DEVELOPMENT AND EVALUATION OF PROLONGED RELEASE KETOPROFEN TABLETS

by

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Thesis submitted in fulfilment of the
requirements for the degree
of Master of Science

October 2006

To my beloved father, mother, brothers and sisters

ACKNOWLEDGEMENTS

Real thanks and holy prayers to Allah who created the Prophets and scientists to discover the science and to civilize the universe in such a unique and proper construction.

I am deeply indebted to Professor, Dr. Saringat Hj Baie, my ever active supervisor for all kinds of help, guidance, invaluable advises and encouragement throughout the study. I am grateful to my co–supervisor Dr. Nurzalina Khan for her fruitful discussions, help and suggestions.

I am grateful to University Sains Malaysia and to Vice-Chancellor, Dato, Prof Dzulkifli Abdul Razak for awarding Graduate Assistance (GA), which give me the opportunity to pursue my master degree. I am also grateful to my friends Musab Arafat, Mohammad Aldoais, Juma Masoud, Mahmoud Adebaibi, Mahmoud Hadad, Farzana Kabir Ahmad, Sabiha Karim, M Ali AL-Sheikh wace, Homam Eltaj.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF EQUATIONS

LIST OF ABBREVIATIONS

British Pharmacopoeia	BP
Carboxymethylethylcellulose	CMEC
Centimeter	cm
Centipoise	cps
Concentration	Conc
Controlled Release	CR
Crystallization temperature	T_c
Degree centigrade	°C
Diameter	d
Difference factor	f_1
Differential Thermal Analysis	DTA
Elimination half-life	$t_{1/2}$
Else where or add others	*et al*
Et cetera	etc
Ethylcellulose	EC
Figure	Fig
Food and Drug Administration	FDA
Force	F
Gastro Intestinal Tract	GIT
Gelucire 50/13	G50/13
Glass Transition	T_g
Gram	g
Heat	Q
Hour	hr

Hydrophile–lipophile balance	HLB
Hydroxypropylmethylcellulose	HPMC
Joule	J
Joule per gram	J/g
Kilogram	kg
Kilogram per Centimeter	kg/cm
Kilogram per Millimeter	kg/mm
Melting temperature	T_m
Microcrystalline Cellulose	MCC
Microgram per Milliliter	µg/ml
Milli Watts	mW
Milliliter	ml
Millimeter	mm
Nanometer	nm
Polyethylene glycol	PEG
Polyvinylpyrrolidone	PVP
Refrigerated Cooling Accessory	RCS
Relative Humidity	RH
Rotation per minute	rpm
Second	s
Similarity factor	f_2
Solid lipid ketoprofen micropellets	SLKM
Standard deviation	SD
Sustained release	SR
Temperature of reference	T_r

Temperature of sample	T_s
Tensile strength	TS
Thermal resistance of the cell	R_T
Thickness	t
Ultraviolet	UV
United State Pharmacopoeia	USP
Weight per weight	w/w

LIST OF APPENDICES

PEMBANGUNAN DAN PENILAIAN TABLET PELEPASAN TERPANJANG KETOPROFEN

ABSTRAK

Suatu sistem perlepasan terpanjang telah dibangunkan menggunakan salutan filem sebagai sistem perlepasan terpanjang drug dan ketoprofen telah digunakan sebagai drug model. Drug berkenaan telah disediakan dalam bentuk tablet yang mengandungi 15% Gelucire 50/13 sebagai bahan pembentuk matriks. Kemudian ia disalut secara berfilem dengan etilselulosa (300cps). Keputusan ujian fizikal yang dijalankan ke atas rumusan-rumusan yang dikaji adalah memuaskan. Kajian kelarutan *in vitro* menunjukkan bahawa ketebalan salutan setebal 0.04 mm adalah cukup untuk mengekalkan kadar pembebasan ketoprofen sehingga 8 jam, yang mana ia adalah setanding dengan sediaan rujukan komersil (Oruvail CR 100 mg) daripada segi profil pembebasan dan jumlah pembebasan ubat. Pengekalan kadar pembebasan sehingga 12 jam juga dicapai dengan ketebalan salutan setebal 0.06 mm. Kadar pembebasan ubat adalah stabil dalam tempoh enam bulan pertama semasa proses penuaan pada 25°C iaitu pada suhu bilik tetapi pembebasan telah menurun sedikit selepas enam bulan proses penuaan yang berikutnya. Kadar pembebasan ubat adalah pada dasarnya tidak bergantung kepada kesan permatangan.

Kajian terma ke atas ketoprofen dengan setiap eksipien individu dalam nisbah campuran 1:1 menunjukkan ciri-ciri endotermik ketoprofen menurun dengan Gelucire 50/13, PVP (K30) dan magnesium stearat. Ini disebabkan oleh berlakunya kehilangan air (dehidrasi), manakala tidak terdapat perubahan pada takat cair ketoprofen dengan etilselulosa dan laktosa. Ketidakhadiran ciri-ciri

endotermik ketoprofen di dalam tablet menunjukkan wujudnya interaksi yang kuat tetapi tidak semestinya disebabkan oleh ketidaksesuaian.

Kajian FTIR menunjukkan kumpulan-kumpulan berfungsi pada ketoprofen adalah stabil dan tidak mempunyai interaksi dengan mana-mana eksipien sama ada dalam bentuk campuran fizikal ataupun tablet.

DEVELOPMENT AND EVALUATION OF PROLONGED RELEASE KETOPROFEN TABLETS

ABSTRACT

A prolonged release system was developed using film coating as drug release controlling system and ketoprofen as model drug. The drug was prepared in tablets containing 15% Gelucire 50/13 as matrix forming material, and then the tablets were film coated with ethylcellulose (300cps). The results of physical tests for the formulations and the coating materials were satisfactory. The *in vitro* dissolution studies showed that the rate of ketoprofen release was sufficiently sustained for up to 8 hours with coating thickness 0.04 mm, and this was found to be comparable with the commercial reference preparation (Oruvail CR 100 mg) in terms of the release profile and extent of drug release. A 12 hours sustained release profile was achieved with coating thickness 0.06 mm. The rate of drug release was stable for the first six months of ageing at room temperature 25°C, but the release was slightly decreased in the next six months of ageing. The rate of drug release was essentially independent of the curing effect.

Thermal study of ketoprofen with each individual excipient at a ratio of 1:1 showed that ketoprofen decreased in its melting endothermic characteristics with Gelucire 50/13, PVP (K30) and magnesium stearate, which was due to the loss of water (dehydration), while there was no changes in the melting point of ketoprofen with ethylcellulose and lactose. The absence of the melting endothermic characteristics of ketoprofen in the tablet indicates a strong interaction but not necessarily of incompatibility.

The FTIR studies showed that the ketoprofen functional groups were stable and did not have any interactions with any excipients in the form of physical mixture as well as in the form of tablet.

CHAPTER 1

INTRODUCTION

1.1 Oral prolonged release dosage forms

Oral administration is the preferred delivery route for various modes of introducing a drug into the body, because it is simple, easy and convenient method of drug administration. Ideally, an oral dosage form should deliver the drug at a specified rate, for a specific period of time and even at a designated location (Juliano, 1980; Szycher, 1991). Blood is usually the medium of transport for the absorbed drug, thus, the ideal plasma concentration levels which produces optimal therapeutic activity must be obtained. However, these drug delivery targets could only be achieved in part through conventional dosage form (Lee and Good, 1987).

Conventional drug delivery systems are designed to release their content promptly for absorption, thus giving a maximum rate and extent of absorption. Hence, wide fluctuations in peak and through steady–state drug levels are frequently obtained with these products, particularly for drugs having short biological half–life. By increasing the frequency of dosing, it may be possible to reduce such undesirable fluctuations particularly with drugs with narrow therapeutic indices. However this may lead to patient inconvenience and poor compliance. In order to overcome this problem, various sustained release formulations have been widely developed to improve the therapeutic performance of drugs, in particular, to increase pharmacological efficacy and reduce side effects (Pather *et al.*, 1998; Sanchez-

Lafuente *et al.*, 2002; Kramar *et al.*, 2003) To be effective such formulations must control the rate of oral drug release for absorption over an extended period of time after each administration.

As mentioned in British Pharmacopoeia (BP 2005), modified release dosage forms include prolonged release, delayed release and pulsatile release dosage forms. Therefore, the terms controlled release and sustained release were included under prolonged release. Prolonged release dosage forms show a slower release of the active substance(s) than that of a conventional release dosage forms. The prolonged release dosage form should be tailored so that variations in components lead to predictable alterations in released profiles. Controlled release (CR) systems are designed to deliver drugs at a predetermined rate and even at a desired location, in order to maintain relative constant drug levels n plasma for an extended period of time (Juliano, 1980; Szycher, 1991; Hashida, 1998). These systems can offer less fluctuation in plasma drug level so that adverse effects could be reduced due to more uniform drug levels. In addition, they could also achieve reduction in the cost for overall treatment and in the frequency of drug administration, hence, leading to improved patient compliance (Lordi, 1986; Khan *et al.*, 1995). Ketoprofen is a very good candidate for formulation of controlled release dosage forms (Habib and Mesue, 1995; Parejo *et al.*, 1998; Palmieri *et al.*, 2002), due to the short half-life (Reynolds, 1996), low bioavailability and local or systemic disturbance in the GI tract (Liversidge, 1981) which could lead to withdrawal of treatment.

1.1.1 Methods of achieving oral prolonged release dosage form

A number of techniques have been used to achieve oral prolonged drug delivery, since it provides many advantages. These advantages include more predictable gastric emptying (Davis, 1986), minimizing local concentration of drug (Eskilson, 1985), less likelihood of dose dumping (Sam, 1985) and lower incidence of inter- and intrasubject variability (Kyroudis *et al.,* 1989; Butler *et al.,* 1998). In general, prolonged release formulations can be divided into different categories based on the methods of preparation and / or the mechanisms of drug release, which will be discussed in the following sections (Lordi, 1986). The methods can be divided into four main categories, namely matrices system, coating or barrier membrane, osmotic pressure and ion-exchange resins. The choice of method for achieving prolonged release in a particular application depends on a number of factors such as the cost, the potency and the properties of the agent, the environmental issues of use and any requirement for biodegradability.

1.1.1 (a) Matrices system

Matrices type or diffusion prolonged dosage forms by using polymeric excipients have been widely utilized to control the release rate of various type of drugs (Hogan, 1989), in which the drug is uniformly dissolved or dispersed throughout the polymer mass. The release pattern depends on the geometry of the system, the identity and nature of the polymer or other carrier material. For those drugs with rapid dissolution, embedding them within slowly dissolving or erodible matrices provides a way of retarding the dissolution rate. Most of the oral matrices prolonged release products utilize either hydrophilic or hydrophobic matrices

systems in which the drug is homogeneously distributed or dissolved in the polymeric matrices.

The matrix system is commonly used for manufacturing sustained release dosage forms because it makes such manufacturing easy. One of the most common approaches used to achieve sustained release is to incorporate a drug in a hydrophobic matrix such as wax, polyethylene, polypropylene, Gelucire and ethylcellulose or a hydrophilic matrix such as carboxymethylcellulose, hydroxypropylmethylcellulose and methylcellulose (Sriwongjanya and Bodmeier, 1998).

It is necessary to have some knowledge of the material properties of the devices in order to predict the kinetics of drug release, so controlled release mechanisms have been described, including diffusion through matrices or across membranes and erosion mechanism. A simple semi-empirical equation was put forward to describe the drug release behavior from a hydrophilic matrices system (Peppas, 1985; Ford *et al.,* 1991) while the release from a hydrophobic monolithic matrices system that resulted in the square–root of time release profile had been described previously by Higuchi (1963). Hydrophilic matrices have become most popular as modified release dosage form for oral administration. Hydrophilic matrices consist of materials that swell and form gels upon contact with water or gastrointestinal fluids. Drug release in such system is controlled by the leaching/diffusion of the active substances through the swollen hydrates matrices, as well as due to the

erosion of the gelled layer (Peppas, 1985). Hydrogel is an important class of the hydrophilic matrices former, which is capable of swelling in water and retaining a considerable amount of water without dissolving in it (Breimer *et al.,* 1985).

1.1.1 (b) Coating / Barrier membrane

Polymeric coating techniques have been widely applied in pharmaceutical industry for many reasons such as taste masking, stability improvement, protective barrier, and especially for the controlled release of drugs for the preparation of various dosage forms (McGinity, 1989). In general, coating dispersions are applied on various drug-loaded cores such as seed, pellet, bead, granule or tablet. Today, films have earned an important place in controlled release drug delivery systems. Many of these systems are tablets or capsules (matrices) covered with a film that helps in achieving the controlled release of a drug. Various materials have been used for the preparation of these systems, in which ethylcellulose is one of the most widely used hydrophobic polymer (Donbrow and Friedman, 1974; Palmieri and Wehrle, 1997; Lin *et al.*, 2001; Ymada *et al.*, 2001). Some important criteria, such as drug release from a system were explained by studies conducted on films or membranes. Often, tablets coated with a film behave differently from the film itself. However, there is no doubt that studies conducted on films help in understanding the behavior of tablets coated with these films. Various properties have been studied in detail such as drug release, dry and wet strengths, effect of plasticizers and adhesion to tablet surfaces (Rowe, 1986; Bodmeier and Paeratakul, 1990, 1993; Bechard *et al.,* 1995; Lehtola *et al.,* 1995; Okutgen *et al.,* 1995).

Enteric coated dosage forms are designed to resist the acidic environment of the stomach and disintegrate in the higher pH environment of the intestinal fluid. It controls the rate of drug release by swelling in water and forming a permeable membrane. The reasons for using an enteric coating are to protect the stomach wall from the effect of the drug contents in a dosage form and/or to protect the drug contents in a dosage from the harmful effect of the gastric contents. Enteric coating can also be used to deliver the active ingredients to a particular region of the intestine, e.g. the upper part of the small intestine, so as to enhance the bioavailability of the drug (Leopold, 1999).

The film coating membrane for conventional dosage form should have good solubility in aqueous fluid to facilitate the dissolution of the active ingredient, while modified release action requires a polymer system with low water solubility or permeable membrane. In this latter system the release rate of drug is determined by its diffusion through a water insoluble membrane. The uniformity of tablet coating is very important as it affects the organoleptic quality of tablets and functionality of the coating, especially in the case of modified release formulations. The rate of drug release depends upon the thickness of the coated film (Fourman *et al.*, 1995), and/or the porosity of the coating membrane. Rowe (1985) reported that the ethylcellulose with hydroxypropyl methylcellulose are widely used in the formulation of delayed or sustained drug release film coatings. The water insoluble ethylcellulose is usually chosen as the coating material and the water soluble hydroxypropylmethylcellulose as the minor component. The drug is released through pores created in the film coating by the dissolution of the dispersed phase.

The use of amylose-ethylcellulose film coatings as oral colon specific drug delivery system has been also reported by Lee *et al.* (2000).

1.1.1 (c) Osmotic pumps

Osmotic systems for controlled drug-delivery applications are well established and suitable for oral administration. Osmotic pumps for controlling the drug release are unique, dynamic and widely employed in clinical practice (Santus and Baker, 1995; Singh *et al.*, 1999). The device consists of an outside layer of semi permeable membrane coating a compressed core which has a mixture of drug and osmotic agent. When the device is placed in water, osmotic pressure generated by the osmotic agent within the core causes water to move into the device, which forces the dissolved drug to move out of the delivery orifice. The absorption of the water by the core depends on the osmotic pressure generated by the core components and the semi permeable membrane. The release rate of the drug from an osmotic device is relatively unaffected by the pH and hydrodynamics of the external dissolution medium. Osmotic systems are appropriate to drugs with a broad range of aqueous solubilities. Depending on the aqueous solubility, the drug is released either as a solution or as a suspension. The *in vivo* rate of drug release from osmotic device is comparable to the *in vitro* rate, producing an excellent *in vitro/in vivo* correlation (Thombre *et al.*, 2004).

The osmotic preparation can be designed as single unit tablets with single orifice, so the drug solution can flow through it. This single orifice formed in the membrane by boring with a laser beam. Osmotic system can be also designed as multiple

units tablet in which the drug solution can flow through a number of pores formed during the uptake of water (Aulton, 2002).

Due to some reasons osmotic systems can be to some extent complex to manufacture, such as, the tablet core components may have poor to marginal flow and compression characteristics, in most systems a laser drilling process is needed to form the delivery port(s) and a solvent based process is used to apply the semi permeable membrane coating onto the tablet cores. Even if there are some manufacturing complexity, osmotic drug-delivery systems have been successfully used in many commercial products (Thombre *et al.*, 2004).

In the middle of 1970s, Theeuwes *et al.* (1975) developed an elementary osmotic pump to achieve controlled drug delivery. The delivery of the drug from the system is controlled by solvent influx across a semipermeable membrane, which in turn carries the drug outside through a laser drilled orifice. The osmotic and hydrostatic pressure differences on either side of the semipermeable membrane govern fluid transport into the system. Osmotic system has been applied to deliver drugs such as testosterone (Kazuto *et al.*, 1999), diltiazem HCl (Prabakaran *et al.*, 2003) and pseudoephedrine (Sapna *et al.*, 2003).

1.1.1 (d) Ion-Exchange Resins

Ion-exchange resins (IER), or ionic polymer networks (which is designed to provide controlled release for ionizable drugs), have been used for many years in pharmaceutical formulations. Ion exchange materials are insoluble substances containing loosely held ions which are able to be exchanged with other ions in solutions which come in contact with them. Ion exchange is the reversible interchange of ions (of like charge) between a liquid and a solid phase, involving no radical change in the structure and properties of the solid. The solid phases in the ion exchange process are referred to as IER, and are usually the polymers with integrated ionic moieties. Based on the nature of the ionic species being interchanged, ion exchange resins are insoluble polymers that contain acidic or basic functional groups which have salts which are also insoluble, and this enables them to exchange either positively charged ions (cation exchangers) such as amino or quaternary ammonium groups and negatively charged ones (anion exchangers) such as carboxylic groups, or sulfonic groups in repeating positions on the resin chain (Sriwongjanya and Bodmeier, 1998). These materials are totally insoluble in all solvents and at all pHs, combined with their large particle size means that they are not absorbed by the body, and so have proven to be non-toxic and very safe. A drug resin complex is formed by prolonged exposure of drug to the resin.

Their uses range from simple excipients for tablet disintegration to the rate controlling function in prolonged release formulations. An added advantage is that the technique provides some protection for very bitter or irritating drugs. Recently,

the ion exchange approach has been combined with coating to obtain more effective sustained release product. Ion exchange resins for controlled drug delivery was adapted from analytical and protein chemistry (Kogan *et al.*, 1991; Novic *et al.*, 2001).

In practice, drug in an ionic form (usually in solution) is mixed with the appropriate IER to form a complex, known as resinate. The performance of resinate is governed by several factors, such as the pH and temperature of the drug solution, the molecular weight and charge intensity of the drug and IER, ionic strength of the drug solution, degree of cross linking and particle size of the IER and contact time between the drug species and the IER (Plaizier-Vercammen, 1992; Liu *et al.*, 2001). The liberation of free-drug ions happened when resinate from the delivery system reaches the site of delivery, the exchange process is reverted. Therefore the ionic strength and pH at the site of delivery play a key role in the liberation of immobilized drug from the resinate. The presence of highly activated counter ions at the site will cause drug delivery at the desired target via the ion exchange process to be occurring, resulting in the exchange of ions and drug release. The IER devoid of drug is eliminated or biodegraded from or at the site of delivery (Hui *et al.*, 1987).

1.1.2 Advantages and disadvantages of oral prolonged release dosage forms

Oral prolonged release dosage forms offer advantages over conventional dosage forms that deliver all of the active agent over a short period of time, therefore these forms gained medical acceptance due to their ability to achieve better therapeutic effects. If the therapeutic levels of a drug are controlled and maintained for an extended period of time, the dosing frequency can thus be reduced to once or twice daily which in turn can lead to increased patient convenience, improved pharmacokinetic profiles and compliance (Urquhart, 2000). The incidence and severity of untoward systemic side effects related to high peak plasma drug concentration will also be reduced. A reduction in the total amount of drug administered over the period of treatment will be achieved. This contributes to the reduced incidence of systemic and local side effects. Also, prolonged release can improve treatment of many chronic illnesses where symptom breakthrough occurs if the plasma concentration of drug drops below the minimum effective concentration. prolonged release can also reduce the incidence and severity of untoward systemic side effects related to high peak plasma drug concentration. Through the combination of a reduction in dosing frequency and an optimization of the amount of drug entering systemic circulation, a controlled release formulation may increase the efficacy of the compound and may improve patient compliance (Theeuwes, 1983; Urquhart, 2000). Hence, a better disease management and reliable therapy can be achieved with controlled release dosage forms (Welling and Dobrinska, 1987).

Another important benefit is the elimination of local gastrointestinal irritation and erosion arising from exposure of gastric mucosa to high drug concentrations released from the conventional dosage forms (Levy and Hayes, 1960; Boroda *et al.*, 1973).

Moreover, in view of the constant delivery of drug, prolonged release systems require a smaller amount of drug to produce therapeutic blood level for a given duration. This, in turn, will improve the economics especially for drugs that are expensive and difficult to extract or to obtain. It is claimed that cost savings are made from the better disease management that can be achieved with controlled release products (Lachman *et al.*, 1986).

However, prolonged release dosage forms have several potential disadvantages. They include cost, unpredictable and often poor *in vitro* and *in vivo* correlation, dose dumping, reduced potential for dosage adjustment and increased potential for first pass clearance. The removal of drug after administration is difficult with controlled release preparation if adverse effects are noted, also if the drug cannot be accommodated. The physician has less flexibility in adjusting dosage regimens (Lachman *et al.*, 1986). Nevertheless, the advantages and potential benefits with prolonged release dosage forms appear to outweigh the disadvantages, and the growing interest in design and development of prolonged release dosage forms makes them more likely to be preferred in future.

1.2 Evaluation of prolonged release dosage forms

1.2.1 *In vitro* evaluation

To ensure and promote better safety drug use by patients, it is necessary to establish appropriate guidelines for the design and evaluation of drug dosage form. The *in vitro* characteristics and quality of the product is essential in the development and evaluation of dosage forms. For solid prolonged release dosage forms, drug release characterization is the most important among various *in vitro* tests because the *in vitro* dissolution test can serve the purpose of providing necessary quality and process control, determining stability of the relevant release characteristics of the product and facilitating certain regulatory determinations and judgments concerning minor formulation changes. Therefore the purpose of the *in vitro* evaluation is to minimize or eliminate the risk of marketing an unsafe product, guaranteeing the efficacy of the product, which meets the regulatory requirements (Skelly *et al.*, 1993).

Dissolution testing is the most important *in vitro* test. Dissolution studies are carried out to evaluate the potential effect of formulation and process variables on the bioavailability of a drug, to ensure that preparations comply with product specifications and to indicate the performance of the preparation under *in vivo* conditions. However, the dissolution rate of a specific dosage form is essentially an arbitrary parameter that may vary with the dissolution methodology, such as type of apparatus, medium and agitation. Some of the attributes essential for a good *in vitro* dissolution are, the output should be reproducible and associated in some way with *in vivo* data, the system should be sufficiently sensitive in discriminating

between *in vitro* variables that may yield differences *in vivo* and the system should be flexible and have a wide range of application to products (Gupta and Robinson, 1992).

Basically most of the pharmaceutical solid and solid dispersion dosage forms undergo dissolution testing. The *in vitro* test conditions should have meaningful relationships to the conditions in gastrointestinal tract and should be a part of dissolution test methodology. There are several factors that affect the dissolution rate of drug dosage forms. The physicochemical properties of the drug substance play a prime role in controlling its dissolution from the dosage form (Wagner, 1975). These include particle size, crystalline state such as polymorphism and state of hydration and also physical properties such as density and viscosity of the dissolution media affect the dissolution rate (Banakar, 1983).

Several instruments and techniques have evolved in dissolution testing and are divided into two categories. These are the beaker methods and the flow through column system. Both are easy to operate and the procedure readily automated. The dissolution process and the design of the dissolution apparatus affect the dissolution rates through a number of factors. These include the geometry and design of the container, the intensity and type of agitation, composition, volume, and the temperature of the dissolution medium. These factors, in turn, affect the abrasion rate of the intact solid dosage form on the particles, the dispersion of the disintegrated particles, the homogeneity of the dissolution fluid and the reproducibility of the system from run to run (Shargel and Andrew, 1999).

1.3 Thermal analysis

1.3.1 Introduction

For a recent few decades, we have observed remarkable development in thermal analysis, especially in new techniques by which chemical and structural changes in the sample can be directly observed (Ozawa, 2000). Thermal analysis methods provide fundamental knowledge about the properties of polymers for processing and application. It comprises of a group of techniques in which a physical property of a substance is measured as a function of temperature, while the substance is subjected to a controlled temperature program (Wendlandt, 1974; Warne, 1992). In differential thermal analysis (DTA), the temperature difference that develops between a sample and an inert reference material is measured, when both are subjected to identical heat treatments. The related technique of differential scanning calorimetry (DSC) relies on differences in energy required to maintain the sample and reference at an identical temperature (Ford and Timmins, 1989).

1.3.2 Differential Scanning Calorimetry (DSC)

In thermal analysis, differential scanning calorimetry (DSC) and differential thermal analysis (DTA) are the most important methods. Both DSC and DTA may detect the enthalpy changes, which occur in a sample as it is heated or cooled under fixed conditions. DSC is often considered to be more evolved than DTA, as DSC is able to provide quantitative and qualitative data (Ford and Timmins, 1989).

1.3.3 Principles of DSC

There are two types of DSC systems in common use, namely the power compensation and the heat flux DSCs (Griffin and Laye, 1992). In power compensation DSC the temperatures of the sample and reference are controlled independently using separate, identical furnaces. The temperatures of the sample and reference are made identical by varying the power input to the two furnaces; the energy required to do this is a measure of the enthalpy or heat capacity changes in the sample relative to the reference.

In heat flux DSC, the sample and reference are connected by a low resistance heat flow path (a metal disc). The assembly is enclosed in a single furnace. Enthalpy or heat capacity changes in the sample cause difference in its temperature relative to the reference; the resulting heat flow is small compared with that in differential thermal analysis (DTA) because the sample and reference are in good thermal contact. The temperature difference is recorded and related to enthalpy change in the sample using calibration experiments. The differential temperature is converted into heat flow using the equation below (Haines *et al.*, 1998).

$$\Delta Q / dt = (T_s - T_r) / R_T \qquad \textit{Equation 1.1}$$

Where Q is heat (J), t is time (s), R_T is the thermal resistance of the cell (Kw^{-1}), T_s is the temperature of the sample (K) and T_r is the temperature of the reference (K). Figure 1.1 shows the most popular DSC design. Two pans are placed on a pair of

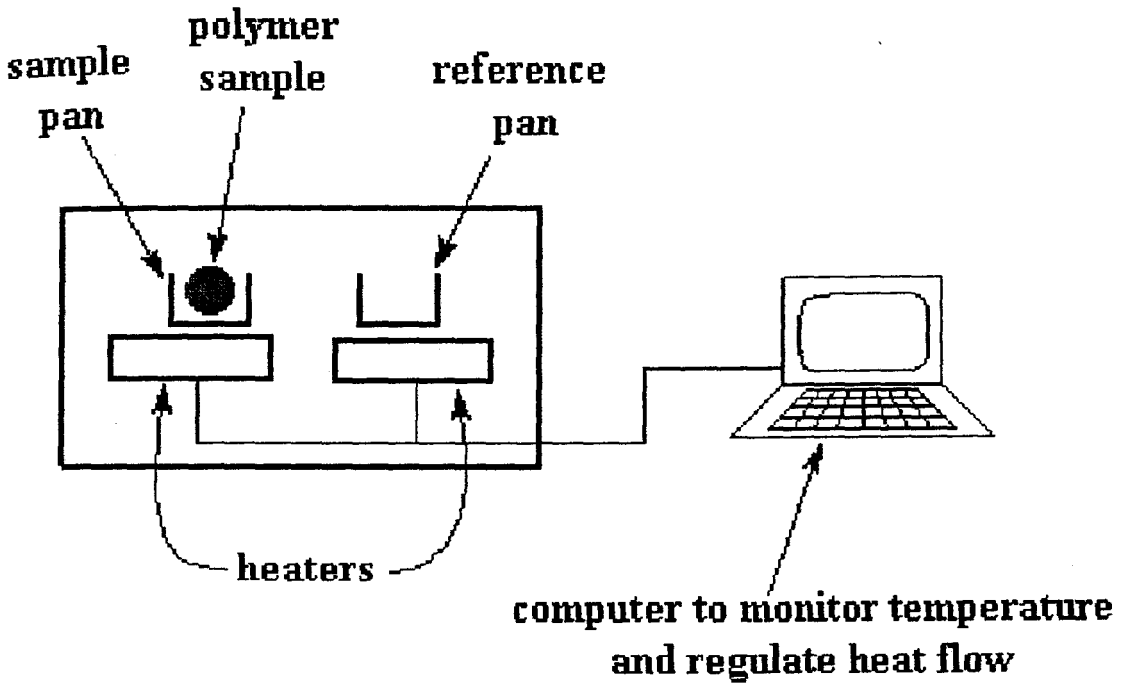

Figure 1.1. The design of Perkin Elmer Differential Scanning Calorimeter Pyris 6 (Perkin Elmer Ltd, UK)

identically positioned platforms connected to a furnace pan by a common heat flow bath. The polymer sample is placed in one pan, whereas the reference sample is placed in the other pan. The connection of computer into the furnace is utilized in order to turn the furnace on and also to monitor the heat of two pans at a specific rate.

1.3.4 Application of DSC

DSC is the most widely used of all thermo-analytical techniques. It is used primarily to characterize polymers and organic materials, as well as metals, ceramics, and composites. Basically the DSC measurement is a function of differential heat flow with temperature for compounds that exhibit thermal transitions. These transitions are typically melting, crystallization, and the glass transition (T_g). Such measurements provide quantitative and qualitative information about physical and chemical changes that involve endothermic or exothermic processes. DSC has proven to be a power tool in elucidating as to whether a drug and its carrier may interact when fused together or may be stable (Dordunoo *et al.,* 1996), and so, facilitates the selection of a formulation that consists of the optimal drug carrier ratio (Mura *et al.,* 1995; Mooter *et al.,* 1998).

Figure 1.2 shows a typical scan for a polymer. When DSC starts heating the two pans, the computer plotting the heat absorbed by the polymer against temperature, initially by straight line. When polymer is heated a little more, after a certain temperature, plot will shift upward suddenly, this happens because the polymer has just gone through the glass transition. At this point, the heat is being absorbed

by the samples and there is an increase in the heat capacity of the sample during the process. The crystallization temperature (T_c) is reached when the polymer sample has gained enough energy to move into an ordered arrangement of crystal. When the molecules of the polymer fall into these crystalline arrangements, they give off heat, which is detected as exothermic peak in the plot of heat flow versus temperature. The melting temperature (T_m) is reached when the polymer undergoes an endothermic thermal transition, which is called the melting temperature. When T_m is reached, the temperature of the polymer will not rise until all the crystals have melted.

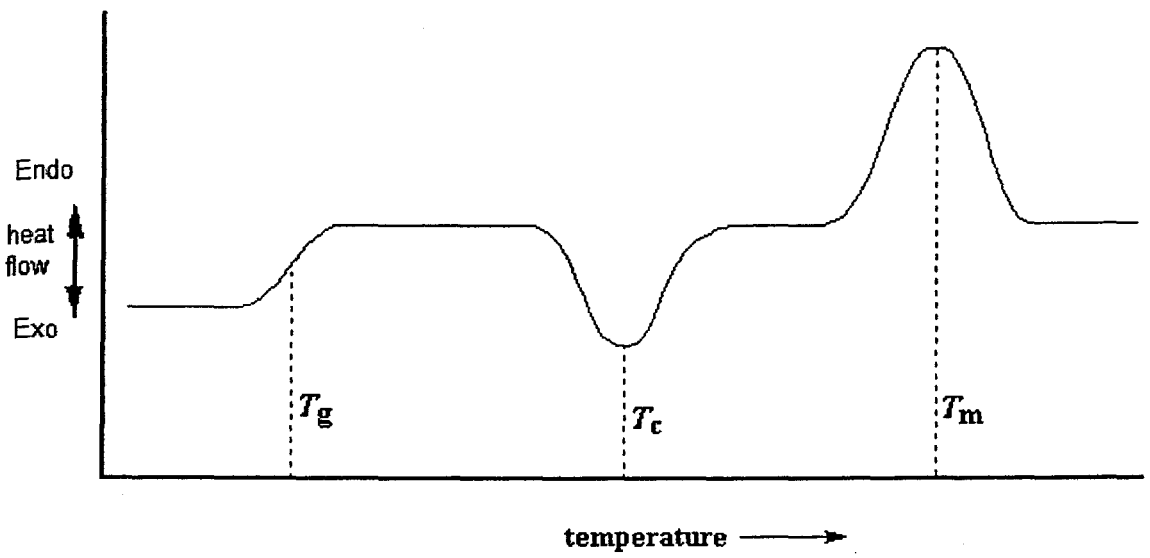

Figure 1.2 A possible DSC thermal profile during thermal processes (Ford and Timmins, 1989)

1.4 Mechanical properties

Mechanical properties occur as a result of the physical properties inherent to each material, and are determined through a series of standardized mechanical tests, such as tensile strength and elongations which can be measured to evaluate the film properties. Tensile strength tells about how much stress is needed to break the film sample, but it does not tell anything about what happens to film sample while trying to break it, therefore that is the reason why it is important to study the elongation behavior of polymer sample. These properties are important characteristics to predict the stability and release property of film coated dosage forms (Sakellariou *et al.*, 1985; Johnson *et al.*, 1991; Parikh *et al.*, 1993; Obara and McGinity, 1994; Baie and Sarwar, 1995).

1.5 Permeability Studies

Since the drug release from a coated dosage form depends upon the porosity of the membrane, permeability studies were conducted to provide useful information regarding the potential effects of the permeability of the film (Wang, 1994). Several studies have been performed on permeability properties for enteric films (Parker *et al.*, 1974; Spiteal and Kinget, 1980; Guo *et al.*, 1993; Saettone *et al.*, 1995). All of the above studies used the same design of the transmission cell. It consisted of a screw-capped, cylindrical glass bottle with a circular hole in the screw cap. A circular piece of film was placed between two rubber gaskets, which were then fixed inside the screw cap. The bottle contained moisture absorbent material, placed in controlled relative humidity environment.

6 FTIR – Introduction

ɔurier Transform Infrared (FTIR) spectroscopy is a powerful analytical tool for ıaracterizing and identifying organic molecules. Using the IR spectrum, chemical ɔnds and the molecular structure of organic compounds can be identified. FTIR is ıe preferred method of infrared spectroscopy. In infrared spectroscopy, IR ıdiation is passed through a sample. Some of the infrared radiation is absorbed y the sample and some of it is passed through (transmitted). The resulting pectrum represents the molecular absorption and transmission, creating a ıolecular fingerprint of the sample. Like a fingerprint, no two unique molecular tructures produce the same infrared spectrum. This makes infrared spectroscopy seful for several types of analysis.

TIR is most useful for identifying chemicals that are either organic or inorganic Bell, 1972). FTIR can be used to identify chemicals from spills, paints, polymers, oatings, drugs, and contaminants. Therefore, FTIR is a rapid technique that is ery efficient in industrial applications, such as weathering (Nagai *et al.,* 1997) or nalysis of blends (Fischer *et al.,* 1997) and to study the interactions between the rug and the polymer blends. FTIR is perhaps the most powerful tool for the lentification of the interaction between the polymer and the drug blends at the ıolecular level, which allows a comparative investigation of drug performance, in ıe solid state, either when mixed with the required excipients in the formulation of ıe matrix tablets or in other pharmaceutical dosage forms. The idea of using an TIR to study drug–polymer blends is that it can provide valuable information ɛgarding the interactions of drug–polymer blends, which cause changes in the

)ration dipole of the molecules. This will appear as changes in the frequency and ndwidth of interacting groups in the spectrum (Nair *et al.*, 2001; Eerikainen *et al.*, 04; Vueba *et al.*, 2006).

ıe term Fourier Transform Infrared Spectroscopy (FTIR) refers to a fairly recent velopment in the manner in which the data is collected and converted from an erference pattern to a spectrum. Today's FTIR instruments are computerized ıich makes them faster and more sensitive than the older dispersive instruments wing, 1985).

7 Ethylcellulose

hylcellulose is one of the most widely used water insoluble hydrophobic polymer, can be applied either as an organic solution or as an aqueous colloidal dispersion seudolatex). Ethylcellulose is essentially tasteless, odorless, colorless, ncaloric and physiologically inert (Donbrow and Friedman, 1974; Spiteal and nget, 1980; Iyer *et al.,* 1990). Ethylcellulose contains 44 to 51% of ethoxy groups anufactured by the reaction of ethyl chloride or ethyl sulfate with cellulose ssolved in hydroxide Depending on the degree of ethoxy substitution, different scosity grades are obtained and available. This material is completely insoluble in ıter and gastrointestinal fluids, and thus cannot be used alone for tablet coating. is usually combined with water soluble additives, such as hydroxypropyl ethylcellulose, to prepare films with reduced water solubility properties (Lachman *al.*, 1986; Sadeghi *et al.*, 2000).

Ethylcellulose has been extensively used as a pharmaceutical vehicle in a number of dosage forms. It has a long history of use in the pharmaceutical field as a coat to various forms, including tablets, granules and powders (Donbrow and Friedman, 1974; Palmieri and Wehrle, 1997; Lin *et al.*, 2001; Ymada *et al.*, 2001), as a tablet binder (Chowhan, 1980), in the preparation of microcapsules and microspheres (Bodmeier and Chen, 1989), and also as film and matrices forming material for sustained release dosage forms (Shaikh *et al.*, 1987; Shlieout and Zessin, 1996; Pather *et al.*, 1998). The permeability of ethylcellulose membrane can be increased by the addition of water soluble materials such as PEG 400 as plasticizer (Wood and Syarto, 1964) and polyvinylpyrrolidone (PVP).

However, ethylcellulose shows some major disadvantages, which have a negative influence on the production time such as significant curing effects. Therefore, to accelerate the film formation process and avoid stability problems a curing step (thermal treatment) at elevated temperatures above the minimum film formation temperature (MFT) directly after the coating process has been recommended (Gilligan and Li Wan, 1991; Hutchings *et al.*, 1994).

1.8 Gelucires

Gelucires are solid waxy materials, which are the saturated polyglycolized glycerides consisting of mono-, di-, and tri-glycerides and mono-, di-fatty acid esters of polyethylene glycol (Baykara and Yuksel, 1991; Gattefossé, 1999; Vicente, 2000). They are derived from natural products such as olive oil, cotton seed oil, sunflower oil and palm oil. Gelucires have very wide applicability in the