PREPARATION AND EVALUATION OF FENOFIBRATE-GELUCIRE 44/14 SOLID DISPERSIONS

by

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ABSTRAK

Potensi formulasi berasaskan sebaran pepejal menggunapakai Gelucire 44/14 sebagai pembawa untuk meningkatkan pelarutan serta biokeperolehan oral fenofibrat, sejenis drug yang tak mudah larut, telah disiasat. Penyebaran pepejal dengan nisbah drug-pembawa yang berbeza disediakan dengan menggunakan kaedah cantuman konvensional dan dicirikan menggunakan analisis terma, mikroskopi optik dan ujian pelarutan. Keputusan ujian pelarutan ini dibandingkan dengan keputusan dua lagi fenofibrat, iaitu serbuk drug itu bersaiz mikron dan tablet komersial yang mempunyai biokeperolehan supra. Tiada peningkatan ketara dalam pelarutan drug melebihi kadar pelarutan fenofibrat bersaiz mikron diperolehi dari pepejal penyebaran yang disediakan. Pengurangan dalam pelarutan drug tersebut boleh disabitkan kepada kehadiran hablur-hablur drug yang besar yang terbentuk semasa penyediaan penyebaran pepejal tersebut. Namun begitu, setelah pengubahsuaian dilakukan ke atas kondisi-kondisi penyediaan, dengan menambahkan drug pada suhu yang rendah secara relatif dan dengan penambahan polietilin glikol (PEG) 400 untuk merendahkan takat lebur matriks, mengakibatkan pemerolehan hablur drug yang lebih kecil serta penghakisan matriks yang lebih cepat. Akibatnya, pelarutan lengkap dicapai setelah kira-kira 60 minit ujian berbanding pelarutan sebanyak 65% untuk serbuk drug yang bersaiz mikron. Penilaian *in vivo* penyebaran pepejal fenofibrat-Gelucire 44/14 yang mengandungi polietilin glikol (PEG) 400 menunjukkan bahawa takat serapan drug, seperti yang dinyatakan

oleh $AUC_{0-\infty}$, dipertingkatkan sebanyak kira-kira 60% berbanding dengan takat serapan fenofibrat yang bersaiz mikron. Berdasarkan keputusan kajian ini, dapat disimpulkan bahawa apabila kaedah cantuman konvensional gagal mengurangkan saiz partikel drug, teknik penambahan partikel drug yang bersaiz ke dalam matriks pada suhu yang rendah harus dipertimbangkan. Hasil kajian juga menyarankan bahawa penurunan takat lebur matriks boleh meningkatkan kadar pelarutan.

PREPARATION AND EVALUATION OF FENOFIBRATE-GELUCIRE 44/14 SOLID DISPERSIONS

ABSTRACT

The potential of solid dispersion-based formulation using Gelucire 44/14 as a carrier to enhance the dissolution and oral bioavailability of fenofibrate, a poorly water-soluble drug, was investigated. Solid dispersions with different drug-to-carrier ratios were prepared by the conventional fusion method and characterized using thermal analysis, optical microscopy and dissolution testing. The dissolution results were compared with those of two fenofibrate formulations; the micronized drug powder and commercial tablet having suprabioavailability. No substantial increase in the drug dissolution, over that of micronized fenofibrate, could be obtained from prepared solid dispersions. Decreased drug dissolution was attributed to the presence of large drug crystals formed during the preparation of the solid dispersions. However, modifying the preparation conditions, by adding the drug to the carrier at a relatively low temperature, and incorporating polyethylene glycol (PEG) 400 to lower the melting point of the matrix, resulted in much smaller drug crystals and rapidly eroding matrices being obtained. Consequently, complete drug dissolution was achieved after approximately 60 minutes of the test, compared with 65% dissolution for micronized drug powder. *In vivo* evaluation of fenofibrate-Gelucire 44/14 solid dispersion containing polyethylene glycol (PEG) 400 showed that the extent of drug absorption, expressed as $AUC_{0-\infty,}$ was increased by approximately 60% over that of micronized fenofibrate. On the basis of the

results of this study, it was concluded that when the conventional fusion method fails to reduce the drug particle size, the technique of incorporating drug microparticles into the matrix at lower temperatures is worth considering. The findings also suggest that lowering the melting point of the matrix can increase the dissolution rate.

CHAPTER 1. INTRODUCTION

Drug absorption from solid oral dosage forms depends on the release of the drug substance from the delivery system, the dissolution of the drug under the physiological conditions and the drug permeability across the gastrointestinal tract (Ansari *et al.,*2004). Poorly water-soluble drugs are expected to have dissolution-limited absorption. Increasing the drug solubility may substantially contribute to improved drug absorption, and consequently, drug bioavailability. Solid dispersion techniques have been used to enhance the dissolution and oral bioavailability of many poorly soluble drugs (Habib, 2000).

1.1 Solid dispersions

1.1.1 Historical background

The work of Sekiguchi and Obi (1961) was the first to show the possibility of increasing oral absorption of a drug incorporated into a 'eutectic mixture'. Sulfathiazole in a 'eutectic mixture' with urea showed higher oral absorption and excretion than ordinary sulfathiazole. The term 'solid-in-solid solutions' was first used by Levy (1963) and Kanig (1964) who indicated that many drugs could form 'solid-solid solutions' with mannitol. Later, Chiou and Niazi (1971) reported that sulfathiazole-urea fused mixtures, at specific concentrations, formed 'solid solutions' or 'amorphous precipitations', in which the dissolution rate of sulfathiazole was increased significantly. Furthermore, 'glassy solutions' were obtained after cooling the melts of 5 and 20% of griseofulvin in citric acid, and again, the dissolution rate of the drug was increased (Chiou & Riegelman, 1969). Finally, Chiou and Riegelman (1971a) brought together all the previous terms and

classified them into categories under the term ‘solid dispersions’.

1.1.2 Definition of solid dispersions

According to Chiou and Riegelman (1971a), a solid dispersion is "the dispersion of one or more active ingredients in an inert carrier at solid-state prepared by melting (fusion), solvent or the melting-solvent method". The carrier used has traditionally been a water-soluble or water-miscible polymer such as polyethylene glycol (PEG) or polyvinylpyrrolidone (PVP) or low molecular weight materials such as urea, citric acid and mannitol. However, the proliferation of publications in the solid dispersions area has led to a broadening of these definitions to include water-insoluble matrices such as Gelucires (Craig, 2002). Table 1.1 shows different materials used as carriers for solid dispersions.

1.1.3 Methods of preparing solid dispersions

1.1.3(a) Melting or fusion method

In this method, a physical mixture of the drug and the carrier is heated until it is melted. The melt is then cooled, and the resultant solid dispersion is pulverized and sieved (Sekiguchi & Obi, 1961).

The question of whether the drug needs to be dissolved in the molten carrier or not has not been fully resolved (Craig, 2002). Indeed, Craig and Newton (1991) used a low temperature fusion method to prepare solid dispersions; they added the drug to the molten carrier at a relatively low temperature. By using this method, the structure of the drug particles remains largely unchanged during the manufacturing process.

Table 1.1 Different materials used as carriers for solid dispersions (Vadnere, 2002)

Sugars	Dextrose, Sucrose, Galactose, Sorbitol, Maltose, Xylitol, Mannitol, Lactose
Acids	Citric acid, Succinic acid
Polymeric materials	Polyvinylpyrrolidone (PVP), Polyethylene glycols (PEG), Hydroxypropyl-methylcellulose, Methylcellulose, Hydroxyethylcellulose, Hydroxypropylcellulose, Cyclodextrins, Pectin, Galactomannan
Insoluble or enteric polymers	Hydroxypropylmethylcellulosephthalate, Eudragit L-100, Eudragit S-100, Eudragit RL, Eudragit RS
Surfactants	Polyoxyethylene stearate, Poloxamer 188, Deoxycholic acid, Tweens, Spans
Miscellaneous	Pentaerythritol, Pentaerythrityltetracetate, Urea, Urethane, Hydroxyalkylxanthins

Nevertheless, the cooling rate used may significantly affect the aging behavior of the solid dispersions. It has been reported that the crystallinity of drug in solid dispersions is less affected by aging when a slow cooling rate is used because thermodynamically more stable systems are produced (Duclos *et al.*, 1990; Saers *et al.*, 1993; Serajuddin, 1999). On the other hand, rapid cooling of molten mixtures is desirable because it leads to instantaneous solidification, resulting in the drug molecules being trapped in the carrier matrix (Chiou & Riegelman, 1971a). For rapid cooling, Sekiguchi and Obi (1961) used ice bath with vigorous stirring, Goldberg *et al.* (1966) poured the fused mixture onto ferrite plate. On the other hand, Chiou and Riegelman (1969) used stainless steel plates cooled by flowing air or water on the opposite side of the plate. However, a solid mass was formed after cooling the molten mixture, so it was necessary to pulverize the solidified mixture before it could be tested. To avoid the pulverization process which would change the physical structure of solid dispersions, Kanig (1964) used the spray congealing technique. By using this technique, solid dispersions in pellet form were obtained.

Direct filling of molten mixtures into hard gelatin capsules was first reported by Francois and Jones in 1978. Using this method for preparing solid dispersions was described later by Chatham in 1987. Subsequently, an automatic capsule filling machine was adapted to fill liquids instead of powders. Using this approach, pulverization and its potential negative effects on the structure of solid dispersions could be avoided.

1.1.3(b) Solvent method

This method includes dissolving the drug and the carrier in a common organic solvent, followed by evaporating the solvent at elevated temperature, under vacuum, or by freeze-drying or spray-drying the mixture (Serajuddin 1999). Tachibana and Nakamura (1965) used this method to prepare a solid dispersion of beta-carotene in polyvinylpyrrolidone (PVP) by using chloroform as a cosolvent.

1.1.3(c) Melting-solvent method

In this method, the drug is dissolved in a minimum amount of an organic solvent, and then it is added to the molten carrier. Chiou and Riegelman (1971a) used this method to prepare spironolactone-polyethylene glycol 6000 solid dispersion without removing the solvent. They reported that 5-10% (w/w) of liquid compound could be incorporated into polyethylene glycol 6000 without significant loss of its solid property.

1.1.3(d) Hot-melt extrusion

In this technique, the blend of drug and carrier is processed with a twin-screw extruder of the same type used in the polymer industry. The blend is simultaneously melted, homogenized and then extruded and shaped as tablets, granules, pellets, sheets, sticks or powder. An important advantage of the hot melt extrusion method is that the drug-carrier mixture is only subjected to elevated temperatures for a few minutes, which enables both the drug and the carrier to remain thermally stable (Zhu, 2002).

1.1.3(e) Supercritical fluid process

This process includes dissolving the drug and carrier in supercritical CO_2 under precise conditions of temperature and pressure, followed by rapid depressurization. Supercritical CO_2 is nontoxic and it has the potential as an alternative for organic solvents (Vadnere, 2002).

1.1.4 Classification of solid dispersions

1.1.4(a) Simple eutectic mixture

Simple eutectic mixture can be obtained from the rapid solidification of the fused liquid of two components that show complete liquid miscibility and negligible solid□solid solubility. Upon cooling, the molten mixture forms a microfine dispersion of the two components with a concomitant decrease in the melting points of the two components (Chiou & Riegelman, 1971a; Craig, 2002). It was reported that chloramphenicol and paracetamol formed eutectic mixtures with urea (Sekiguchi *et al.* , 1964; Goldberg *et al.*,1966).

1.1.4(b) Solid solution

In this class, the drug and the carrier crystallize together in a homogeneous one-phase system, and the particle size of the drug is reduced to its molecular size (Chiou & Regielman,1971a). In other words, the dissolution of the drug in the carrier occurs in the solid state. Hence, this system would be expected to yield much higher rates of dissolution than simple eutectic systems. Examples include digitoxin, hydrocortisone acetate and prednisolone dispersions in polyethylene glycol 6000 (PEG 6000) (Chiou & Riegelman, 1971b). In practice, the occurrence of solid solubility of less than 2% is considered insignificant (Habib, 2000).

1.1.4(c) Amorphous precipitation in a crystalline carrier

The active ingredient in some solid dispersions may precipitate out as an amorphous deposit in the crystalline carrier, such as the dispersion of sulfathiazole in urea (Chiou & Riegelman, 1971a; Ford, 1986). In amorphous materials, molecules are randomly arranged, in contrast to crystalline materials where the molecules are arranged in an ordered three-dimensional array (Martin *et al.*, 1993).

1.1.4(d) Glassy solutions or suspensions

Amorphous polymers, such as polyvinylpyrrolidone (PVP), can form glassy systems in which the drug is dispersed either as molecules or as particles (Craig, 2002). The glassy material is characterized by transparency and brittleness below the glass transition temperature, and the lattice energy of a glass solution is less than that of a solid solution. On heating, a glassy material softens progressively and continuously without a sharp melting point. Taylor and Zografi (1997) reported that indomethacin and polyvinylpyrrolidone (PVP) formed a glass solution.

1.1.4(e) Compound or complex formation

This system is characterized by complexation of two components in a binary system during solid dispersion preparation. For example, it was reported that digoxin and hydroquinone formed a complex which exhibited a high dissolution rate (Bochner *et al.*, 1977).

1.1.5 Characterization of solid dispersions

Several methods have been used to characterize solid dispersions, such as differential scanning calorimetry (DSC), X-ray diffraction (XRD), infrared

spectroscopy (IR), hot stage and electron microscopy, and dissolution testing. Among these, thermal and spectral methods (i.e. DSC, XRD and IR) are of special interest. The main purpose of using these methods is to differentiate between crystalline and non-crystalline structure of solid dispersions.

1.1.5(a) Differential scanning calorimetry

When a material is heated or cooled, there is a change in its structure (e.g. melting or crystallization), or its composition (e.g. oxidation). These changes are connected with heat exchange. Some of these changes are endothermic (i.e. heat consuming process such as melting), and others are exothermic (i.e. heat producing process such as crystallization) (Clas *et al.*, 2002). Differential scanning calorimetry (DSC) is used for measuring the differences in heat flow between a sample and a reference during a controlled change of temperature. DSC analysis allows quantitative and qualitative information to be obtained about the physical and chemical changes that occur in the sample. DSC is used extensively in pharmaceutical industry to determine the melting points, purity, and glass transition temperatures of materials (Souillac & Rytting, 1999). In the solid dispersion area, DSC is a powerful tool in evaluating the drug-carrier interactions, determining the solubility of a drug in a polymeric carrier, detecting polymorphic modifications and examining age-induced changes (Ford & Timmins, 1989). The absence of the drug melting peak in the DSC thermal profile of a solid dispersion indicates that the drug is dispersed molecularly, or it exists in the amorphous form. Moreover, since polymorphs generally have different melting points, DSC can be used to detect polymorphism. This property is extremely important when long-chain organic compounds are studied, because nearly all these compounds

exhibit polymorphism (Martin *et al.*, 1993). Figure 1.1 shows a diagram of a DSC system, and a typical thermal profile of a material that undergoes glass transition, recrystallization and meting.

1.1.5(b) X-ray diffraction

Diffraction of X-rays is the basic technique for obtaining information on the atomic structure of crystalline solids. The phenomenon of X-ray diffraction by crystals results from a scattering process in which X-rays are scattered by the electrons of the atoms without change in wavelength (Balta-Calleja & Vonk, 1989). The crystallinity in a sample is reflected by a characteristic fingerprint region in the diffraction pattern. In a solid dispersion, the crystallinity in the drug can be separately identified from crystallinity in the carrier by using the X-ray diffraction. Therefore, it is possible to differentiate between solid dispersions in which the drug is molecularly dispersed, and solid dispersions in which the drug is present in the crystalline form. However, crystallinities of under 5-10% cannot generally be detected with X-ray diffraction (Leuner & Dressman, 2000).

1.1.5(c) Fourier transformed infrared spectroscopy

Fourier transformed spectroscopy is widely used because of its rapid providing of high resolution spectra with samples in the nanogram range (Ikan & Crammer, 1987). Structural changes and lack of crystal structure can lead to changes in bonding between functional groups which can be detected by infrared spectroscopy. Since not all peaks in the IR spectrum are sensitive to crystalline changes, it is possible to differentiate between those that are sensitive to changes in crystallinity and those that are not (Leuner & Dressman,

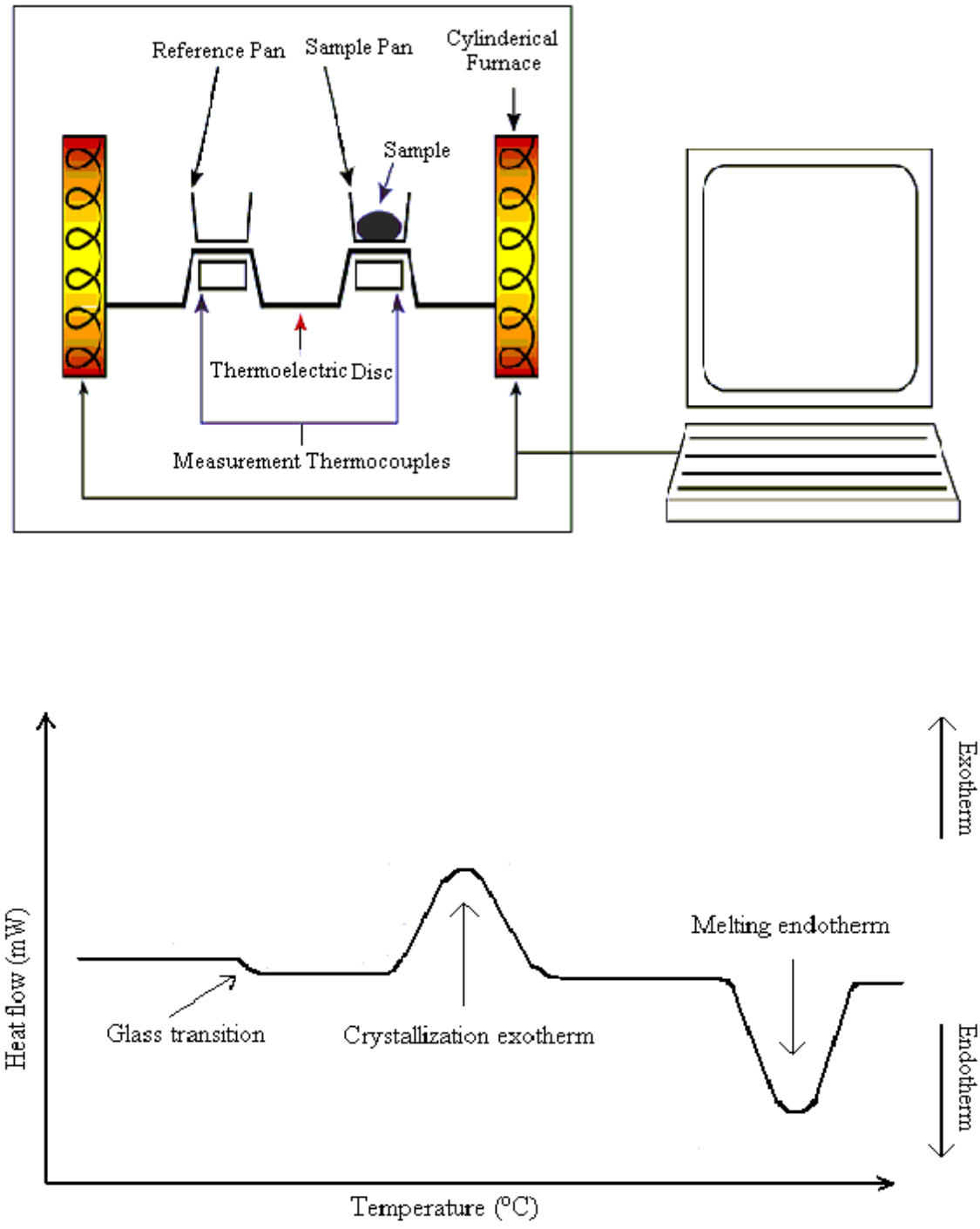

Figure 1.1 Diagram of a DSC system (top), Typical thermogram (below).

2000; Taylor & Zografi,1997).

1.1.6 Advantages of solid dispersions

1.1.6(a) Increased dissolution rate

The fact that more than 40% of newly discovered drugs have little or negligible water solubility presents a serious challenge to the successful development and commercialization of new drugs in the pharmaceutical industry (Connors & Elder, 2004). Solubility and permeability are the main factors that control oral bioavailability of a drug substance. Generally, when the drug solubility in water is less than 10 mg/ml, dissolution is the rate-limiting step in the process of drug absorption (Habib, 2000).

Factors influencing drug dissolution rate in aqueous solution are described in Noyes-Whitney equation:

$$\frac{dC}{dT} = AD(C_S - C)/h \qquad (1.1)$$

where dC/dT is the rate of dissolution, A is the surface area available for dissolution, D is the diffusion coefficient of the drug, C_s is the solubility of the drug in the dissolution medium, C is the concentration of drug in the medium at time t and h is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving drug (Leuner & Dressman, 2000). According to this equation, dissolution rate can be increased through increasing the surface area, and this can be achieved through reducing the particle size.

Different methods have been used to reduce the particle size, such as micronization, recrystallization, freeze drying and spray drying. Micronization of poorly soluble drugs by milling has been used for many years in the pharmaceutical industry in order to enhance the dissolution rate of those drugs. For example the dissolution rate of micronized spironolactone was higher than that of the standard form (McInnes *et al.*, 1982). However, fine particles may not always produce the expected faster dissolution. This primarily results from the aggregation and agglomeration of fine particles. In addition, poor wettability of fine powders may reduce the dissolution rate (Bloch & Speiser, 1987; Rippie, 1986).

Solid dispersion techniques have been used to enhance the dissolution rate of many poorly water soluble drugs. Particle size reduction and reduced agglomeration would both increase the exposed surface area of the drug. When solid solutions or amorphous precipitations are formed, particle size of the active ingredient is reduced to the minimum level. In addition, the carrier material may contribute to increasing the dissolution rate through its solubilizing and wettability-enhancing properties. It was reported that urea increased the dissolution rate of chlorpropamide incorporated into urea, through its solubilizing properties (Ford & Rubenstein, 1977). The enhancement in dissolution rate as a result of solid dispersion formation, relative to pure drug, varies from as high as 400-fold to less than two-fold (Vadnere, 2002).

1.1.6(b) Enhanced oral bioavailability

Drug dissolution is a prerequisite to drug absorption and in vivo effectiveness for almost all drugs given orally (Antal, 2001). This can be explained by Fick's

first law which describes the diffusion of a substance through a membrane:

$$\frac{dm}{dt} = -DA\ \frac{dc}{dx} \qquad (1.2)$$

where dm/dt is the diffusion rate, D is the diffusion constant, A is the membrane surface area, dc is the change in concentration, and dx is the membrane thickness. From this law, it can be inferred that the drug flux through the intestinal wall, during the diffusion process, is directly proportional to the concentration gradient between drug in the gut and drug in the blood (Stavchansky & McGinity, 1990). This may explain why poorly soluble drugs are represented very often by low absorption and poor bioavailability (Bloch & Speiser, 1987). Many studies indicated that increased dissolution rate of poorly soluble drugs, from their solid dispersions, led to an improvement in the oral bioavailability of those drugs. Examples include, but not limited to, phenytoin dispersions in polyethylene glycol 4000 (PEG 4000) (Yakou *et al*., 1984), nitrofurantoin dispersions in polyethylene glycol 6000 (PEG 6000), polyvinylpyrrolidone (PVP) and mannitol (Ali & Gorashi, 1984), digitoxin dispersions in deoxycholic acid (Reddy *et al*., 1976), tolbutamide dispersions in polyvinylpyrrolidone (PVP) (Sekikawa *et al*., 1979), sulfamethoxazole dispersions in polyvinylpyrrolidone (PVP) (Sekikawa *et al.*, 1982) and dicumarol dispersions in polyvinylpyrrolidone (PVP) (Sekikawa *et al.*, 1983). The aforementioned examples, and many others, show the importance of solid dispersion techniques as a mean of increasing the oral bioavailability of poorly water-soluble drugs. Moreover, the enhanced bioavailability of some drugs, formulated in solid dispersions, has led to a reduction in the therapeutic dose of those drugs. For example the dose of reserpine, dispersed in polyvinylpyrrolidone (PVP), was reduced to one third of its usual value (Stupak & Bates, 1972); similarly, the dose

of griseofulvin, dispersed in polyethylene glycol (PEG), was reduced from 500 mg to 250 mg (Barrett & Bianchine, 1975).

1.1.7 Limitations of solid dispersions

Despite an active research interest, the commercial application of solid dispersion in dosage form design has been very limited. Only two products, griseofulvin in polyethylene glycol and nabilone in polyvinylpyrrolidone solid dispersions, were marketed during the three decades following the initial work of Sekiguchi and Obi in 1961 (Serajuddin,1999).

Main problems limiting the commercial application of solid dispersion involve (a) the physical and chemical stability of drugs and vehicles, (b) method of preparation, (c) reproducibility of its physicochemical properties, (d) its formulation into dosage forms, and (e) the scale-up of manufacturing processes.

1.1.7(a) Stability

Physical instability of solid dispersions such as phase separation and subsequent crystallization may reduce the dissolution rate of the active ingredients. Since many solid dispersions contain amorphous or molecularly dispersed drugs, they are often susceptible to crystallization during storage (Ford, 1986). Similarly, certain carriers may exist in thermodynamically unstable states in solid dispersions and undergo changes with time (Serajuddin, 1999). Andronis *et al.* (1997) reported that moisture might facilitate the crystallization of amorphous drugs, and for this reason solid dispersions should be protected from moisture. Various studies reported reduced dissolution rates of drugs, incorporated into solid

dispersions, upon ageing. Solid dispersion systems such as chlorpropamide-urea, indomethacin-polyethylene glycol 6000, and phenylbutazone-polyethylene glycol 6000 showed reduced dissolution rates of active ingredients on storage (Ford & Rubinstein, 1981; Ford & Rubinstein 1979; Khalil & Mortada, 1978).

1.1.7(b) Method of preparation

When fusion method is used, high melting temperature may chemically decompose drugs and/or carriers. On the other hand, total removal of toxic organic solvents used in the preparation of the dispersions is the main problem associated with the solvent method. Hence, the extrusion method provides a good alternative to the fusion and solvent methods.

1.1.7(c) Reproducibility of physicochemical properties

Manufacturing conditions may greatly influence the physicochemical properties of solid dispersions (Franco *et al.*, 2001). Various investigators observed that heating rate, maximum temperature used, holding time at a high temperature, cooling method and rate and method of pulverization might affect the properties of solid dispersions prepared by the melting method including the particle size distribution. In addition, the nature of solvent used, ratio of drug/solvent or carrier/solvent, as well as the rate and method used to evaporate the solvent may significantly influence the physicochemical properties of solid dispersions formed (Serajuddin, 1999).

1.1.7(d) Dosage form development

Pulverizing, sieving, mixing and compressing of solid dispersions, which are usually soft and tacky, are difficult. This may reduce the chance of developing suitable solid dosage forms of drugs dispersed in solid dispersions.

1.1.7(e) Scale-up of manufacturing processes

The physicochemical properties and stability of solid dispersions may be affected by scale-up processes because heating and cooling rates of solid dispersion prepared in a large scale may differ from that of a small scale. It is also expensive and not practical to evaporate hundreds and even thousands of liters of organic solvents to prepare solid dispersions for kilogram quantities of drugs (Serajuddin, 1999).

1.2 Gelucires

1.2.1 Definition

The utility of lipid-based oral formulations has been recognized for many years (Porter & Charman, 2001). Gelucires are a family of lipid-based excipients comprising glycerides and esters of polyethylene glycol (PEG), these two components conferring hydrophobic and hydrophilic properties to the vehicle. Each Gelucire is characterized by two numbers, the first referring to the nominal melting point of the base and the second to the HLB value (Craig, 1995). Gelucires come in a variety of grades with different melting points (from 33 ºC to 65 ºC) and HLB values (from 1 to 14). Gelucires are described under lauroyl macrogolglycerides monograph in the British Pharmacopoeia (BP, 2005).

1.2.2 Pharmaceutical applications of Gelucires

The wide range of materials within the Gelucires group results in a wide range of properties, particularly in terms of melting/crystallization behavior and hydrophobicity. Consequently, it is possible to choose the Gelucire according to the particular formulation requirement, either in terms of manufacturing method or the rate of drug release (Craig, 1995). Different rates of drug release can be obtained by mixing the same active substance with Gelucires of different melting points and HLB values (Howard & Gould, 1987). Table 1.2 shows different applications of different Gelucires.

Table 1.2 Pharmaceutical uses of some Gelucires.

Types of gelucires	Uses
Gelucire 33/01, Gelucire 39/01, Gelucire 43/01	Vehicle, oily phase for ointment.
Gelucire 44/14	Emulsifier for solid and semi solid self-microremulsifying drug delivery systems, bioavailability enhancer.
Gelucire 50/13, Gelucire 53/10	Hydrophilic glyceride for semi-solid formulations.
Gelucire 50/02, Gelucire 50/13, Gelucire 54/02, Gelucire 70/02	Coating and matrix agents for sustained release formulations.

1.2.3 Gelucire 44/14

Gelucire 44/14 is an inert semi-solid waxy material, which is amphiphilic in nature. It has unique emulsifying properties that make it ideal for prompt release formulations. The suffixes 44 and 14 refer to its nominal melting point and HLB value respectively.

1.2.3(a) Chemical composition

Gelucire 44/14 is prepared from the reaction of hydrogenated palm kernel oil with polyethylene glycol 1500 (PEG 1500). Its composition is approximately:

- 20% mono-, di- and triglycerides,
- 72% mono- and di- fatty acids esters of PEG 1500,
- 8% free PEG 1500.

Table 1.3 shows the fatty acid distribution in Gelucire 44/14.

Table 1.3 Fatty acid distribution in Gelucire 44/14 (Gattefossè, 2001)

Caprylic acid C8	Capric Acid C10	Lauric acid C12	Myristic acid C14	Palmitic acid C16	Stearic Acid C18
4–10%	3–9%	40–50%	14–24%	4–14%	5–15%

Because of its unique balance of short, medium and long chain fatty acids, Gelucire 44/14 forms an exceptionally stable fine dispersion when in contact with the gastrointestinal fluids (Roussin & Laforet, 1997).

1.2.3(b) Pharmaceutical applications of Gelucire 44/14

Numerous drugs have been formulated with Gelucire 44/14. Solubilization properties and low melting point of Gelucire 44/14 make it a suitable carrier for many poorly water–soluble drugs. Drugs dispersed in Gelucire 44/14, alone or in a mixture with other excipients, showed enhanced solubility and dissolution, for example, UC–781 (thiocarboxanilide derivative) (Damian *et al.*, 2000), DMP 323 (protease inhibitor drug) (Aungst *et al.*, 1997), REV 5901 (5-lipoxygenase inhibitor) (Serajuddin *et al.*, 1988), temazepam and triamterene

(Dordunoo *et al.*, 1991). Moreover, improved oral bioavailability of drugs dispersed in Gelucire 44/14, alone or in a mixture with other excipients, has also been reported. Examples include α-tocopherol (Barker *et al.*, 2003), albendazole (Savio *et al.*, 1998), REV 5901 (Sheen *et al.*, 1991), piroxicam (Yuksel *et al.*, 2003), halofantrine (Khoo *et al.*, 2000), PG301029 (antiviral agent) (He *et al.*, 2005) and flurbiprofen (Soliman & Khan, 2005).

Reduced drug particle size, increased wettability of drug particles, emulsifying properties of the carrier, lymphatic drug transportation and enhanced drug permeability are among the proposed mechanisms underlying the improved bioavailability of drugs dispersed in Gelucire 44/14 (Serajuddin *et al.*, 1988; Hauss *et al.,*1998; Saha & Kou, 2000).

1.3 Fenofibrate

1.3.1 Introduction

Fibric acid derivatives (fibrates) play an important role in the management of hyperlipidemia. Indeed, they are among the most effective agents available for lowering serum triglycerides (Penn *et al.,* 2006*)*. Clofibrate, the first member of this group, was described in 1962. Subsequently, gemfibrozil, fenofibrate, bezafibrate and ciprofibrate were introduced. Fenofibrate was launched in 1975 in a conventional formulation; while micronized and supra-bioavailable formulations were developed in 1990 and 2001 respectively.

1.3.2 Description

Fenofibrate, 2 - [4 - (4 - chlorobenzoyl) phenoxy] - 2 - methyl - propanoic acid 1-methyethylester, has a molecular weight of 360.84 and it is hydrophobic in nature (log P=5.24). Having low solubility and high permeability, fenofibrate is considered as a Class II drug according to the Biopharmaceutics Classification System (Granero *et al.*, 2005). Fenofibrate exists in the form of white or almost white, crystalline powder. It is practically insoluble in water, very soluble in methylene chloride and slightly soluble in alcohol (BP, 2005). It has a melting point of 79-82 ºC. Figure 1.2 shows the chemical structure of fenofibrate and fenofibric acid.

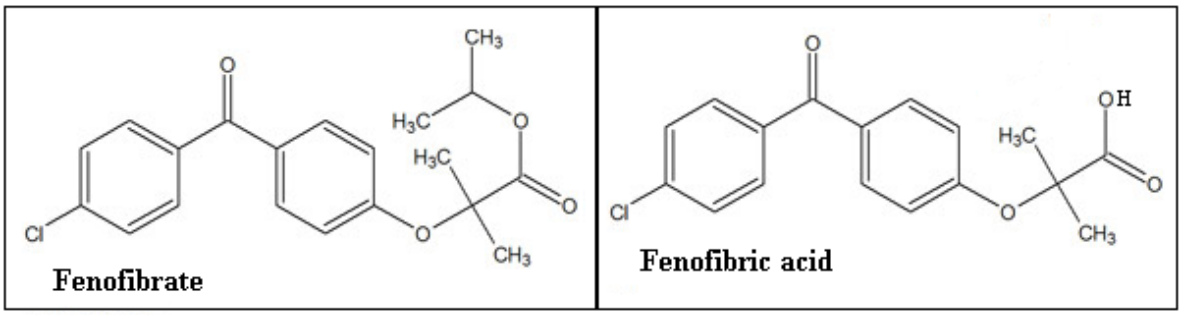

Figure 1.2 The chemical structure of fenofibrate and fenofibric acid.

1.3.3 Clinical pharmacology

The lipid-modifying effects of fenofibric acid, the active metabolite of fenofibrate, are characterized by a reduction in low density lipoprotein cholesterol (LDL-C) and total cholesterol (TC) levels, a marked reduction in plasma triglycerides (TG) levels and an increase in high density lipoprotein cholesterol (HDL-C) levels (Adkins & Faulds, 1997). Fenofibric acid appears to have a wide range of effects on the synthetic and catabolic pathways of cholesterol and triglyceride metabolism (Najib, 2002).

Fenofibric acid is a potent synthetic activator of the peroxisome proliferator-activated receptor alpha (PPARα) and it is believed that most of its effects are mediated by this receptor. Activation of PPARα increases the ratio of apoprotein apo C-II, an activator of lipoprotein lipase, to apoprotein apo C-III, an inhibitor of lipoprotein lipase. As a result, lipolysis and elimination of triglyceride-rich particles from plasma is increased. In addition, activating PPARα induces an increase in the expression of apolipoprotein-AI and apolipoprotein-AII, which are the major protein constituents of HDL-C. This may explain the mechanism by which fenofibric acid increases the HDL-C levels (Kersten *et al.*, 2000; Mahley & Bersot, 2001).

Potential beneficial nonlipid effects of fenofibric acid include reductions in spontaneous platelet aggregation and plasma fibrinogen, and a reduction in serum uric acid levels (Balfour *et al*, 1990; Guay, 1999).

1.3.4 Pharmacokinetic properties

Fenofibrate is a prodrug, which after absorption is hydrolyzed to its active metabolite, fenofibric acid (Balfour *et al.*, 1990). A study using radiolabeled fenofibrate showed that only fenofibric acid was found in the plasma and no unchanged fenofibrate could be detected (Benedetti *et al*., 1986). Fenofibric acid is extensively bound to plasma albumin (~99%), The plasma half-life is about 20 hours, which allows a once daily dosage regimen (Adkins & Faulds, 1997). Fenofibric acid is excreted predominantly in the urine, mainly as the glucuronide conjugate, but also as a reduced form of fenofibric acid and its glucoronides. Based on urinary excretion data, oral bioavailability of standard

fenofibrate, under fasting conditions, was estimated to be 30% (Desager & Harvengt, 1978). However, taking fenofibrate in its standard formulation during a meal increases its oral bioavailability to 60% (Munoz *et al*., 1994).

1.3.5 Fenofibrate formulations with enhanced bioavailability

Since the aqueous solubility of fenofibrate is less than 0.5 mg/l (Law *et al.*, 2003), its dissolution may represent the rate-limiting step in the oral absorption of the drug. Conventional formulations that incorporate unmilled or non-micronized forms of fenofibrate have incomplete or slow dissolution. Furthermore, these conventional formulations exhibit low and/or variable oral bioavailability. One approach in producing pharmaceutically acceptable fenofibrate formulations involves the use of micronization technique. U.S. Pat. No. 4,895,726 (Curtet *et al.*, 1990) disclosed a method of improving the dissolution, and consequently, the bioavailability of fenofibrate. According to this patent, fenofibrate powder is co-micronized with a solid wetting agent. Sodium lauryl sulfate is described as the solid wetting agent of choice. The bioavailability of fenofibrate was significantly improved over the non-micronized form. Moreover, it was found that 67 mg of the new formulation gave the same absorbed amount as did 100 mg of the conventional formulation. As a result, the daily dose of fenofibrate was reduced from 300 mg, of the standard form, to 200 mg of the micronized form (Guichard & Sauron, 1993).

In another attempt to increase fenofibrate oral bioavailability, a suprabioavailable formulation was developed and introduced to the market in 2001. The formulation combines the micronization technology with a new micro-coating process. The formulation is prepared by coating micronized fenofibrate particles directly onto an

inert excipient core (Figure 1.3). As a result, the micronized fenofibrate particles are immediately exposed to the dissolution medium and a significant increase of the dissolution rate from the tablet is obtained. By using this technique, the oral bioavailability of fenofibrate could be increased by 25%. Therefore, a dose of 160 mg of the new suprabioavailable tablet is sufficient to give plasma levels equivalent to those previously achieved by a dose of 200 mg of the micronized fenofibrate capsule (Guichard *et al.*, 2000).

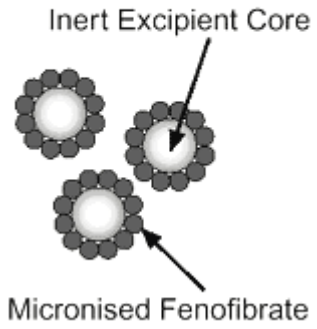

Figure 1.3 Fenofibrate suprabioavailable formulation

1.4 Summary and scope of the study

Solid dispersions provide a simple and effective method of increasing solubility and oral bioavailability of poorly water-soluble drugs. More specifically, solid dispersions prepared with self-emulsifying carriers, such as Gelucire 44/14, are of a special interest due to their unique properties. Hence, the present study was carried out to investigate the utility of Gelucire 44/14 for formulating solid dispersions of fenofibrate with aim of enhancing its oral bioavailability. Previous techniques used to improve the oral bioavailability of fenofibrate, such as co-micronization and microcoating, are

time-consuming and/or costly. Simple melt-fusion technique, as employed in this study, offers a more economical means of producing fenofibrate, with enhanced oral bioavailability, in a solid dispersion dosage form.

This study was conducted in stages with the following objectives:

1. To prepare and characterize fenofibrate-Gelucire 44/14 solid dispersions.
2. To develop a new formulation of fenofibrate with increased dissolution rate.
3. To develop a simple HPLC method for analysing fenofibric acid in plasma.
4. To compare the oral bioavailability of fenofibrate in the developed formulation with that of micronized fenofibrate.