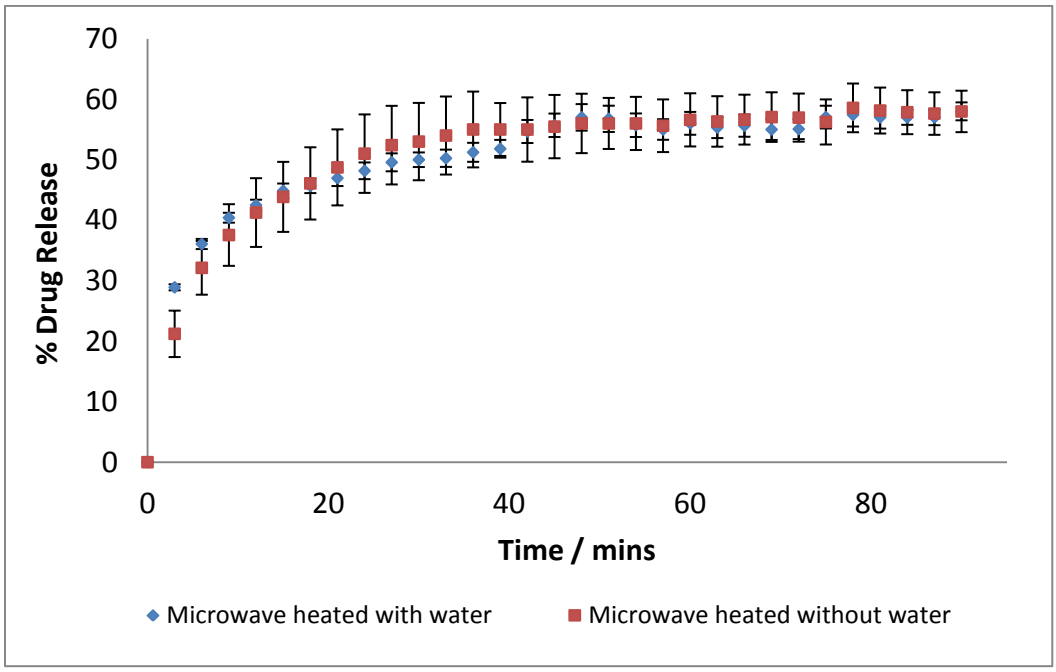

Figure 5.5.1.2 – A drug release profile for flurbiprofen and SA (ratio 1:3), formulated using microwave heating both with and without the presence of water during the formulation process

Figure 5.5.1.2 displays no overall difference in total drug release, with 45% (±1%) of flurbiprofen released when water is present during the formulation process. This is in comparison with 44% (±6%) for the formulation prepared without water present. After ninety minutes, both formulation release 58% (with water 58% ±1% and without water 58% ±3%). Upon calculation of the rate, Table 5.5.1.2, it appears that the formulation prepared with water may release a slightly higher percentage of flurbiprofen, 9.64% per minute compared with 7.07%. However after this time period both rates decrease and the same amount of the drug is released.

Rate (% release per minute)		
Time (Mins)	MW With	MW Without
0-3	9.64	7.07
3-15	1.28	1.81
15-30	0.37	0.64

Table 5.5.1.2 Rate of release of flurbiprofen from SA when prepared with or without the presence of water during formulation

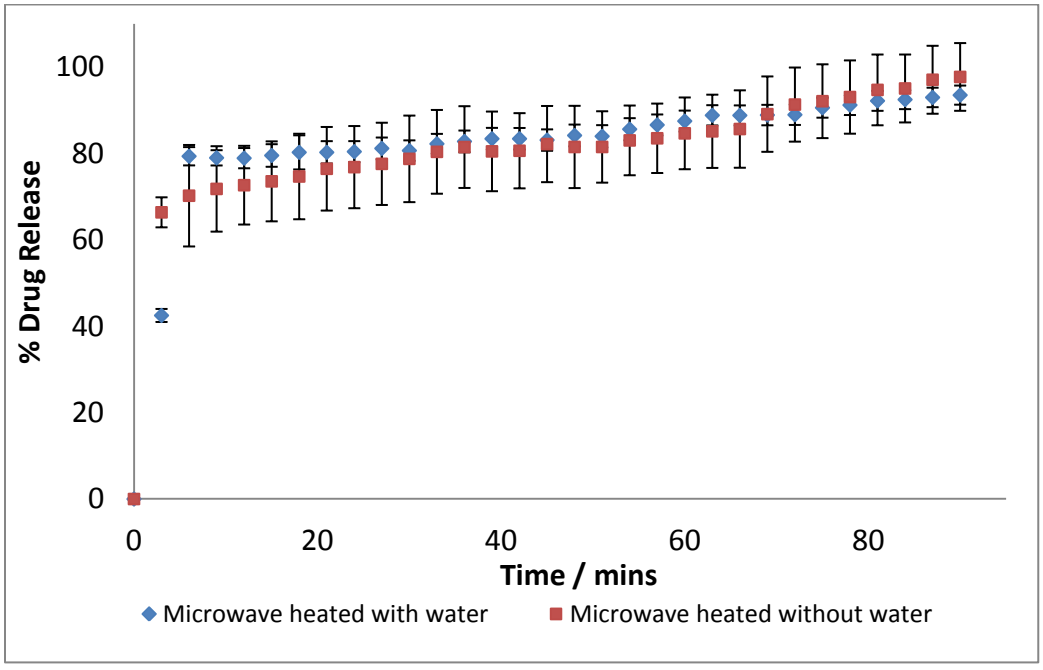

Figure 5.5.1.3 – A drug release profile for flurbiprofen and PVP (ratio 1:1), formulated using microwave heating both with and without the presence of water during the formulation process

Figure 5.5.1.3 illustrates microwave formulated flurbiprofen and PVP 1:1 with and without water present during formulation. It can be seen from the release profiles that a slight difference may exist between the two formulations, however it is difficult to be certain with the error associated with each data point. After fifteen minutes, the formulation prepared with water present released 80% (±3%) compared with 74% (±9%). After ninety minutes 94% (±2%) was released for the formulation prepared with water compared with 98% (±8%). It is possible that a difference does exist but because of the error associated with the dissolution, it can be said that no sigificant difference exists between the formulations. Upon calculation of the rate, Table 5.5.1.3, the formulation prepared without water released flurbiprofen at a faster rate when compared with the formulation prepared with water.

Rate (% release per minute)		
Time (Mins)	MW With	MW Without
0-3	14.17	22.13
3-15	2.46	0.56
15-30	0.08	0.34

Table 5.5.1.3 Rate of release of flurbiprofen from PVP 1:1 when prepared with or without the presence of water during formulation

All the release profiles illustrated so far indicate that the presence of water doesn't affect the overall drug release. However this trend doesn't apply to all the flurbiprofen formulations. Figures 5.5.1.4 to 5.5.1.5, are examples where the presence of water reduced the overall release of the drug.

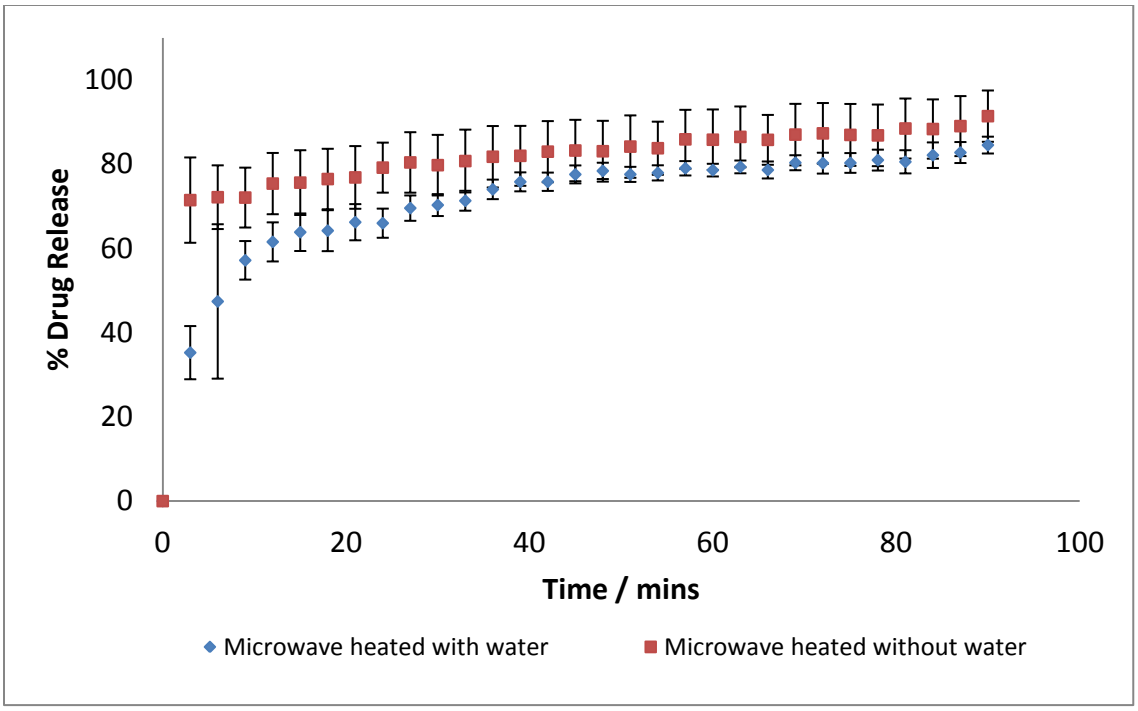

Figure 5.5.1.4 – A drug release profile for flurbiprofen and PVP (ratio 1:9), formulated using microwave heating both with and without the presence of water during the formulation process

Rate (% release per minute)		
Time (Mins)	MW With	MW Without
0-3	11.75	23.82
3-15	2.38	0.38
15-30	0.46	0.33

Table 5.5.1.4 Rate of release of flurbiprofen from PVP 1:9 when prepared with or without the presence of water during formulation

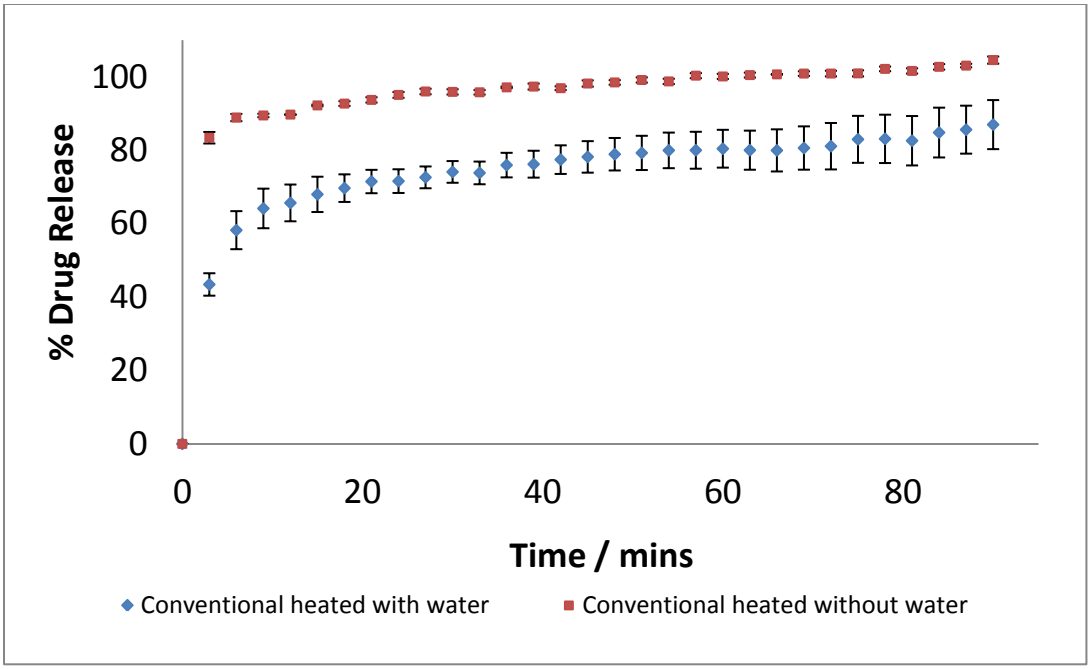

Figure 5.5.1.5 – A drug release profile for flurbiprofen and PVP (ratio 1:9), formulated using conventional heating both with and without the presence of water during the formulation process

Rate (% release per minute)		
Time (Mins)	CN With	CN Without
0-3	14.48	27.80
3-15	1.88	0.61
15-30	0.38	0.28

Table 5.5.1.5 Rate of release of flurbiprofen from PVP 1:9 when prepared with or without the presence of water during formulation

Figure 5.5.1.4 and Figure 5.5.1.5 both illustrate where the presence of water during formulation has decreased the percentage drug release. Figure 5.5.1.4 is flurbiprofen and PVP 1:9 formulated using microwaves with and without the presence of water. It can be seen from the graph that a higher percentage drug release appears from the formulation without water with 76% (±4%) of flurbiprofen released in the first fifteen minutes compared with 64% (±8%). After the ninety minutes 91% (±6%) was released

for the formulation without water present compared with 85% (±2%). This is also illustrated in the rate calculation, Table 5.5.1.4.

Figure 5.5.1.5 also illustrates a significant difference between the two formulations, 68% (±5%) was released from the formulation prepared with water and 92% (±1%) for the formulation prepared without water present during formulation. After ninety minutes 87% (±7%) was released for the formulation with water compared with 100% (±1%) for the formulation prepared without water. This is also seen in the rate calculation, Table 5.5.1.5.

Table 5.5.1.6 demonstrates all the results obtained for flurbiprofen and the two different excipients. In some cases no difference occurred, which is illustrated by the statement of 'no difference' in the table. When the formulation with water resulted in a higher percentage drug release this is illustrated by the statement 'with' in the table, and conversely, when the formulation without water resulted in a higher release it is identified as 'without'.

Drug/Excipient	**MW**	**CN**
	With/Without	**With/Without**
Flurbiprofen/SA 1:3	No Difference	No Difference
Flurbiprofen/PVP 1:1	No Difference	No Difference
Flurbiprofen/PVP 1:9	Without	Without

Table 5.5.1.6 – A summary to indicate conditions that created the greatest drug release for flurbiprofen with the two different excipients formulated with and without the presence of water over a ninety minute time period

5.5.2 The influence of microwave heating compared with conventional heating on subsequent drug release

Microwave and conventional heating were compared for flurbiprofen to determine if the formulation method selected influenced the drug release. The results are discussed below and a summary of all the results can be seen at the end of this section in Table 5.5.2.5.

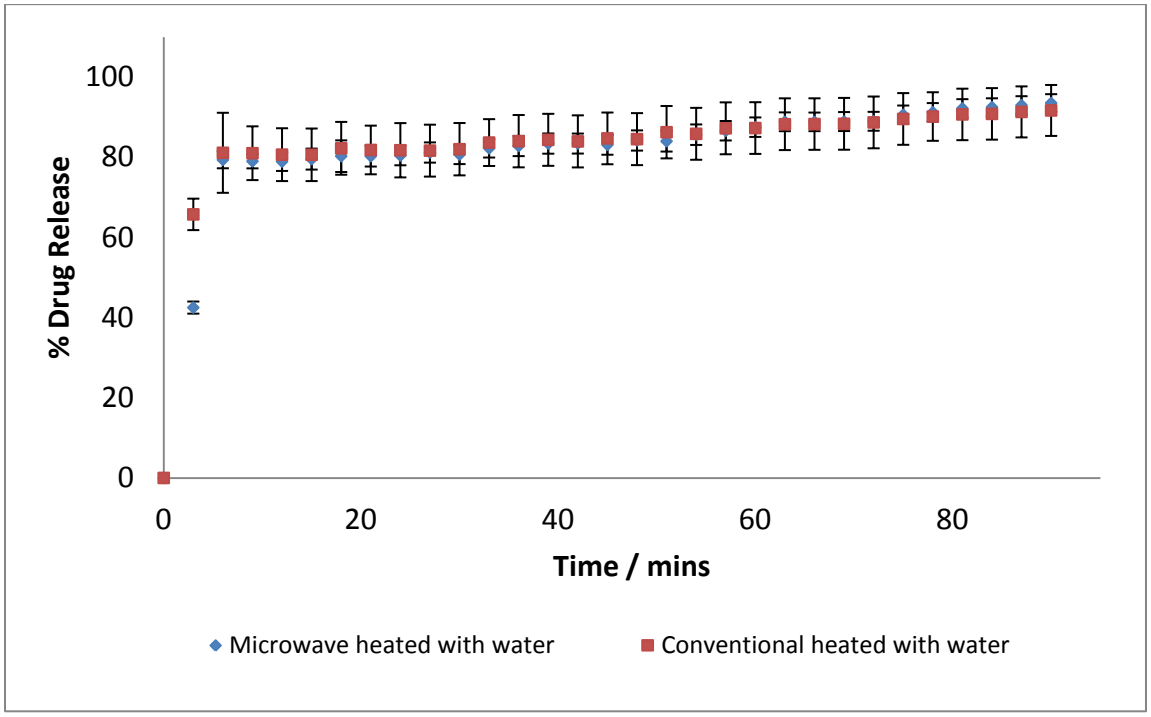

Figure 5.5.2.1 – A drug release profile for flurbiprofen and PVP (ratio 1:1), formulated using microwave and conventional heating, in both cases with water present as a solvent

Figure 5.5.2.1 demonstrates the release profiles for flurbiprofen and PVP 1:1 formulated using microwaves and conventional heating. For this particular formulation the choice of heating method has made no significant difference to the overall drug release. However for the first five minutes a slight difference in the initial release of the drug is seen, with the conventional formulation releasing a higher percentage of the drug 66% (±4%) compared with 43% (±4%). Despite this initial difference both formulations can be seen to ultimately release the same amount of flurbiprofen. Fifteen minutes into the dissolution around 80% of the drug was released for both formulations, 80% (±2%) for

conventional heating compared with 81% (±6%). After ninety minutes both formulations released over 90% of the drug, 94% (±2%) for conventional heating compared with 92% (±6%). The initial difference in the percentage drug release is also evident from the rate calculation, Table 5.5.2.1.

Rate (% release per minute)		
Time (Mins)	Microwave Heating	Conventional Heating
0-3	14.17	21.92
3-15	2.46	0.98
15-30	0.08	0.05

Table 5.5.2.1- Rate of release of flurbiprofen from PVP 1:1, microwave heating compared to conventional heating

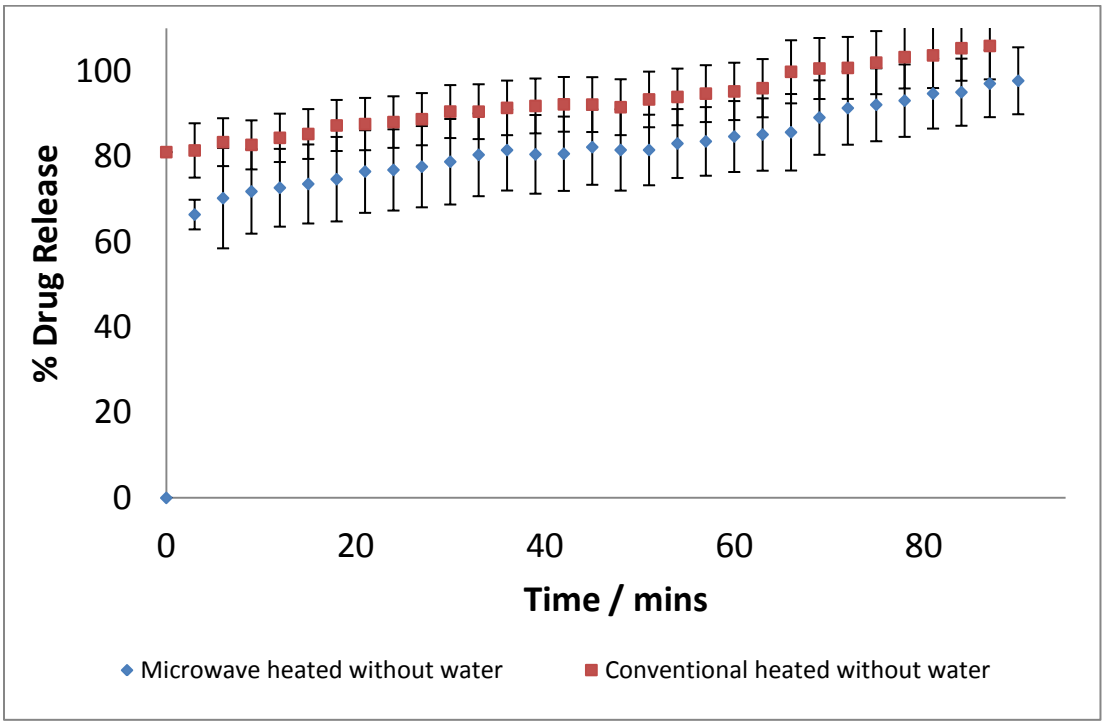

Figure 5.5.2.2– A drug release profile for flurbiprofen and PVP (ratio 1:1), formulated using microwave and conventional heating, in both cases without water present as a solvent

Figure 5.5.2.2 demonstrates flurbiprofen and PVP 1:1 formulated without water present using microwave and conventional heating. It can be seen from the graph that the conventional heating method may release more of the drug but because of the errors that are associated with this dissolution it is difficult to be certain. However for the first fifteen minutes of the dissolution 84% (±6%) of flurbiprofen was released from the conventional formulation. This is compared with 74% (±9%) for the microwave formulation, and from these results it is apparent that a possible difference may be present. After ninety minutes 98% (±8%) of flurbiprofen was released from the formulation prepared using microwave heating compared with around 100% (±8%). There is also a difference in the rate between the two formulations, Table 5.5.2.2.

Rate (% release per minute)		
Time (Mins)	Microwave Heating	Conventional Heating
0-3	22.13	27.01
3-15	0.56	0.27
15-30	0.34	0.29

Table 5.5.2.2- Rate of release of flurbiprofen from PVP 1:1, microwave heating compared with conventional heating

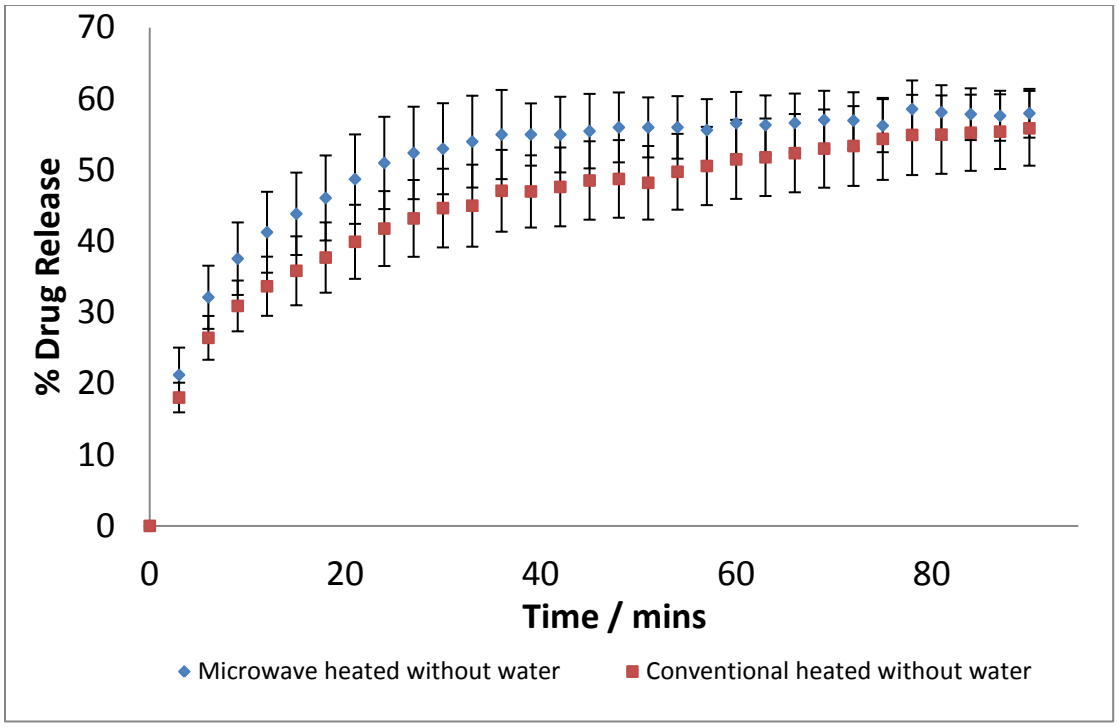

Figure 5.5.2.3 – A drug release profile for flurbiprofen and SA (ratio 1:3), formulated using microwave and conventional heating, in both cases without water present as a solvent

Figure 5.5.2.3 illustrates flurbiprofen and SA formulated using microwaves and conventional heating. It is possible from the graph that a difference has occurred between the two different formulations, with the microwave formulation releasing 44% (±6%) compared with 36% (±5%) for the conventional formulation. However it is difficult to be certain because of the error associated with the results, and at the end of the ninety minutes both formulations released over 50% (58% ±3% compared with 56% ±5% for the conventional formulation). Upon calculation of the rate, Table 5.5.2.3, there is a slight difference for the first three minutes of the dissolution with the microwave formulation releasing the drug at a faster rate.

Rate (% release per minute)		
Time (Mins)	MW Without	CN Without
0-3	7.07	6.01
3-15	1.28	1.43
15-30	0.37	0.59

Table 5.5.2.3- Rate of release of flurbiprofen from PVP 1:1, microwave heating compared with conventional heating

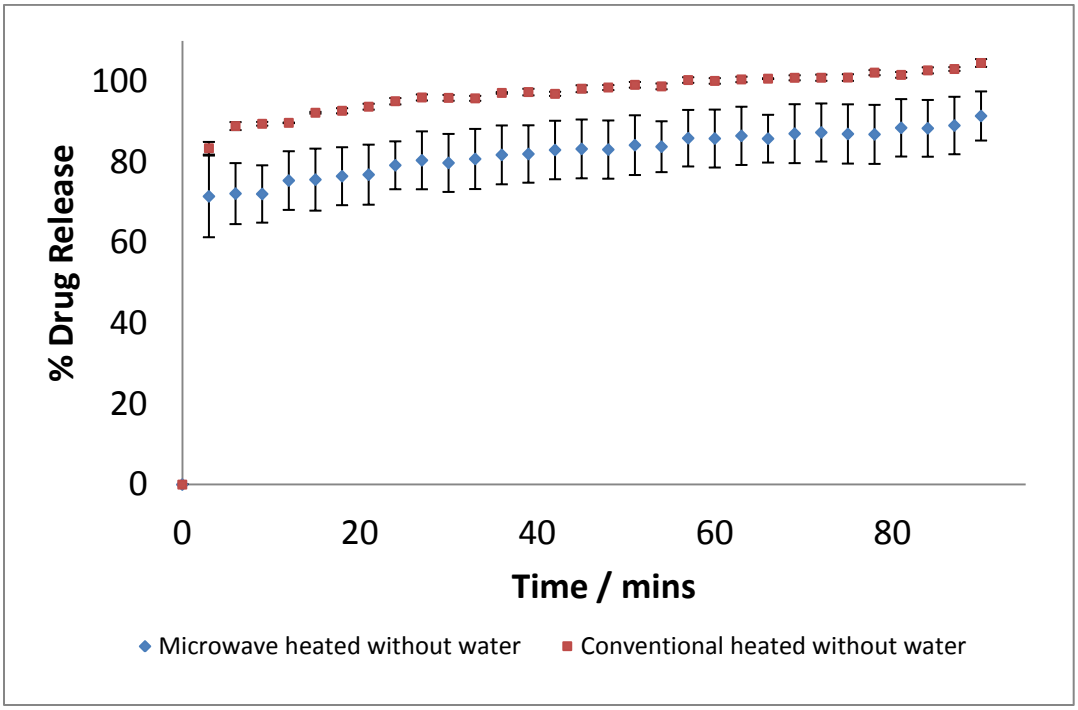

Figure 5.5.2.4 – A drug release profile for flurbiprofen and PVP (ratio 1:9), formulated using microwave and conventional heating, in both cases without water present as a solvent

Figure 5.5.2.4 displays a formulation where the choice of heating method has affected the percentage drug release. From the release profiles it is clear that the conventional method gave a higher percentage drug release. Within fifteen minutes 92% (±1%) of flurbiprofen was released from the conventional formulation compared with 76% (±8%). After ninety minutes approximately 100% (±1%) of flurbiprofen was released from the conventional formulation compared with 91% (±6%). Once the rate, Table 5.5.2.4, for each formulation was calculated a difference was also seen, with the conventional

formulation releasing the drug faster than the microwave formulated flurbiprofen and PVP.

Rate (% release per minute)		
Time (Mins)	MW Without	CN Without
0-3	23.82	27.80
3-15	0.38	0.61
15-30	0.33	0.28

Table 5.5.2.4 - Rate of release of flurbiprofen from PVP 1:9, microwave heating compared with conventional heating

The graphs illustrated above are examples of the different flurbiprofen formulations prepared using microwaves and conventional heating. Table 5.5.2.5 illustrates all the results obtained for flurbiprofen and the two different excipients prepared using microwaves and conventional heating. In some cases no difference occurred, which is illustrated by the statement of 'no difference' in the table. When microwave heating showed a higher percentage drug release this is illustrated by the statement 'MW' in the table. When conventional heating illustrated a higher percentage drug release this is indicated by the statement 'CN' in the table.

Drug/Excipient	**With**	**Without**
	MW/CN	**MW/CN**
Flurbiprofen/SA 1:3	No Difference	No Difference
Flurbiprofen/PVP 1:1	No Difference	No Difference
Flurbiprofen/PVP 1:9	No Difference	CN

Table 5.5.2.5 – A summary to indicate conditions that created the greatest drug release for flurbiprofen with excipients analysed for differences between microwave and conventional heating

5.5.3 Excipients

Formulation method parameters, such as the heating method and presence of a solvent, are not the only factors that affect drug release, excipient selection can also play a vital role.

In particular, it was found that the excipient which released the greatest amount of flurbiprofen was PVP in the 1:1 and 1:9 ratio using both microwaves and conventional heating and in the presence of water. Whilst the excipient that released the smallest amount of flurbiprofen was SA formulated using microwaves and conventional heating, with and without the presence of water.

In summary, based on these results, if formulating flurbiprofen to enhance drug release it would be advisable to formulate using PVP, 1:1 and 1:9, either with or without water using microwaves or conventional heating. In contrast, if formulating flurbiprofen to retard drug release it would be advisable to formulate with SA, with or without water, and using microwaves or conventional heating.

5.5.4 Summary

To summarise, in the majority of cases water has little or no effect on the release of the drug. However when a difference was seen, a higher percentage drug release occurred when water was not present during formulation.

Upon analysis of the flurbiprofen formulations when subjected to microwaves and conventional heating, it became apparent that the choice of the method made no significant difference to the release of the drug in the majority of cases. The only difference occurred with flurbiprofen and PVP 1:9 and the highest drug release was seen when the drug and excipient were formulated using conventional heating.

Also to increase the release of flurbiprofen, PVP seems to be advantageous but to slow the rate down for the drug then SA could be used.

Ibuprofen, ketoprofen and flurbiprofen are in Group two of the Biopharmaceutical Classification System (BCS). These have high permeability but low solubility, however to extend this research further it was decided to formulate a drug within a different group, one where the solubility is not an issue. From this, it was decided to use paracetamol (BCS group 1), and to formulate the drug without water using the microwave and conventional methods.

5.6 Paracetamol

5.6.1 The influence of microwave heating compared with conventional heating on subsequent drug release

Paracetamol was formulated with the four different excipients using microwave and conventional heating and therefore the following results are a comparison between the two different heating methods. A summary of all the results can be seen at the end of this section in Table 5.6.1.7.

From all of the results obtained, it appears that the choice of heating method made no significant difference to the release of paracetamol in the majority of cases. However the following graphs illustrate the different formulations that do not fit into this trend, Figures 5.6.1.1 to 5.6.1.3.

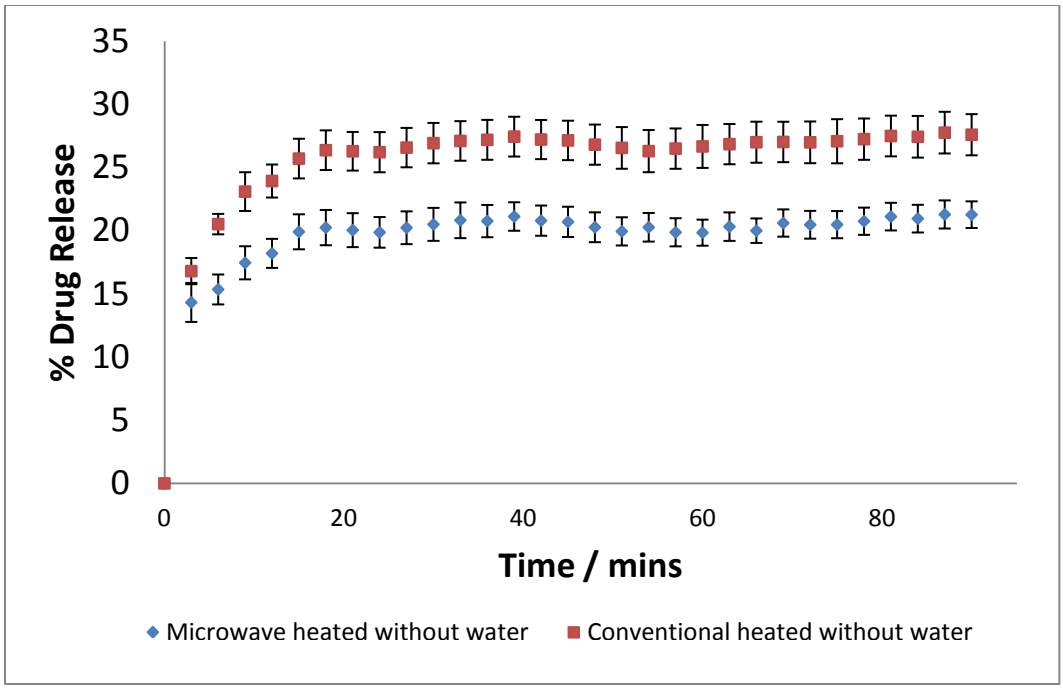

Figure 5.6.1.1 – A drug release profile for paracetamol and SA (ratio 1:3), formulated using microwave and conventional heating, in both cases without water present as a solvent

Figure 5.6.1.1 illustrates paracetamol formulated with SA using microwaves and conventional heating. From the graph it can be seen that the conventional heating method gave a higher percentage drug release. For the microwave formulation within the first fifteen minutes 20% (±2%) of the drug was released compared with 26% (±2%) for the conventional formulation and after ninety minutes the microwave formulation released 21% (±1%) compared with 28% (±2%). The result obtained in Figure 5.6.1.1 was also evident when the rate was calculated, Table 5.6.1.1.

Upon comparison of the release of paracetamol from SA it was noted that the release seemed to be lower than the previous formulations. As a result, it was decided to establish if any problems (degradation or evaporation) were present with paracetamol after the formulation method. Microwave thermogravimetry was employed, illustrating the same conditions for microwave heating but also a way of measuring the weight during the heating process. The results obtained determined that the drug was stable at the formulation temperature (85°C). Consequently no degradation or evaporation was

occurring that would show a decrease in weight but also a decrease in the amount of drug present in the SA formulations.

Rate (% release per minute)		
Time (Mins)	Microwave Heating	Conventional Heating
0-3	4.77	5.60
3-15	0.47	0.71
15-30	0.03	0.06

Table 5.6.1.1 - Rate of release of Paracetamol from SA, microwave heating compared with conventional heating

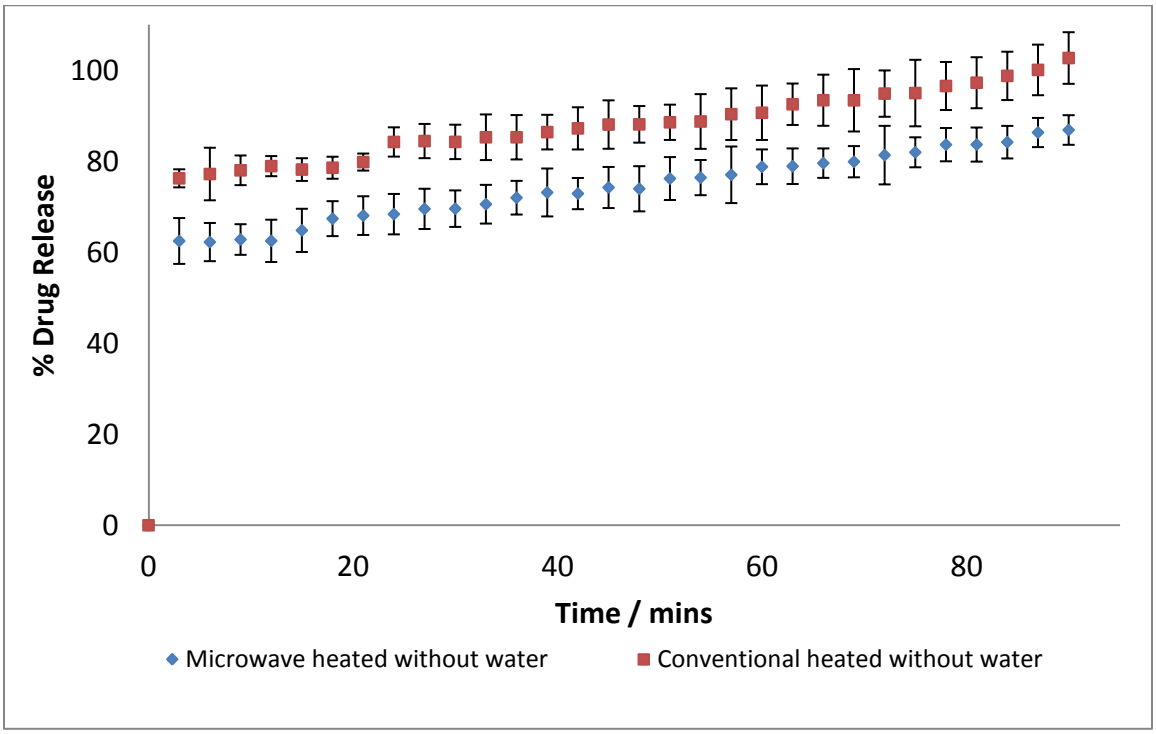

Figure 5.6.1.2 – A drug release profile for paracetamol and PVP (ratio 1:1), formulated using microwave and conventional heating, in both cases without water present as a solvent

Figure 5.6.1.2 displays paracetamol and PVP 1:1 formulated using microwaves and conventional heating. This graph is another example of where conventional heating shows a higher percentage drug release when compared with microwave heating. For the first fifteen minutes, the conventional formulation released 78% (±2%) compared

with 65% (±5%) for the microwave formulation. After ninety minutes approximately 100% (±6%) of the drug was released for the formulation prepared using conventional heating. This again is a higher percentage release when compared with the microwave formulation (87% ±3%). When the rate was calculated, Table 5.6.1.2, it was also evident that the formulation prepared by conventional heating released paracetamol at a faster rate.

Rate (% release per minute)		
Time (Mins)	Microwave Heating	Conventional Heating
0-3	20.83	25.42
3-15	0.16	0.19
15-30	0.29	0.50

Table 5.6.1.2 - Rate of release of Paracetamol from PVP 1:1, microwave heating compared with conventional heating

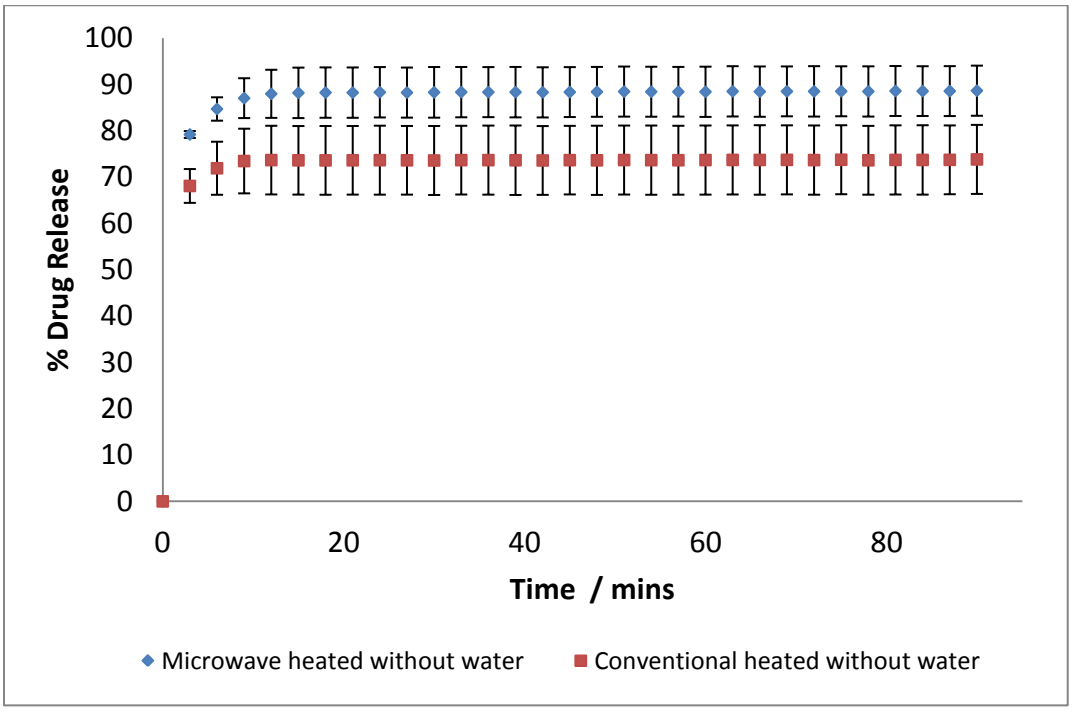

Figure 5.6.1.3 – A drug release profile for paracetamol and 2HPBCD (ratio 1:9), formulated using microwave and conventional heating, in both cases without water present as a solvent

Figure 5.6.1.3 demonstrates that for this particular formulation, microwave heating illustrated a higher percentage drug release, with 88% (±5%) released compared with 74% (±7%) for the conventional formulation. Also at the end of ninety minutes 89% (±5%) of the drug was released from the microwave formulation compared with 74% (±7%).

This is also evident when the rate was calculated, Table 5.6.1.3, with the faster initial rate of release seen from the microwave formulation (and throughout the dissolution). However after the first three minutes, both rates of release dramatically drop indicating that the majority of the drug is released after a short period of time.

Rate (% release per minute)		
Time (Mins)	Microwave Heating	Conventional Heating
0-3	26.40	22.70
3-15	0.71	0.43
15-30	0.01	0.00

Table 5.6.1.3 - Rate of release of Paracetamol from HPBCD 1:9, microwave heating compared with conventional heating

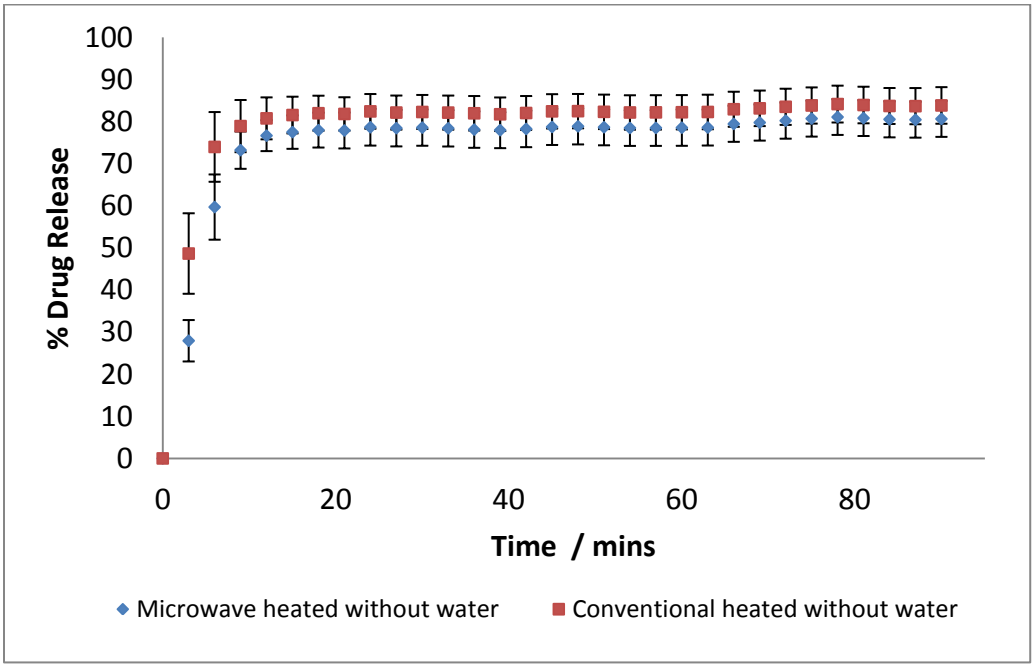

Figure 5.6.1.4 – A drug release profile for paracetamol and BCD (ratio 1:1), formulated using microwave and conventional heating, in both cases without water present as a solvent

Figure 5.6.1.4 displays the release profile for paracetamol and BCD 1:1 formulated using microwaves and conventional heating. It is evident from the graph that the choice of heating doesn't affect the overall percentage drug release. However at the beginning of the dissolution a slight difference exists with the formulation prepared using conventional heating releasing a higher percentage of the drug. For the first fifteen minutes, the conventional formulation released 82% (±4%) compared with 77% (±4%). However after this time period and at the end of the ninety minutes the microwave formulation released 81% (±4%) compared with 84% (±4%). Therefore it can be said that both formulations released the same amount of paracetamol and consequently for this formulation the choice of heating method made no significant difference. After the rate was calculated, Table 5.6.1.4, the initial difference is also apparent with the conventional formulation releasing paracetamol at a rate of 16.22% per minute compared with 9.31% per minute.

Rate (% release per minute)		
Time (Mins)	Microwave Heating	Conventional Heating
0-3	9.31	16.22
3-15	3.87	2.42
15-30	0.07	0.04

Table 5.6.1.4 - Rate of release of Paracetamol from BCD 1:1, microwave heating compared with conventional heating

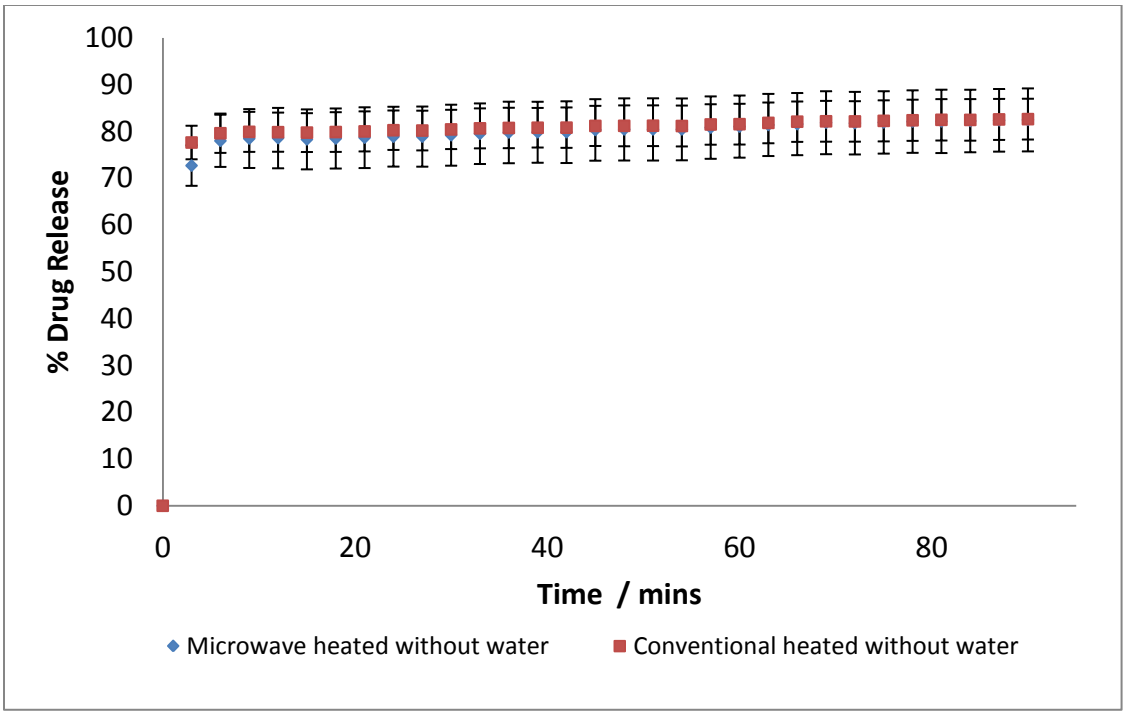

Figure 5.6.1.5 – A drug release profile for paracetamol and BCD (ratio 1:9), formulated using microwave and conventional heating, in both cases without water present as a solvent

Figure 5.6.1.5 demonstrates that the choice of heating method has made no difference to the overall drug release. It is a possibility that for the initial three minutes of the dissolution the conventional formulation releases paracetamol slightly faster than the microwave formulation, however after and for the rest of the dissolution both formulations released the same amount of the drug. For the first fifteen minutes the microwave formulation released 78% (±6%) compared with 80% (±4%) and after ninety minutes 92% (±7%) of paracetamol was released from the microwave formulation compared with 83% (±4%). When the rate was calculated, the observed results from the graph were confirmed, Table 5.6.1.5.

Rate (% release per minute)		
Time (Mins)	Microwave Heating	Conventional Heating
0-3	24.23	25.88
3-15	0.39	0.15
15-30	0.06	0.04

Table 5.6.1.5 - Rate of release of paracetamol from BCD 1:9, microwave heating compared with conventional heating

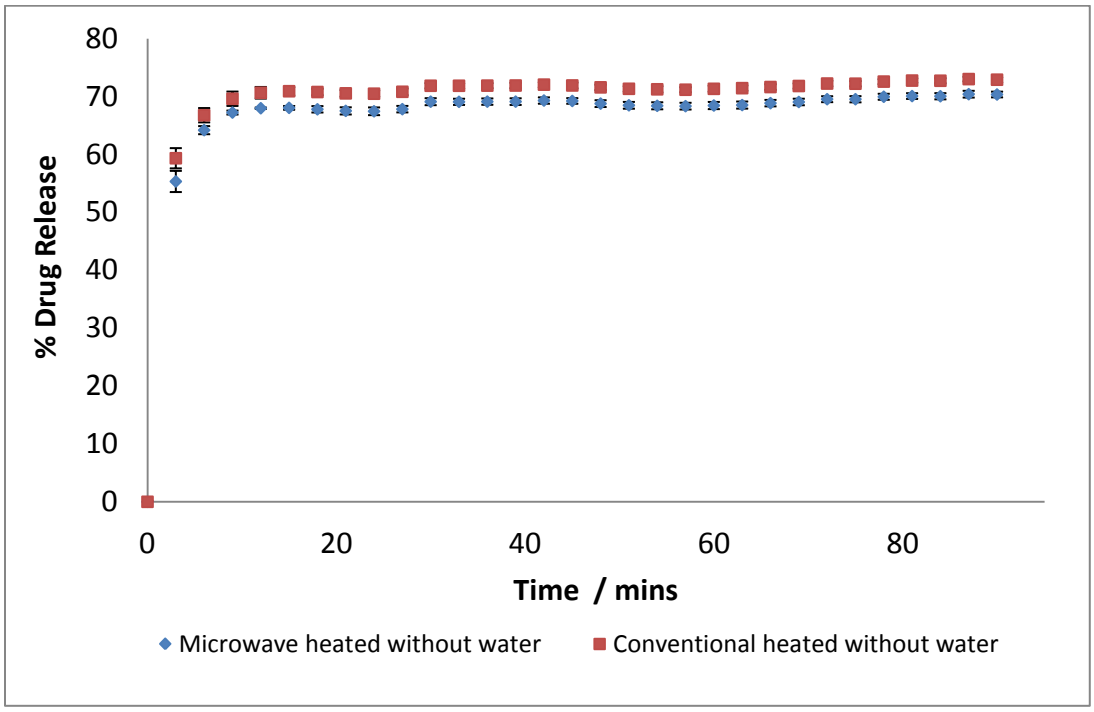

Figure 5.6.1.6 – A drug release profile for paracetamol and 2HPBCD (ratio 1:1), formulated using microwave and conventional heating, in both cases without water present as a solvent

Figure 5.6.1.6 illustrates paracetamol and HPBCD 1:1 formulated using microwaves and conventional heating. It is evident from the graph that the choice of heating method has not affected the percentage drug release. Within the first fifteen minutes 68% (±1%) of paracetamol was released from the microwave formulation, and this is compared with 71% (±1%) for the formulation prepared using conventional heating. After ninety minutes 70% (±1%) of paracetamol was released from the microwave formulation compared with 73% (±1%). Upon calculation of the rate, Table 5.6.1.6, it can be seen

that the conventional formulation released paracetamol faster with 19.78% released in the first three minutes compared with 18.44% per minute for the microwave formulation. However after the initial three minutes the rates drop and both formulations can be seen to release the same amount of the drug (0.90% compared with 0.97% per minute).

Rate (% release per minute)		
Time (Mins)	Microwave Heating	Conventional Heating
0-3	18.44	19.78
3-15	0.97	0.90
15-30	0.05	0.05

Table 5.6.1.6 - Rate of release of paracetamol from BCD 1:9, microwave heating compared with conventional heating

Table 5.6.1.7 illustrates all the results obtained for paracetamol and the four different excipients prepared using microwaves and conventional heating. In some cases no differences occurred, which is illustrated by the statement 'no difference' in the table. When microwave heating showed a higher percentage drug release this is illustrated by the statement 'MW' in the table. When conventional heating illustrated a higher percentage drug release this is indicated by the statement 'CN' in the table.

Drug/Excipient	**Without MW/CN**
Paracetamol/SA 1:3	CN
Paracetamol/BCD 1:1	No Difference
Paracetamol/BCD 1:9	No Difference
Paracetamol/PVP 1:1	CN
Paracetamol/PVP 1:9	CN
Paracetamol/2HPBCD 1:1	No Difference
Paracetamol/2HPBCD 1:9	MW

Table 5.6.1.7 – Summary to indicate conditions that created the greatest drug release for paracetamol and excipients analysed for differences between microwave and conventional heating

5.6.2 Excipient

In particular, it was found that the excipient which released the greatest amount of paracetamol was PVP, in the 1:1 ratio formulated using microwave heating. While the smallest amount of paracetamol was released from SA formulated using microwave heating.

In summary, based on these results, if formulating paracetamol to enhance drug release it would be advisable to formulate using PVP and the microwave heating method.

In contrast, if formulating paracetamol to retard drug release it would be advisable to formulate using SA, and using the microwave heating method.

5.6.3 Summary

Paracetamol does not have poor aqueous solubility and therefore it was decided to formulate without the presence of water. Consequently the choice of heating method was investigated and the results obtained showed that in the majority of cases no significant difference was observed between the two heating methods. However when a difference was seen the conventional method of heating showed a higher percentage drug release.

With respect to excipient choice, when formulating paracetamol to enhance drug release it is advisable to formulate using PVP in the 1:1 ratio and with microwave heating. If however the drug release needs to be delayed then SA should be used.

From all results obtained, it is clear that the choice of heating method and the presence of water can illustrate differences in the percentage drug release. However when the formulation temperature becomes further away from the melting point of the drug, these differences become less apparent. Therefore without the range of drugs and excipients investigated, and a comparison between the heating methods this information would not have been noticed.

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Chapter 6

Conclusions and Future Work

6.1 Conclusion

The first aspect of this research was to investigate the thermodynamic parameters associated with the binding between three different drugs, namely ibuprofen, ketoprofen and flurbiprofen and two excipients, over a temperature range (Objective One). The second aspect was to investigate the compatibility between the different drugs and excipients to ensure the formulation process was a success and had no adverse effects on the drugs themselves (Objective Two). The final part of this research was to analyse and determine how the chosen drugs and excipients behaved after being exposed to the varying formulation parameters by considering the resultant drug dissolution (Objective Three).

6.1.1 Objective One: Drug-Excipient Binding

The first objective of this research was to determine the thermodynamic parameters associated with the binding of ibuprofen, ketoprofen, and flurbiprofen with two excipients, BCD and 2HPBCD. This was investigated using ITC and completed over a temperature range to see if the parameters were temperature dependent. In all cases, information was obtained on the binding constants, stoichiometry, enthalpy, entropy and Gibb's free energy. This information was then used to determine and understand the complexation process including the strength of the interaction between the drug and cyclodextrin and whether the interaction was favourable. This was successfully carried out and in all cases the drug interacted with the BCD and 2HPBCD in a 1:1 ratio, which was unaffected by an increase in the temperature. For ibuprofen, BCD and 2HPBCD, it was concluded that the binding and therefore the interaction between these compounds was favourable and likely to happen. As the temperature increased, there was an increase in the enthalpy of the reaction showing the bonding becomes more exothermic and illustrating an increase in the strength of bonds between the drug and cyclodextrin cavity. The change in Gibbs free energy also indicated a slight increase to a more negative value with an increase in temperature, and a small positive contribution by ΔS (entropy). The negative values for ΔG indicate that the complex has less free energy than the free drug and cyclodextrin, and consequently the negative value for enthalpy, negative values for Gibb's free energy and a slightly positive entropy

suggests binding was favoured and a complex formation was promoted. However when both the binding constants and therefore the enthalpy, Gibb's free energy and entropy were compared for ibuprofen binding to BCD and ibuprofen to 2HPBCD it can be seen that ibuprofen does form a complex with 2HPBCD but it is a relatively weak process (ibuprofen and BCD show significantly more negative values when compared with 2HPBCD). This is because 2HPBCD is a more sterically hindered compound, making it harder for a drug to bind and form a tight complex with this compound. It can also be said that the drug-excipient interactions are temperature dependant as expected.

Ketoprofen was also investigated with BCD and 2HPBCD, and it was seen that as the temperature increases there is a change in the enthalpy, and consequently Gibb's free energy, therefore this reaction is also temperature dependant. As the temperature increases, the enthalpy change for the reaction increased and became more negative showing that the strength of the interaction between ketoprofen and the cyclodextrin cavity increased. Along with this increase in enthalpy, there was an increase in negativity in the Gibb's free energy with a small positive contribution by entropy (ΔS) which would suggest that as the temperature increases, the interaction between the drug and cyclodextrin cavity increases. Consequently the resultant complex has less free energy than the free drug and BCD molecules and therefore binding is favoured. It is apparent from the results that the interaction seen between ketoprofen and 2HPBCD is weaker when compared with ketoprofen and BCD. This therefore may suggest that the substituted groups seen in the structure of 2HPBCD make it difficult for the drug to interact and bind to the cavity of the cyclodextrin, a result previously obtained with ibuprofen.

In the case of flurbiprofen with BCD, the binding constant decreased with increasing temperature which was not witnessed previously. When the enthalpy for each reaction was calculated it was seen to remain constant over the temperature range studied suggesting that the binding mechanism was unchanged. There was also a slight decrease in the Gibb's free energy as the temperature for the reaction increased, with positive entropy that remained the same. These results suggested that a complex was formed and favoured but the strength of it was reduced as the temperature was elevated. For the binding between flurbiprofen and 2HPBCD, the

binding constant, enthalpy and Gibb's free energy all increased with increasing temperature which is a trend previously seen with ibuprofen and ketoprofen. This result therefore suggested that the bond between the flurbiprofen drug molecule and the cyclodextrin cavity increased in strength with increasing temperature. It also showed that the reaction was more exothermic at higher temperatures. There was an increase in ΔG which indicated that at higher temperatures, there was less free energy in the complex than the free drug and cyclodextrin. Therefore because of this and the negative enthalpy of binding and the positive entropy, the complex was favourable and more of the drug was in the complex instead of free state. When the two different excipients were compared, it was noted that the interaction between flurbiprofen and BCD was less favourable as the temperature increased, however the opposite was witnessed for the interaction of the drug and 2HPBCD. Upon comparison of the three different drugs, it was concluded that the more lipophilic the drug, the stronger the interaction between the drug molecule and the cyclodextrin. This was a reflection of the greater affinity of the lipophilic compound towards the less polar internal cavity of the cyclodextrin when compared with water. However, this was not observed for flurbiprofen and BCD. Here there was a decrease in the binding constant, ΔH and ΔG at 310K. This consequently suggests another factor was influential, i.e. the structural differences present for flurbiprofen when compared with ibuprofen and ketoprofen. This may have a subsequent impact on the hydrogen bonding potential with the cyclodextrin cavity causing a decrease in bond strength as the temperature increased. This finding implied that at the highest temperature investigated less of the drug was in a complex with the cyclodextrin because of the loss in strength of the hydrogen bonding.

6.1.2 Objective Two: Formulation Stability

After the first objective was successfully carried out, the second objective was to determine if the chosen drugs, namely, ibuprofen, ketoprofen, flurbiprofen and paracetamol were compatible with the four excipients (SA, BCD, 2HPBCD and PVP). This was determined from the analysis of DSC, SEM and TAM data. In all cases it appeared that the drug and excipient were compatible with no adverse effects observed following the formulation process. DSC was used to determine if the formulation method

made any significant differences to the thermal behaviour of the drug and excipient. Firstly, each of the pure compounds were analysed to illustrate the thermal behaviour before the formulation process was undertaken. After the pure compounds were investigated, each of the formulations were analysed. Any differences in the thermal behaviour were recorded and included a decrease in the melting points of the drugs or a change in the behaviour of the excipients. In the case of ibuprofen, it was found that the choice of heating method made no significant difference to the thermal behaviour of the drug and excipient, with an exception for PVP in the 1:1 ratio. Also in the majority of cases, having water present during the formulation method, made no difference to the thermal behaviour. However there was an exception for BCD (1:9) and PVP in both ratios. When water was present for the ibuprofen and BCD formulation prepared in the 1:9 ratio it can be seen that a clear overlap of the peaks had occurred with an increase in the melting point for the drug. This indicated that the presence of water may have aided the encapsulation of the drug and pushed it towards the cyclodextrin cavity. Also for ibuprofen and PVP a clear decrease of the melting point for the drug was seen, with a difference in the behaviour of the excipient after formulation. These results indicate that an interaction had occurred because of the formulation process.

After ibuprofen was investigated, ketoprofen was also analysed. Firstly, ketoprofen was formulated with SA which caused a change in the thermal behaviour of the drug and excipient, indicated by a decrease in the melt temperature for both. However for this result to be reliable, there would have to be a decrease by a substantial amount of 40ºC. Therefore it may be possible that the formulation was not homogenous throughout and because of the small amount taken for DSC analysis weight errors may have been introduced. To overcome this problem with future formulations it may be advisable to initially mix for a longer period of time, formulate, then grind and re-mix. For the other formulations, it appeared that the choice of heating method did not affect the thermal behaviour of the drug and excipient, other than when ketoprofen was formulated with PVP in the 1:9 ratio using conventional heating. This was a result also obtained for ibuprofen and PVP, although in a different ratio. A logical explanation for this is the fact that during conventional heating the drug and excipient were exposed to heat and moisture for longer periods of time which may enable the

excipient to have swelled to a greater extent. It was also evident from the results that in the majority of cases water affected the thermal behaviour of the drug and excipient when ketoprofen was formulated with BCD and PVP. In both cases, when water was present a broad peak was witnessed with a decrease in the temperature associated with that peak.

Flurbiprofen was investigated with two excipients, namely SA and PVP. This was because of difficulties during formulation of the drug with the remaining two excipients. However from analysis of the drug with the two excipients it appeared that the formulation method made no significant difference to the thermal behaviour of the drug either using microwaves or conventional heating, and with or without the presence of water.

The last drug investigated using DSC was paracetamol, with the four excipients, and without the presence of water. In the majority of cases the choice of heating method made no significant difference to the thermal behaviour of the drug and excipient.

DSC was utilised to investigate the compatibility of the drugs and excipients and also to ensure no adverse effects occurred to the formulation after the heating process. In the majority of cases, it can be said that the choice of excipients were compatible with the different drugs and this was illustrated by a change in the thermal behaviour of the formulation. In some cases no differences were illustrated, this however only became more prominent when the formulation temperature of 85ºC was significantly different from the melting point of the drug, for example paracetamol at 169 ºC. Also there was no evidence that any adverse effects occurred to either the drug or excipient after the formulation process.

Each of the drugs and excipients were analysed using SEM, followed by each of the formulations prepared using microwaves and conventional heating, with and without the presence of water. In the case of ibuprofen, it was apparent that the formulation process did affect the overall physical appearance of both drug and excipient. This was illustrated by a change in the particle shape and size. Choice of heating method did not affect the appearance. Also it was apparent that when water was present during the formulation process, a smaller particle size was observed. This may have occurred because during formulation with water, the mixture was continuously stirred which may

give a smaller particle size. This was a trend seen throughout the different formulations, until PVP was analysed. This drug and excipient formulation showed a larger particle size when exposed to the moisture, and this occurred because PVP swelled upon exposure to moisture.

Ketoprofen was also analysed using SEM, and for this drug and excipients it became evident that there was no significant difference between the two different heating methods. When water was present during formulation, it became apparent that a reduction in the particle size occurred. This indicated that the continuous stirring of any of the ketoprofen formulations during heating helped to reduce particle size, however this was not the case for PVP. This excipient once again showed a larger particle size when water was present.

Flurbiprofen was the next drug analysed with SA and PVP only. However, despite only having two excipients to investigate, the results obtained showed that in the presence of water the resultant formulation had a smaller particle size (apart from PVP). It was also noted that the choice of heating method made no overall difference to the physical appearance.

Lastly, paracetamol was analysed using SEM, this drug was formulated using microwave and conventional heating without the presence of water. Therefore this drug was investigated to determine if any differences were apparent between the two heating methods. From all the different formulations analysed it was evident that the choice of heating method made no significant difference to the final appearance of the drug and excipient.

DSC and SEM have been utilised to determine compatibility of the drugs and excipients and to visually see if the formulation method illustrated any differences in appearance of the resultant formulations. Experiments were then conducted using a TAM to determine the stability of these formulations. However, because of time restrictions it was decided to analyse ibuprofen only. This was because at the formulation temperature, ibuprofen is the only drug that melts.

Firstly, pure ibuprofen was subjected to three different parameters, namely dry 30ºC, 30ºC and 51% RH, and ibuprofen dissolved in phosphate buffer. From these different conditions it was concluded that pure ibuprofen was stable for the four day period. As a result, each of the different formulations were analysed at 30ºC over four days. The results obtained indicated that after the formulation process, ibuprofen appeared stable and as a consequence no adverse effects were seen when the drug was heated and formulated with the four chosen excipients. In all cases, the signal during the experiment remained close to or on 0μW/g indicating no degradation.

6.1.3 Objective Three: Formulation parameters investigated. The influence of formulation solvent on subsequent dissolution and choice of heating method

The third objective was to determine if the presence of water during the formulation process affected subsequent drug release. This was analysed using drug dissolution and ibuprofen, ketoprofen and flurbiprofen were all investigated with the excipients. When ibuprofen was formulated with the excipients and in the presence of water, it was evident that a higher drug release occurred in the majority of cases. It is difficult to determine why these results were obtained but it may be because of the following three reasons. Firstly, ibuprofen is a poorly water soluble drug and when formulated in the presence of water the drug may be forced towards the excipient, aiding complex formation and therefore showing an improvement in dissolution. Secondly, because of the presence of water, ibuprofen may bind to the excipient, but not as efficiently as formulations without water and as a result, a loosely bound complex was formed. Lastly, it was noticed from analysis of the images obtained from the SEM that a smaller particle size was evident when water was present during formulation. As a result, the formulation would dissolve at a faster rate and therefore an improved dissolution rate was seen.

When ketoprofen was formulated with the four excipients and in the presence of water, an improved dissolution was seen.

Flurbiprofen was formulated with SA and PVP, and it was apparent that formulating this drug in the presence of water made no significant difference to the dissolution profile. Both these excipients and the drug are insoluble in aqueous solutions and therefore water was not likely to change the particle size, and as a result the dissolution rate was not enhanced. In addition, flurbiprofen did not melt at the formulation temperature.
Paracetamol was not formulated in the presence of water therefore no comparison between the different formulations was made.

From analysis of all the different formulations it can be concluded that the presence of water did make a significant difference to the overall release of the drug. In the majority of cases, it appeared that when water was present an enhanced dissolution rate was expected. This could be because of a reduction in particle size, or as a result of continuous stirring during the heating method.

Finally, dissolution experiments were conducted to determine if the choice of heating method affects the dissolution profile for a chosen drug. Each of the four drugs were investigated with the excipients either with or without the presence of water during formulation. When ibuprofen was formulated using microwave heating, it was seen that a higher percentage drug release occurred when compared with conventional heating. This result could have occured because of the way microwaves heat, which is by direct interaction with the molecules in contrast to a temperature gradient. Also ibuprofen melts at this temperature which may be beneficial to aid encapsulation.

The next drug analysed was ketoprofen with the four different excipients. From the results obtained it became evident that when this drug was formulated using microwave heating a higher percentage drug release was seen. However, in some cases no difference was seen between the two heating methods. This result suggests for these formulations that the choice of heating method makes no overall difference to the drug release. When microwaves illustrated a higher percentage drug release, this may have occurred because of a more uniform method of heating which may aid encapsulation, which in turn improves the release from the formulation.

Flurbiprofen formulations were also analysed and it can be seen from the results that the choice of heating does not affect the release of the drug in the majority of cases. When a significant difference was observed, the conventionally heated

formulation was seen to release a higher amount of the drug. This may have occurred because the conventional method takes longer to heat the formulation and because the drug doesn't melt it may require this extra time to encapsulate the drug and show an improvement in the dissolution.

For paracetamol in the majority of cases, no significant difference occurred between the two heating methods. This again indicated that the further away the formulation temperature is to the melting point of the drug, the less difference appeared between the two methods. When a difference did occur, the formulation that displayed a higher percentage drug release was the conventional formulation. This may indicate that the further away the formulation temperature is from the melting point of the drug, the longer it may require to encapsulate and show an improvement in the drug release.

From all the results obtained it appeared that when ibuprofen and ketoprofen were formulated using microwaves a higher percentage drug release was evident yet for flurbiprofen and paracetamol this was not the case. Also in some cases, no difference was seen between the two heating methods. This suggests that the choice of method will not necessarily affect the the dissolution profile. Conseqeuntly microwave heating could still be used to formulate in these instances, for example, to reduce energy costs associated with conventional methods. Microwaves also provide a more uniform way of heating reducing any implications associated with uneven heating.

In summary, the chosen analytical techniques allowed all three objectives to be investigated. The different thermodynamic parameters were investigated and determined for the interactions between ibuprofen, ketoprofen and flurbiprofen with the two different cyclodextrins (BCD and 2HPBCD). The formulation method did not appear to cause any adverse effects on the drug and excipients, and all seemed compatible with a change in thermal behaviour and appearance for the majority of the different formulations. From the dissolution profiles, it does appear that the choice of heating method will influence the release profiles for drugs close to the formulation temperature of 85°C, with microwave based formulations displaying a greater extent of drug release. Also drug release appears further enhanced when water is present during the heating stage, which may be the result of a decrease in the particle size.

6.2 Future Work

To extend this work further, some areas that could be investigated are described below.

1. Extend the selection of drugs and excipients studied using ITC

ITC was utilised to analyse the binding interactions between a comparatively small selection of drugs with increasing partition coefficients and two excipients. To extend this further it would be possible to analyse other drugs with different partition coefficients with BCD and 2HPBCD to see if the positive correlation between temperature and lipophilicity continues. It may also be possible to increase the number of excipients to see if similar trends are obtained. Other excipients that could be investigated include α and γ-cyclodextrins, and possibly a few derivatives of the cyclodextrins, including Hydroxyethyl-β-CD, or Methyl-β-CD.

2. Extend the study of the application of microwave heating

The controlled power microwave method to produce pharmaceutical formulations is novel and therefore there are many parameters that could be varied within this aspect of the research area. This could be achieved by varying the amount of the time that each formulation is subjected to the microwave energy. Also by varying the formulation temperature, this may help to determine the optimum conditions for the microwave method. It was also noted that the further away the formulation temperature was from the melting point of the drug the less variation was present between the parameters. Therefore, to investigate further more drugs that have a melting point around the formulation temperature need to be investigated. Also drugs with a melting point considerably different to the formulation temperature need to be investigated to determine if the same trends are witnessed. This method can also be extended to the conventional method so a direct comparison can still be made.

3. Explore alternative analytical techniques

DSC, SEM and a TAM were used to determine any changes to the drug and excipient as a result of the formulation process. Other analytical techniques that may help to illustrate and understand any changes may include XRD (x-ray diffraction) and FT-IR (fourier-transform infra-red). XRD can be used to determine if the

formulation method reduced crystallinity, which may also help to explain the resultant variations in dissolution profiles. As a consequence of formulation, hydrogen bonding occurs between the two components and this could be investigated using FT-IR, which is illustrated by a shift in certain peaks.

During analysis of the DSC profiles it was evident that some changes occurred in the thermal behaviour of the resultant formulations, however for ketoprofen and flurbiprofen no peak was seen for the melt of the drug. This may indicate that the formulation was not homogenous throughout, and to eradicate this problem the initial mixing time can be increased from five minutes to ten or fifteen minutes. Also after the heating method, the formulation can be milled and re-mixed to ensure a homogenous mixture. Again, further analysis may help confirm this theory.

Rather than using a further technique, more work could be conducted using a TAM. For example, the stability of the ibuprofen formulations was investigated using a TAM, to extend this section of work further the amount of time each formulation was analysed could be increased from four days to weeks or months to be certain no problematic instability exists. Also all formulations could to be investigated for stability and therefore ketoprofen, flurbiprofen and paracetamol could be analysed using a TAM.

In addition, MWTG was used to investigate if any degradation or evaporation of the drugs occurred at the formulation temperature. To ensure that no adverse effects occur at the chosen temperature, MWTG can be utilised and used as a screening method to ensure that the drugs can withstand the thermal stress presented during heating.

In summary, the research presented in this thesis has confirmed the potential application of microwave heating for pharmaceutical formulations with accompanying analytical techniques. However, there is far more work that can be undertaken in this area to fully explore all of the possible uses of this novel method of formulation.