Department of Pharmaceutical Sciences, School of Pharmacy, Texas Tech University Health Science Center, Amarillo, USA

Preparation and *in vitro* characterization of a semi-solid dispersion of flurbiprofen with Gelucire 44/14 and Labrasol

M. S. SOLIMAN, M. A. KHAN

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Mansoor A. Khan, R. Ph., Ph. D., Director, FDA/CDER/DPQR, HFD-940, 10903 New Hampshire Avenue, Life Sciences Building 64, Silver Spring, MD 20903, USA (current address)
Khanm@cder.fda.gov

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Flurbiprofen is characterized by low solubility in water and has been implicated in causing gastro intestinal ulceration. The purpose of this study was to increase the dissolution characteristics of flurbiprofen by preparing a semi-solid dispersion with Gelucire 44/14 and Labrasol (F1) in hard gelatin capsules. The results were evaluated by comparing several *in vitro* parameters with powdered drug filled into hard gelatin capsules. The *in vitro* dissolution testing of the dosage forms was performed in different media (simulated gastric fluid, pH 1.2; citrate buffer pH 4.5; phosphate buffers pH 6.8 and 7.2, and water). Characterization of semi-solid dispersions and physical mixtures was performed using Fourier transform-infrared spectroscopy (FT-IR), Differential scanning calorimetry (DSC), particle size analysis and turbidity measurement. The results suggest that all semi-solid dispersions of flurbiprofen showed a remarkable improvement in the rate and extent of drug dissolution. The dissolution of F1 exhibited significant improvement in all dissolution media at different pH. The dissolution of flurbiprofen within 30 min in pH 1.2 was (55%), in pH 4.5 67%, pH 6.8 96%, pH 7.2 98% and in water 88%. FT-IR indicated no strong drug: excipient interactions, and DSC studies indicated a loss of crystalline nature of the drug. The particle size analysis revealed an average size diameter from 194 to 278 nm. Therefore, a semi-solid dispersion of flurbiprofen with Gelucire and Labrasol may have the potential of improved bioavailability because of the enhanced *in vitro* properties.

1. Introduction

Flurbiprofen is a potent nonsteroidal anti-inflammatory drug, indicated for the treatment of rheumatoid arthritis and osteoarthritis, arthralgia, ankylosing spondylitis, and other related conditions (Brogden et al. 1979). It has a short elimination half-life of 3.9 h and is slightly soluble in water. Since the rate of flurbiprofen absorption is controlled by the release of drug from its dosage form into the gastrointestinal tract, the enhancement solubility and dissolution of flurbiprofen have obvious practical significance of enhancing the bioavailability.

Recently, considerable attention has been focused on the improvement of solubility and bioavailability of poorly water-soluble drugs given orally. Techniques have been used to improve the oral bioavailability of these drugs by enhancing their solubility in water and in biological fluids at physiological pH values. The most popular approaches are the incorporation of drugs into inert lipidic vehicles such as oils, surfactant dispersions, and self-emulsifying formulations (Gershanik et al. 2000; MacG regor et al. 1997; Humberstone et al. 1997). Preparation of solid dispersions of drugs with polymers (Chiou et al. 1971; Tantishaiyakul et al. 1999; Bhattacharyya et al. 1993; Fernadez et al. 1993), and inclusion complexes of cyclodextrin enhanced the oral bioavailability of poorly water soluble drugs (Kimura et al. 1997; Masaki et al. 1982). Gelucire excipients have been used in the formulation of semi-solid dispersions (Baykara et al. 1991; Gattefosse 1999; Crison et al. 1997). However, no such preparations have been reported for flurbiprofen to enhance its solubility and dissolution. Gelucires are solid waxy materials that are amphiphilic in character and identified by two values: their melting points and their HLB (hydrophilic-lipophilic balance) values. Gelucires are a family of lipid-based excipients comprising of saturated polyglycolized glycerides consisting of mono-, di-, and tri-glycerides and of mono- and di-fatty acid esters of polyethylene glycol. The nature and proportion of each component are specific to a given grade of gelucire. Gelucire 44/14 is a semi-solid excipient from this group. It is characterized by two numbers, the first indicates a nominal melting point of 44 °C and the second to the hydrophile-lipophile balance (HLB) value of 14 (Gattefosse 1999; European Pharmacopoeia 2002). This number reflects the proportion of water soluble to lipid soluble moieties in each material (Craig et al. 1995). Gelucire 44/14 is composed largely of esters of lauric acid (Craig et al. 1995). Gelucire forms a microemulsion system upon contact with water and appears to lead to enhancement of the solubility and absorption of drugs (Barker et al. 2003; Itoh et al. 2002). Labrasol, of the same chemical nature as Gelucires, is a clear liquid surfactant with an HLB value of 14 (European Pharmacopoeia, 2002).

A number of studies have investigated the *in vitro* and *in vivo* release characteristics of drug dispersions in Gelucire alone and in combination with other bases. These include the studies by Nilufer et al. (2003) whereby Gelucire was used in combination with Labrasol in enhancement the solubility and bioavailability of piroxicam as a semi-solid dispersion. Dennis et al. (1990) used a combination of Gelucire 50/13 and 50/02 as a means of formulating the poorly water-soluble drug ketoprofen, while Green et al. (1999) utilized Gelucire 50/13 in combination with Carbopl 974P to deliver nicotine to the colon for the treatment of ulcerative colitis. Barker et al. (2003) investigated the structure and bioavailability of α-tocopherol dispersions in Gelucire 44/14. However, for reasons that have not yet been elucidated, Gelucire 44/14 appears to promote rapid drug release and bioavailability. This is exemplified by the studies of Dordunoo et al. (1991) who reported increases in the dissolution rate of temazepam and triamterene when formulated in Gelucire 44/14 compared to polyethylene glycol dispersions. Similarly, Serajuddin et al.(1988) showed improved dissolution of a poorly soluble drug, [α-pentyl-3-(2-quinolinylmethoxy) benzenemethanol], when dispersed in Gelucire 44/14 compared to polyethylene glycols. Studies have also indicated improved oral absorption of drugs dispersed in Gelucire 44/14 (Sheen et al. 1991; Pozzi et al. 1991; Aunget et al. 1997). For example, Aungst et al. (1997) reported marked improvements in the absorption in dogs of DMP 323 from a dispersion in Gelucire 44/14 compared to equivalent polyethylene glycol or polyethylene glycol/polyvinylpyrrolidine dispersions. Itoh et al. (2002) used Gelucire for the improvement of physicochemical properties of N-4472 by formulating it as self-microemulsifying system. Nurzalina et al. (2003) studied the influence of drug incorporation on the structure and release properties of solid dispersions in lipid matrices. El Massik, et al. (2003) using semi-solid matrix filled capsules for improving dissolution and stability of phenytoin sodium formulation. Seo et al. (2003) reported the preparation of agglomerates containing solid dispersions of diazepam by melt agglomeration in a high shear mixer.

In a preliminary study in our laboratory, the improvement of dissolution rate of flurbiprofen by using Gelucire and Labrasol was investigated and semi-solid dispersions of the drug were prepared with gelucire 44/14 and Labrasol in different ratios. The dispersion F1 containing 21.1% of Gelucire and 78.9% of Labrasol with 50 mg of flurbiprofen provided 55% dissolution of flurbiprofen within 30 min in pH 1.2, 67% in pH 4.5, 96% in pH 6.8, 98% in pH 7.2, and 88% in water.

The purpose of the present work was to investigate the *in vitro* performance of the semi-solid dispersions filled into hard gelatin capsules, and its characterization by FT-IR, DSC, particle size and turbidity.

2. Results and discussion

2.1. Particle size and turbidity

Well formulated lipid based systems are known to yield emulsion droplets when introduced into an aqueous environment. The nature and amount of the excipient used determine the overall quality of the emulsions obtained. Therefore particle size determinations were carried out to evaluate the dependency of surfactants Gelucire and Labrasol on emulsion droplet size.

Table 1 summarizes the composition of the semi-solid dispersions of flurbiprofen with different amounts of Gelucire and Labrasol. Table 2 shows the particle size with different compositions of Gelucire and Labrasol. From this table, the particle size of flurbiprofen semi-solid dispersion with Gelucire and Labrasol with its coefficient of variation indicate the formation of nanoemulsified system with water. This is in agreement with the α-tocopherol nanoemulsified systems with Gelucire 44/14 observed by Barker et al. (2003) and the emulsifying systems of N-4722 reported by Itoh et al. (2002). As seen in Table 2, all formulations are in the nanometer size range except F 10 which is in the micrometer size range. When the amount of Gelucire decreases and the amount of Labrasol is constant as in F2 to F4 the particle size increases, and also when the amount of Labrasol is decreased and the amount of Gelucire is constant as in F7 to F10 the particle size is increased. Therefore optimal levels of Gelucire and Labrasol are necessary to obtain low particle sizes. These systems tend to have lower interfacial tensions. As representative examples, the interfacial tensions observed with formulations F1, F2, and F5 had values of 33, 32.6, and

Table 1: Formulations of flurbiprofen semi-solid dispersion

Formula No	Drug	Gelucire	Labrasol
F1	50	80	300
F2	50	60	300
F3	50	40	300
F4	50	20	300
F5	50	–	300
F6	50	80	280
F7	50	80	260
F8	50	80	240
F9	50	80	200
F10	50	80	–

Table 2: Particle size and turbidity of flurbiprofen semi-solid dispersion

Formula No.	Mean diameter (nm) ± Cv	Turbidity (NTU)	% Release in 30 min
F1	194.3 ± 0.331	191	95.29
F2	194.6 ± 0.324	200	97.17
F3	206.4 ± 0.365	219	74.89
F4	215.4 ± 0.415	230	72.88
F5	191 ± 0.418	116.7	78.53
F6	218.7 ± 0.265	216	100.24
F7	253.2 ± 0.15	237	98.03
F8	257 ± 0.392	241	93.62
F9	216.3 ± 0.335	235	85.27
F10	5861.1 ± 0.998	600	33.81

n = 3

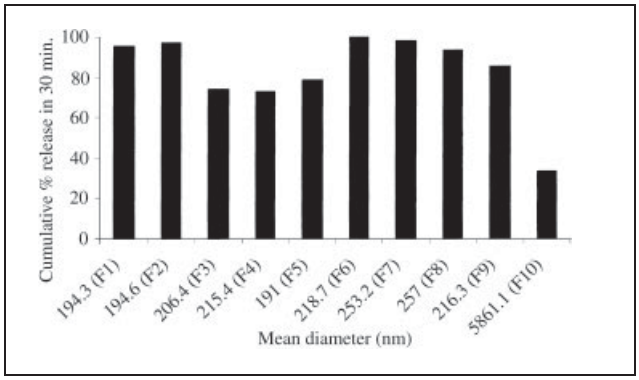

Fig. 1: Relationship between mean diameter of particle size and cumulative percent release of flurbiprofen formulations

32.5 dynes/cm (measured on Fisher semiautomatic model 21 tensiometers). When Labrasol was excluded from the system, the resultant droplets were in the micrometer size range (F10 has a size of 5861.1 nm ± 0.998) and the interfacial tension was found to be 34.5 dynes/cm. From Table 2, it can be seen by a careful observation that all formulations with nanometer particle size give a drug release of more than 72% after 30 min (t_{30} values) while F10 in micrometer size range give less drug release of about 30% after 30 min. For convenience, a representative figure was plotted to show the inverse relationship of particle size with dissolution Fig. 1.

Turbidity values have been reported to be of use in SNEDDS characterization by Nazal et al. (2002). In the turbidity measurement, the amount of scattered light (when an incident light is subjected to strike small particles) is measured and used in turbidity calculations as per the Rayleigh's theory (Pouton 1985). Light scattering by colloids conforms to Raleigh theory, which predicts that light scattering or measured turbidity τ in a simplified equation can be given by

$$\tau = K \cdot n \cdot v^2$$

in which K is a machine constant, v is particle volume and n is the number of particles (Pouton 1985). The measured turbidity of the formulations is given in Table 2. All formulations with particle sizes in the nanometer range have low turbidity as shown for F1 to F9 formulations except F10. The F10 formulation has a particle size in the micrometer range, and has a high turbidity. We can also notice a direct correlation between the particle size and turbidity as reported by (Pouton 1985). Fig. 2 shows the correlation between turbidity and dissolution rate.

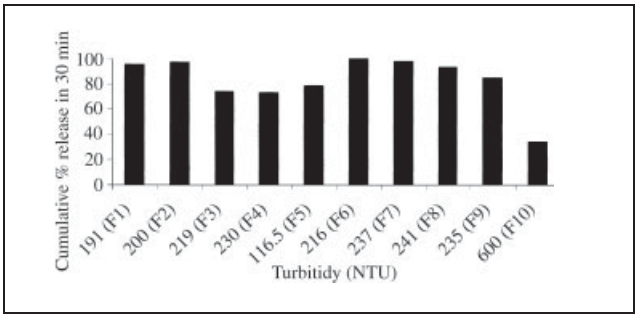

Fig. 2: Relationship between mean turbidity (NTU) and cumulative percent release of flurbiprofen formulations

2.2. Physicochemical characterization of semi-solid dispersions

The physical state of drugs in the polymer as semi-solid dispersion F1 was studied by FT-IR and DSC. Also the physical mixtures of drug with the same composition of F1 were tested with (FT-IR and DSC).

FT-IR spectrums are mainly used to determine if there is a molecular change of drugs due to interaction with its excipients such as polymers (Rosario et al. 2002). In the present investigation, the IR spectrum of flurbiprofen (Fig. 3) shows the characteristic peaks of flurbiprofen as stretching band of the carboxyl group around 1790 cm^{-1} and C–F stretching around 1220 cm^{-1}. A closer examination of the spectra of physical mixtures and semisolid dispersion reveals the disappearance or reduction of the carbonyl group at 1790 cm^{-1} indicating an interaction. These interactions appear to be weak and reversible due to the fact that flurbiprofen was recovered completely from the formulations when recovery and dissolution studies were performed. However, its implications in long term stability needs to be explained in future work.

Further indications about the crystalline status of the drug in a semi-solid dispersion formulation come from DSC. The DSC thermograms in the temperature range of 30–165 °C are shown in Fig. 4. DSC run of the pure drug exhibits a sharp endothermic peak around 117 °C, corresponding to the melting point at 114 and 117 °C. The dispersion of flurbiprofen as semi-solid dispersion and physical mixture with Gelucire and Labrasol resulted in a complete suppression of the drug fusion peak. This sug-

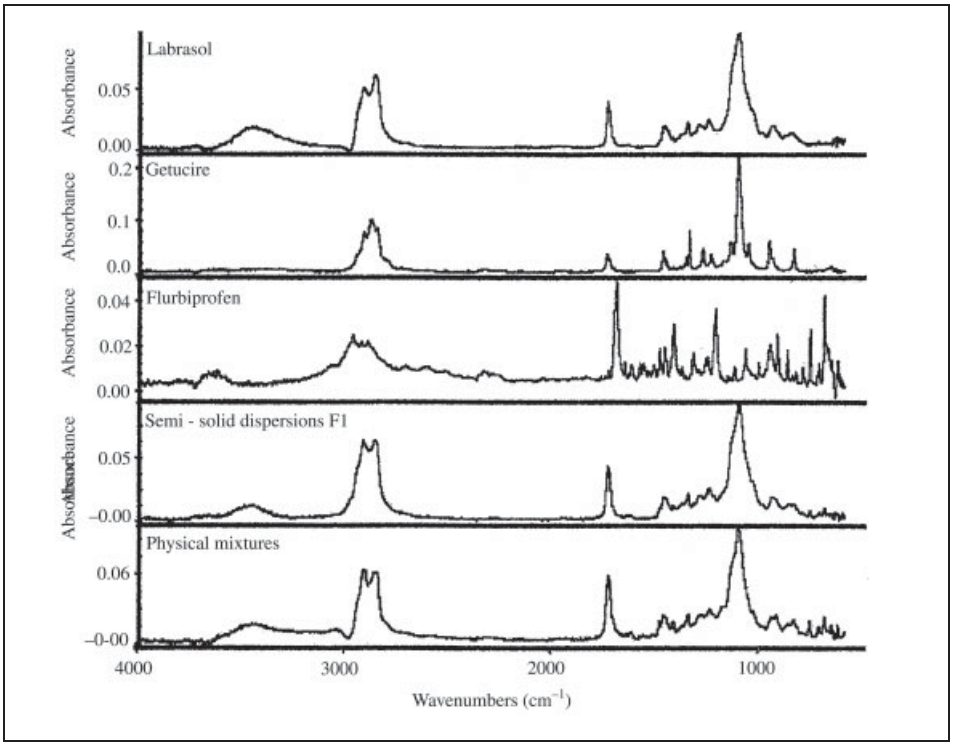

Fig. 3:
FT-IR spectra: (1) Labrasol: (2) Gelucire; (3) Flurbiprofen; (4) Semi-solid dispersion of F1; (5) Physical mixture of F1

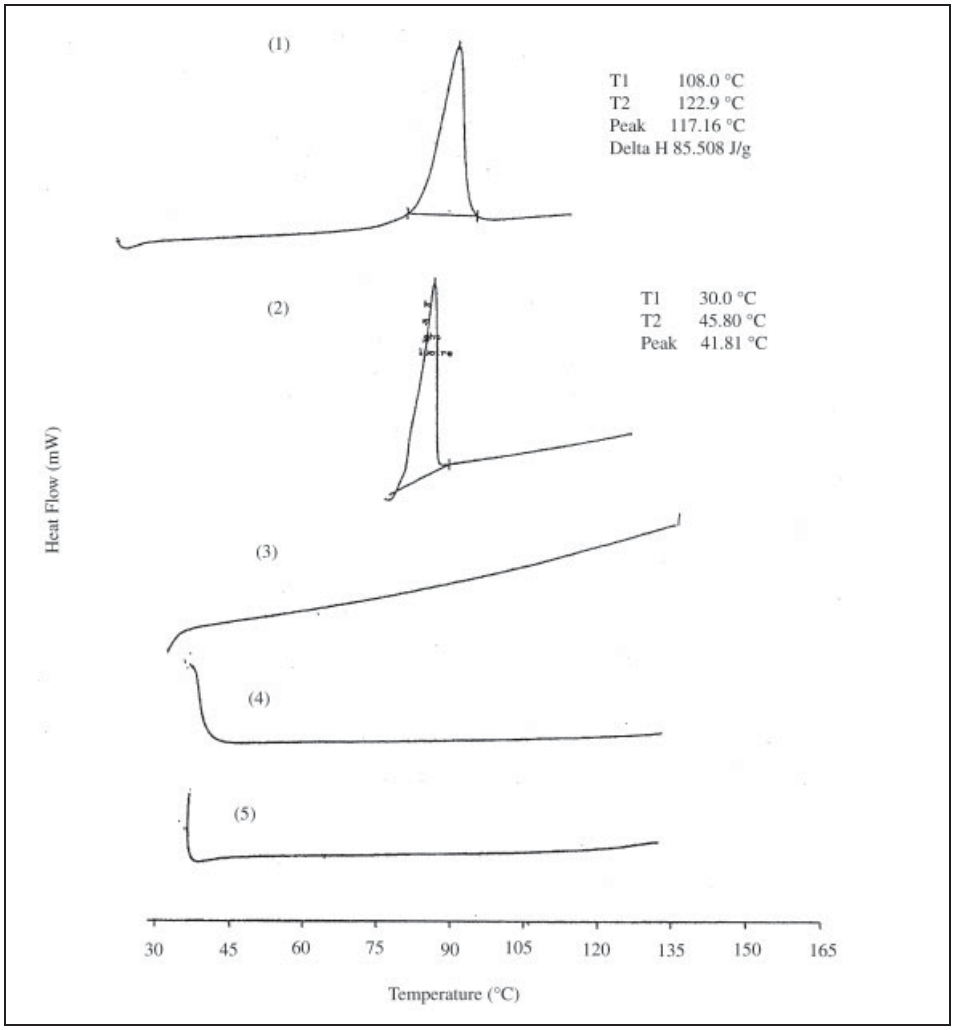

Fig. 4:
DSC thermograms: (1) Flurbiprofen; (2) Gelucire; (3) Labrasol; (4) Physical mixture of F1; (5) Semi-solid dispersion of F1

gests a homogeneous dissolution of the drug in polymer or due to its conversion to amorphous form both in the physical mixture and semisolid dispersion. The enhanced dissolution of flurbiprofen from the semisolid dispersions could be a consequence of thermodynamic changes as amorphous forms are known to be high energy forms with greatest solubility. Therefore, flurbiprofen appears to undergo a microcrystallization in the polymer which when contacted with water gives nano or microemulsions (Barker et al. 2003; Itoh et al. 2002).

2.3. Dissolution study

The dissolution of flurbiprofen F1 and plain drug was determined in media with different pH values. As seen in Fig. 5, pure flurbiprofen shows a pH-dependent and incomplete dissolution behavior as expected for acidic molecules. At low pH, flurbiprofen is expected to be nonionized with low aqueous solubility. Therefore the dissolution is less. At higher pH the drug is in ionized form and the dissolution is high. The dispersion of drugs in a semi-solid dispersion with Gelucire and Labrasol strongly influenced their dissolution rate. Pure flurbiprofen dissolution at pH 1.2, 4.5 and water was lower than the dissolution at pH 6.8 and 7.2. For the dispersion of flurbiprofen in Gelucire 44/14 and Labrasol as semi-solid dispersion F1, the dissolution in 30 min was more in different pH as compared to pure drug. These results are summarized as follows; The percentage release of plain flurbiprofen was 24 in pH 1.2, 30 in pH 4.5, 68 in pH 6.8, 60 in pH 7.2, and 31 in water. On the other hand, the percentage release of flurbiprofen from F1 semi-solid dispersion after 30 min in different media was as follows; 55 in pH 1.2, 67 in pH 4.5 , 97 in pH 6.8, 100 in pH 7.2 and 88 in water.

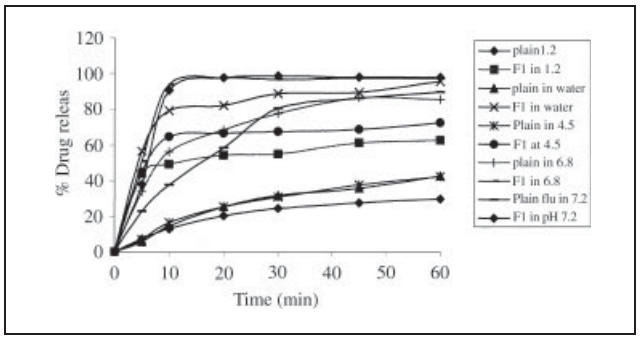

Fig. 5: Dissolution profiles of flurbiprofen from semi-solid dispersion and plain drug in different dissolution media

2.4. Effect of Gelucire and Labrasol on the dissolution of flurbiprofen

The effect of Gelucire on the dissolution of flurbiprofen can be understood clearly from Fig. 6. When the amount of Gelucire decreased and the amount of Labrasol was constant, the drug release decreased as shown in F2 to F5. Also as shown in Fig. 7, when the amount of Labrasol was decreased and the amount of Gelucire was con-

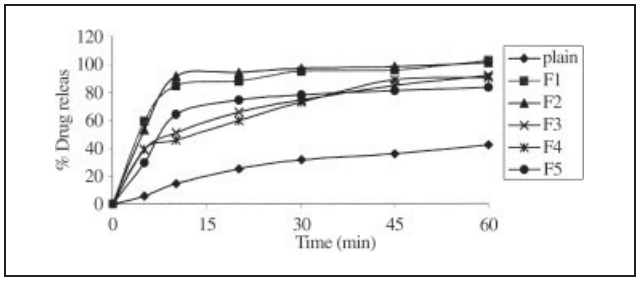

Fig. 6: Effect of Gelucire on dissolution of flurbiprofen semi-solid dispersion in water

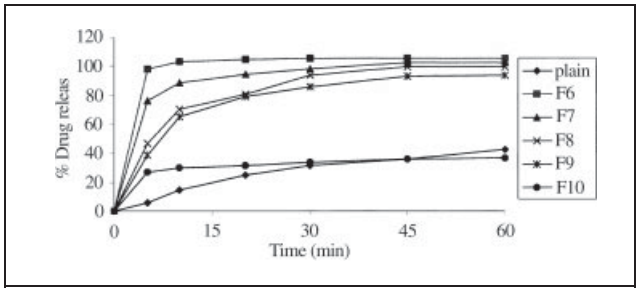

Fig. 7: Effect of Labrasol on dissolution of flurbiprofen semi-solid dispersion in water

stant, the drug release decreased as shown in F7 to F10. The F1 and F6 gave the best drug release among all formulae. Therefore, a proper ratio of Gelucire and Labrasol results in production of formulations in nano range particle size that gives the highest drug solubility and bioavailability.

2.5. Stability of capsules

The visual observation of capsules filled by the semi-solid dispersion showed after three months no effect on the integrity of gelatin capsule.

2.6. Conclusions

The present study has shown that it is possible to increase the dissolution rate of the poorly water-soluble drug flurbiprofen, by preparing a semi-solid dispersion with Gelucire and Labrasol filled in hard gelatin capsules. The preparations provided faster dissolution characteristics *in vitro* than the plain flurbiprofen. Gelucire and Labrasol were compatible with flurbiprofen as indicated by a lack of interaction by the FTIR studies. The preparation in general had low turbidity values and nano sized droplets upon exposure to water. A higher dissolution rate was obtained with F1 in all dissolution media used after 30 min indicating the formation of nano range particle size with the use of a proper ratio of Gelucire and Labrasol. This would be advantageous with regard to a rapid onset of action, especially in various painful conditions where an acute analgesic effect is desired.

3. Experimental

3.1. Materials

Flurbiprofen was obtained from BASF Corporation (Mount Olive, NJ). Gelucire® 44/14 (lauroyl macrogolglycerides) and Labrasol® (caprylocaproyl macrogolglycerides) were supplied by Gattefosse (Saint-priest Cedex, France). Hard gelatin capsules were provided by Shionogi Qualicaps (Whitsett, NC). All chemicals were used as received.

3.2. Methods

3.2.1. Preparation of semi-solid dispersions

Flurbiprofen was added to the molten base comprising Gelucire 44/14 and Labrasol at about 50 °C. The mixture was stirred and then poured into a plastic injector and volumetrically filled into hard gelatin capsules at a temperature close to the solidification point (about 30 °C) of the material. This would help prevent the precipitation of the solid drug in the molten vehicle. The contents of the semi-solid dispersions were filled into hard gelatin capsules.

3.2.2. Preparation of physical mixtures

Flurbiprofen 50 mg, Gelucire 80 mg and Labrasol 300 mg were mixed on a plate of glass and triturated well. The resultant mixture was stored in glass bottles.

3.2.3. Determination of particle size

The particle size of emulsions obtained with semi-solid dispersion was determined using a Nicomp Particle Sizing System Zw380 (Santa Barbara, CA). One milliliter of the sample was taken in a 6 mm × 50 mm disposable culture tube and the intensity was adjusted in order to obtain the particle size distribution. The volume diameter was obtained from the particle sizing system output. The data is given in Table 2.

3.2.4. Turbidity

Turbidity profiles of the capsules filled with semi-solid dispersion formulations given in nephlometric turbidity unit (NTU) were obtained by a Orbeco-Hellige Turbidimeter, Model 966 (Orbico Analytical System Inc., Farmingdale, NY). A low-pressure flow cell was used to allow direct turbidity measurements during dissolution. The instrument was carefully calibrated with formazin standards. Accuracy of the instrument is essential especially for small and diluted emulsions with high surfactant concentrations. Accuracy of the above turbidimeter, is approximately ± 0.01 NTU with stray light less than or equal to 0.01 NTU. Table 2 shows the data of particle size and turbidity.

3.2.5. FT-IR spectroscopy

IR spectra of pure drug, Gelucire, Labrasol, physical mixtures and semi-solid dispersions were obtained with a Thermo Nicolet NEXUS 470 FT-IR (Madison, WI.), using KBr disks. The scanning range used was 4000 to 500 cm^{-1} at a scan period of 1 min.

4.2.6. Differential scanning calorimetry

DSC was used to characterize the semi-solid dispersions and the physical mixtures. The equipment used was a Perkin-Elmer DSC 7. The instrument was calibrated using an indium standard. About 3–5 mg of samples were accurately weighed in small aluminum pans. The pans were covered with aluminum lids and then sealed. An empty aluminum pan similarly sealed was used as reference. The samples were heated from 30 to 150 °C at a rate of 10 °C per min in an atmosphere of nitrogen. After completion of the run, thermograms were normalized to 1 mg weight. Peak onset and heat of fusion (J/g) were recorded and the thermograms were plotted on a Hewlett-Packard recorder.

3.2.7. Dissolution testing

Dissolution studies of the semi-solid dispersions, and pure flurbiprofen in hard gelatin capsules were carried out in triplicate using USP Apparatus 2 (Vankel 7000). The dissolution media were 900 ml of water, 0.1 N HCl, acetate buffers at pH 4.5, and phosphate buffers at pH 6.8, 7.2. The paddle rotation speed was kept at 50 rpm. In all experiments, 3 ml of dissolution sample was withdrawn at 5, 10, 20, 30, 45 and 60 min and replaced with an equal volume of the fresh medium to maintain a constant total volume. Samples were assayed by UV spectrophotometry (GBC UV/Vis 918 at 247 nm). Cumulative percentages of the drug dissolved from the preparations were calculated.

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