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ORIGINAL ARTICLE

Formulation of immediate release pellets containing famotidine solid dispersions

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Abstract Famotidine (FM) is a potent H2-receptor antagonist used for the treatment of peptic ulcer. It has a low and variable bioavailability which is attributed to its low water solubility. In this study, the dissolution of the drug was enhanced by a preparation of solid dispersion using two hydrophilic carriers, namely Gelucire 50/13 and Pluronic F-127. The prepared solid dispersions were characterized by differential scanning calorimetry (DSC), which indicated that there were no signs of interaction of the drug with the carriers used in the case of solid dispersions containing higher polymeric contents (1:3 and 1:5). FM solid dispersions in the matrices of Gelucire 50/13 and Pluronic F-127 (1:3) were used to prepare pellets. The scanning electron microscope (SEM) images of pellets showed that the pellets have spherical shape and their size depends on the carrier used. The dissolution of the drug from either solid dispersion or pellets was performed. The dissolution study depicted that, the presence of the drug in solid dispersion enhanced its dissolution in comparison with the drug itself. Also, the drug release from the manufactured pellets was found to be improved in the case of solid dispersions (drug:carrier 1:3). A complete drug release occurred after 30 min from pellets containing solid dispersions, while only about 30% of the loaded FM was released from pellets containing untreated drug after 2 h.

1. Introduction

Solid dispersion technique was selected as it was utilized in a limited number of researches to increase the solubility of famotidine. Solid dispersion (SD) is defined as the dispersion of one or more active ingredients in inert carriers at solid state prepared by fusion, solvent, or solvent-fusion methods (Chiou and Riegelman, 1971; Ford and Rubinstein, 1978). It has been widely used to improve the dissolution rate, solubility and oral absorption of poorly water-soluble drugs (El-Badry and Fathy, 2005; El-Badry and Fathy, 2006; Douroumis et al., 2007; Thybo et al., 2007). In solid dispersions, the particle size

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of the drugs is reduced, the wetability and the dispersibility are enhanced; therefore, drug dissolution is improved markedly (Craig, 2002; Abdul-Fattah and Bhargava, 2002; Sethia and Squillante, 2004). Gelucire 50/13 and poloxamer 407 are among the several carriers which have been employed in preparing solid dispersions (Newa et al., 2008; Yassin et al., 2009). Gelucire is a family of vehicles derived from the mixtures of mono-, di- and triglycerides with polyethylene glycol (PEG) esters of fatty acids. These Gelucires are available with a range of properties depending on their hydrophilic-lipophilic balance (HLB) and melting point range (33–65 °C) (Sutananta et al., 1994; Ainaoui and Vergnaud, 1998). They have a wide variety of applications in pharmaceutical formulations as in the preparation of fast release and sustained release formulations (Ainaoui et al., 1997; Cavallari et al., 2005). Poloxamer 407 (P407), also known as Lutrol or Pluronic F127, belongs to the category of non-ionic surface active agent. It is polyoxyethylene–polyoxypropylene–polyoxyethylene block copolymer (Pluronics). It is used in the formulation of dosage forms owing to their low toxicity and ability to form a clear solution or gel in aqueous media (Alexandridis and Hatton, 1995). Pluronic F127 is also useful in the preparation of topical, rectal and ocular formulations (Dumortier et al., 2006; Chiappetta and Sosnik, 2007; Zhang et al., 2002; Ricci et al., 2005).

Famotidine (FM) is indicated for active and maintenance therapy of different types of ulcers and hypersecretory conditions. The mechanism of action, pharmacological effects, site of action, and clinical uses are the same as for the other H2-receptor antagonists, but on equimolar bases, it is reported to be about 7.5 and 20 times more potent than ranitidine and cimetidine, respectively, in inhibiting gastric acid secretion. However, it is relatively free of side effects despite its high potency (Burks, 1995; Page et al., 1997; Kadar, 1998). Famotidine reportedly undergoes minimal first-pass metabolism and its oral bioavailability in man has been reported to be low and variable (ranging from 40% to 50%) due to its poor aqueous solubility, high polarity, and gastric degradation (Hassan et al., 1990; Islam and Narurkar, 1993). Since for poorly water-soluble drugs (like famotidine) the dissolution rate is often the rate-limiting step for bioavailability, the dissolution rate is a function of the solubility and the surface area of the drug. Thus, dissolution rate will increase if the solubility of the drug is increased, and it will also increase with an increase in the surface area of the drug.

Multiple-unit dosage forms have several advantages compared with single-unit dosage forms including more stable plasma profiles and little risk of local side effects (Sandberg et al., 1988). Among the various types of multiple-unit dosage forms, pellets have attracted more attention due to their unique clinical and technical advantages. Pellets as a drug delivery system offer therapeutic advantages such as less irritation of the gastro-intestinal tract and a lowered risk of side effects due to dose dumping (Bechgaard and Nielsen, 1978). In addition, pellets disperse freely in the gastrointestinal (GI) tract, and so, they invariably maximize drug absorption, reduce peak plasma fluctuation, and minimize potential side effects without appreciably lowering drug bioavailability (Eskilson, 1985).

The present study aims to improve FM dissolution rate by the preparation and characterization of FM solid dispersions in the water soluble matrices of Gelucire 50/13 and Pluronic F-127. In addition, immediate release pellets containing FM or FM solid dispersion systems will be formulated so as to study the impact of solid dispersions on the in vitro dissolution rate of the drug from the pellets.

2. Experimental

2.1. Materials

Famotidine (FM) was kindly supplied by Riyadh Pharma (Riyadh, Saudi Arabia). Gelucire 50/13, having a melting point of 50 °C and HLB value of 13, was provided by Gattefosse (Cedex, France). Pluronic F-127 (Lutrol F127) was provided by BASF Aktiengesellschaft (Ludwigshafen, Germany). Microcrystalline cellulose (Avicel® PH101) was purchased from Serva Feinbiochemica (Heidelberg, Germany). Lactose monohydrate was purchased from Winlab (Leicestershire, UK). All other materials and reagents were of analytical grade of purity.

2.2. Preparation of solid dispersion

Solid dispersions at various weight ratios of 1:1, 1:3 and 1:5 of FAM:carriers were prepared by melting method. FM was added to the molten carrier. The drug–polymer blend was heated 10 °C above the melting point of each carrier for 5 min with continuous stirring. The system was placed in a freezer at −20 °C for 24 h. The resulting solid mass was crushed, ground gently with a mortar and pestle and passed through 500-μm sieve. The samples were kept in a desiccator until the next experiments.

2.3. Preparation of physical mixture

Physical mixtures (PM) of Famotidine with Gelucire 50/13, and Pluronic F-127 (at 1:1, 1:3 and 1:5 weight ratios of FM:drug) were prepared by blending them by mixing using a spatula followed with sieving (500 μm).

2.4. Differential scanning calorimetry (DSC)

The samples (3–5 mg) were hermetically sealed in aluminum pans and heated at a constant rate of 10 °C/min, over a temperature range of 25–250 °C. Thermograms of the samples were obtained using differential scanning calorimetry (DSC-60, Shimadzu, Japan). Thermal analysis data were recorded using a TA 50I PC system with Shimadzu software programs. Indium standard was used to calibrate the DSC temperature and enthalpy scale. N_2 was used as purging gas at a rate of 30 ml/min.

2.5. Wet massing studies using a mixer torque rheometer

The mixer torque rheometer was used in the present study to determine the binder ratio required for wet massing during extrusion/spheronization processes for manufacturing pellets. It consists of a 135-ml capacity stainless steel bowl equipped with two mixing blades with rotational speed ranging between 20 and 150 rpm (MTR-3, Caleva, Dorset, England). The data acquisition and analyses were carried out by a personal computer using data acquisition system and software package supplied by the equipment manufacturer.

Powders were mixed in a turbula mixer (type S27, Erweka, Apparatebau, Germany) and 15 g sample of this dry blend was

utilized in the wet massing studies. Five milliliters of granulating fluid was added in multiple additions over seven wet massing intervals. Each wet massing interval consisted of a one minute mixing period and a 20-s data logging (collection) period with the MTR operating at 50 rpm. Mean line torque was monitored during the granulation process.

2.6. Manufacture of pellets

The composition of FM or FM solid dispersions containing pellets is:

FM or FM solid dispersion equivalent to	149	5 g
(avicel 7:3 lactose) ad	151	100 g
Distilled water	153	Q.S.

For the preparation of pellets, avicel, lactose and FM, or solid dispersions containing FM, were mixed in the turbula mixer at a certain weight and the powder mixture was wetted with the binder (water). Next, the resulting wet mass was extruded at a speed of 90 rpm with a screen pore size of 1 mmØ (Mini Screw Extruder, Model MSE1014, Caleva, Dorset, England) through 1 mm diameter die. Spheronization was performed in a spheronizer (Model 120, Caleva, Dorset, England) with a rotating plate of regular cross-hatch geometry, at a speed of 700 rpm, for 5 min. Pellets were then dried on a tray in a hot oven at 50–60 °C for 6 h.

2.7. Pellet drug content

FM content of the manufactured pellets was determined spectrophotometrically at 285 nm in triplicate. Pellets were crushed in a porcelain mortar and about 25 mg of the crushed pellets was dispersed in 20 ml of distilled water under sonication for 5 min. The supernatant was filtered and measured spectrophotometrically. The FM content was calculated using a pre-constructed calibration curve.

2.8. Morphological analysis

The morphological characteristics of particles were observed by scanning electron microscopy (SEM). The samples were sputter-coated with a thin gold palladium layer under an argon atmosphere using a gold sputter module in a high-vacuum evaporator. The coated samples were then scanned and photomicrographs were taken with an SEM (Jeol, JSM-1600, Tokyo, Japan).

2.9. Particle size analysis

The size distribution of the manufactured pellets was investigated using laser light diffraction (Mastersizer Mastersizer Scirocco 2000, Malvern Instruments, Grovewood Road, UK). For a typical experiment, about 300 mg of pellets was fed into the sample micro feeder. All samples were analyzed five times and average results were taken. The sizes below which 10% ($d(0.1)$), 50% ($d(0.5)$) and 90% ($d(0.9)$) of the pellets were present were used to characterize the pellet size distribution. The mean diameter was taken as the average of $d(0.1)$, $d(0.5)$ and $d(0.9)$ values.

Span value was used to represent size uniformity and dispersity of the microspheres. Hence, a small span value indicates a narrow particle size distribution. Span value was calculated from the following formula (Chen et al., 2004):

$$\text{Span} = (D_{90} - D_{10})/D_{50}$$

2.10. In-vitro release studies

The release measurements were performed using USP dissolution apparatus 1 (Caleva Ltd., model 85T), at 50 rpm using a continuous automated monitoring system which consists of an IBM computer PK8620 series and PU 8605/60 dissolution test software, Philips VIS/UV/NIR single beam eight cell spectrophotometer Model PU 8620, Epson FX 850 printer, Watson–Marlow peristaltic pump and flasks containing 500 mL of distilled water. The temperature was maintained at 37 ± 0.5 °C. An accurately weighed amount of the prepared formulation was added to each flask. For each formula, release was run in triplicate and absorbance was recorded automatically at 285 nm. The percentage of drug release was determined as a function of time.

3. Results and discussion

3.1. Differential scanning calorimetry (DSC) of solid dispersion

Fig. 1 depicted thermograms of FM, Gelucire 50/13 their PM and SDs. FM displayed a sharp endothermic peak at 162.99 °C corresponding to its melting point (24–25) with heat of fusion about −552.47 mJ (Table 1). Gelucire 50/13 showed an endothermic peak at 41.55 °C due to its melting point. Thermal traces for physical mixture, PM (1:3) showed a weak peak appearing at 161.83 °C with heat of fusion about −192 mJ. For FM-Gelucire solid dispersion at 1:1 ratio, it showed a very weak broad peak shifted to a lower melting point. The peak appeared at 161.47 °C with heat of fusion about −67.33 mJ. At higher drug to polymer ratios (1:3 and 1:5), thermal profiles of FM in solid dispersions exhibited a single endothermic peak corresponding to the fusion of the carrier and the peak of the drug disappeared completely. Fig. 2 demonstrates DSC scan of

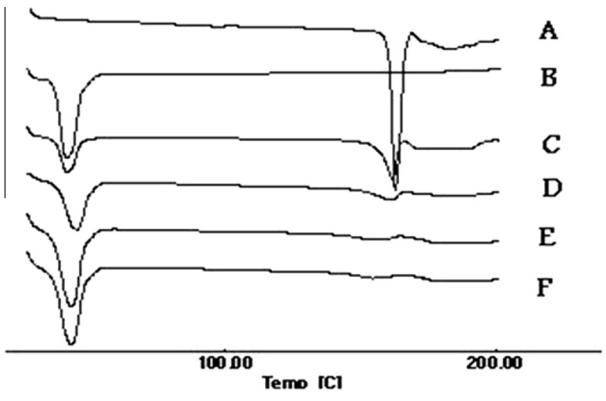

Figure 1 DSC curves of FM (A), Gelucire 50/30 (B), FM-Gelucire (1:3) physical mixture (C), FM-Gelucire (1:1) solid dispersion (D), FM-Gelucire (1:3) solid dispersion (E) and FM-Gelucire (1:5) solid dispersion (F).

Table 1 Endothermic peaks and ΔH of FM-Gelucire 50/30 and FM-Pluronic solid dispersions (SD) as well as the 1:3 physical mixtures (PM) compared with the individual components.

System	Polymer		Drug	
	Peak °C	ΔH (mJ)	Peak °C	ΔH (mJ)
Drug	= =	= =	162.99	−552.47
Gelucire 50/13	41.55	−580.10	= =	= =
Drug:Gelucire				
PM 1:3	41.63	−201.87	161.83	−192.35
SD 1:1	45.22	−404.89	161.47	−67.33
SD 1:3	43.12	−543.89	= =	= =
SD 1:5	45.10	−560.5	= =	= =
Poloxamer 407	55.08	−663.87	= =	= =
Drug:Pluronic				
PM 1:3	55.67	−618.41	161.7	−264.51
SD 1:1	53.8	−166.34	154.44	−106.56
SD 1:3	55.30	−248.06	= =	= =
SD 1:5	55.03	−554.35	= =	= =

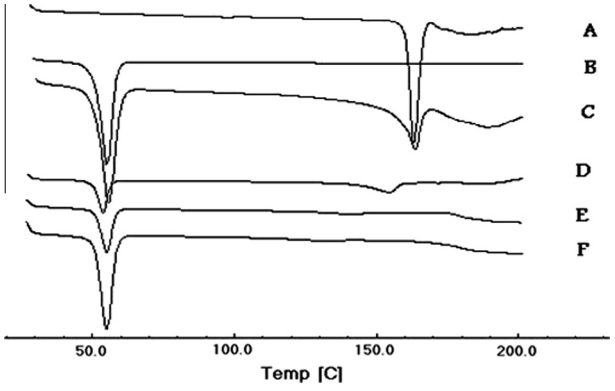

Figure 2 DSC curves of FM (A), Pluronic (B), FM-Pluronic (1:3) physical mixture (C), FM-Pluronic (1:1) solid dispersion (D), FM-Pluronic (1:3) solid dispersion (E) and FM-Pluronic (1:5) solid dispersion (F).

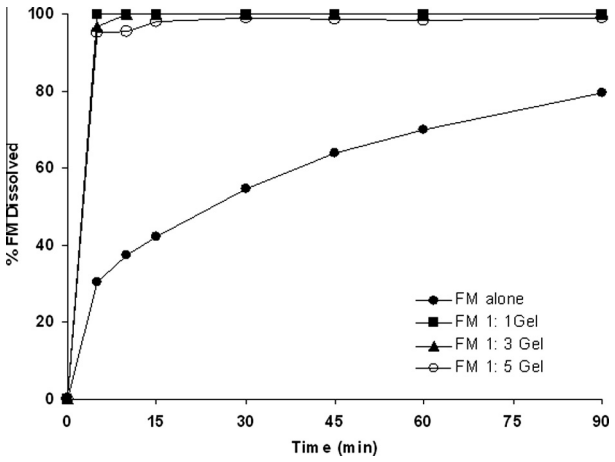

Figure 3 Dissolution profile of FM-Gelucire 50/30 solid dispersions.

FM, Pluronic F-127, their PM and solid dispersions. In the case of PM (1:3), the peak of FM was shallow, broad and appeared at 161.72 °C with heat of fusion −264.51 mJ, while it

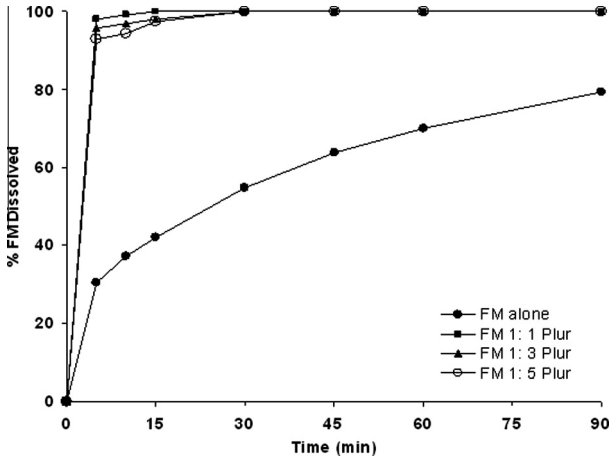

Figure 4 Dissolution profile of FM-Pluronic solid dispersions.

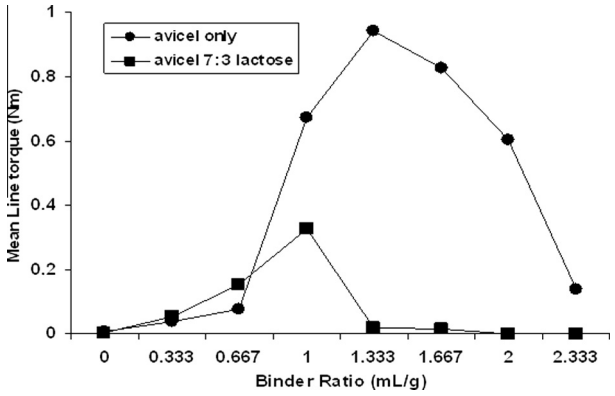

Figure 5 Mean torque for Avicel® PH101 and Avicel® PH101-lactose (7:3) mixture using water as a binder.

became very shallow and shifted to 154.44 °C with heat of fusion −106.56 mJ. On the other hand, the characteristic peak of the drug disappeared completely at drug to polymer ratios of 1:3 and 1:5. All PM (1:3) and solid dispersions exhibited endothermic peaks due to the fusion of Gelucire 50/13 and pluronic

Table 2 Volume weighted mean particle size and the $d(0.1)$, $d(0.5)$, $d(0.9)$ and span values of different pellet formulae loaded with FM (5% w/w as determined by laser diffractometry.

Pellet formula containing	Mean (μm)	$d(0.1)$ μm	$d(0.5)$ μm	$d(0.9)$ μm	Span value
Untreated FM	1233.16	899.58	1218.65	1580.81	0.56
FM 1:3 Gelucire solid dispersion	1186.70	864.41	1167.86	1545.79	0.58
FM 1:3 Pluronic solid dispersion	1084.21	771.82	1061.14	1419.68	0.61

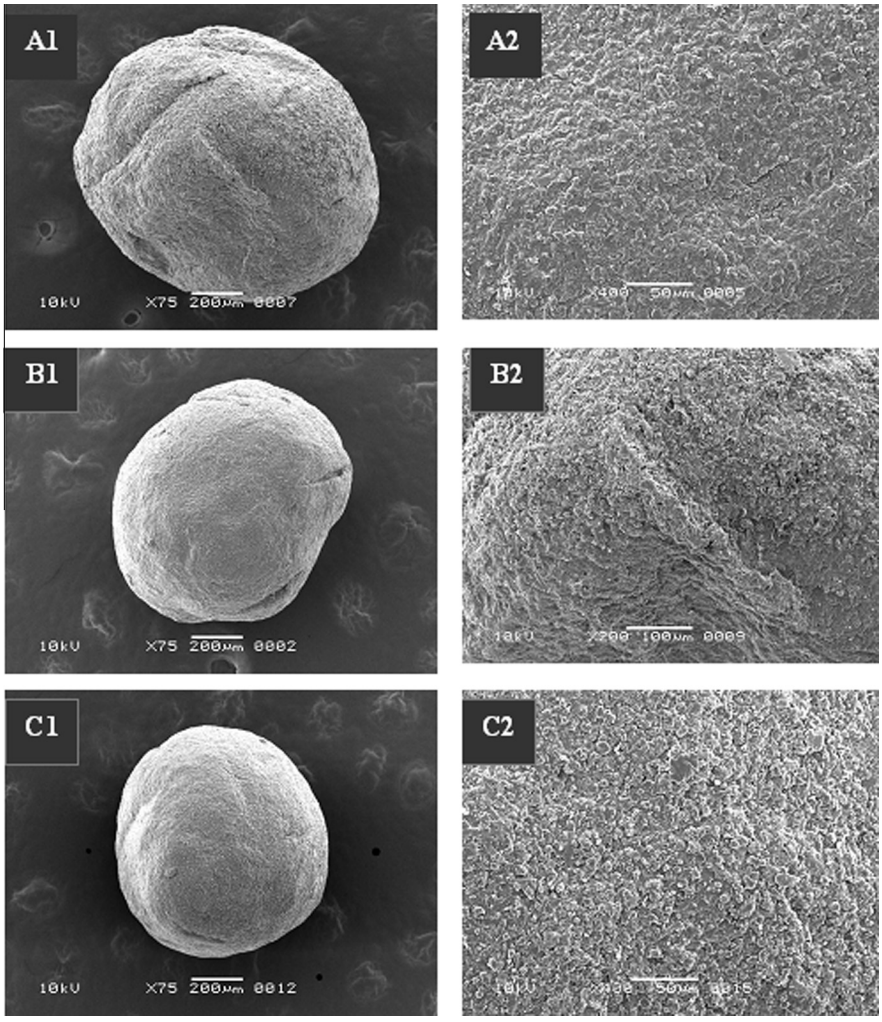

Figure 6 (A) Scanning electron micrographs of pellets containing untreated FM, (B) pellets containing FM-Pluronic (1:3) solid dispersion and (C) pellets containing FM-Gelucire (1:3) solid dispersion.

F-127 around 41 and 55 °C, respectively. The results from DSC indicated a decrease in crystallinity of FM when dispersed in the carriers' matrices. This is in agreement with (El-Badry et al., 2009), who reported that the DSC thermograms showed the significant change in the melting peak of the indomethacin when prepared as SDs using either Gelucire 50/13 or PEG 4000 suggesting the change in crystallinity of the drug. The same finding was reported by (El-Badry, 2011), who reported that the preparation of solid dispersion of meloxicam using Gelucire 50/13 enhanced the solubility and dissolution of the drug due to causing the transformation of the drug to amorphous form.

3.2. In vitro dissolution of FM solid dispersions

Fig. 3 shows the in vitro dissolution profiles of FM from its Gelucire 50/13 solid dispersions of different drug to polymer weight ratios. Untreated FM exhibited a relatively slower dissolution rate, in which about 30% were dissolved within the first 5 min. In addition, only 79% of the loaded drug was dissolved after 90 min. The dispersion of FM in the matrices of Gelucire 50/13, however, effectively improved the drug dissolution rate. The drug showed that 100%, 97% and 95% were dissolved from FM 1:1 Gelucire, FM 1:3 Gelucire and FM 1:5 Gelucire solid dispersions, respectively, within the first

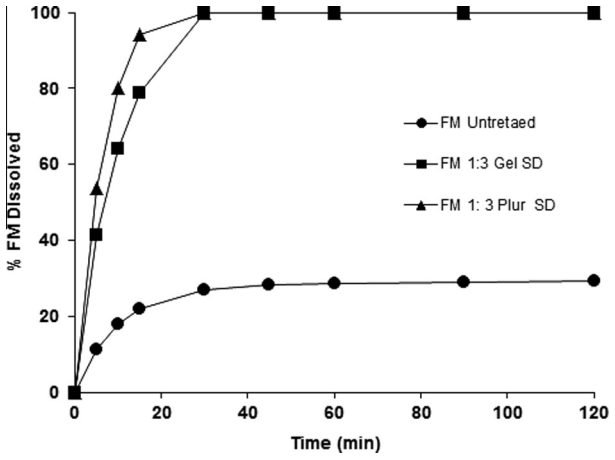

Figure 7 In vitro release profiles of FM from pellets containing solid dispersions compared to the untreated drug.

5 min. The plots of the cumulative amount of the drug dissolved from FM-Pluronic F-127 solid dispersions in different ratios are shown in Fig. 4. The dispersion of the drug in the Pluronic matrices caused a pronounced enhancement of FM dissolution rate, regardless of the drug to polymer weight ratios used. This increase in the dissolution rate of FM may be attributed to the fact that the drug in a solid dispersion system may simultaneously crystallize out in the very minute crystals embodied in water-soluble matrices. This causes an increase in the specific surface area of the drug leading to an increase in its dissolution rate (Yoshioka et al., 1995; Lynne and Zografi, 1997; Suzuki and Sunada, 1997). Moreover, the rapid dissolution of these water-soluble matrices is accompanied by rapid dissolution of the embodied minute drug crystals. Polymer encircling the drug decreases aggregation and agglomeration of drug particles, which can readily dissolve the drug and cause water to contact and wet the drug particles and so increase its dissolution rate.

3.3. Pellets' wet masses, sizes and shapes

Pellets were prepared from those wet masses that showed the highest mean torque value. Fig. 5 shows the rheological profiles for Avicel PH 101 alone and when mixed 7 parts with 3 parts lactose. It is clearly evident that there is an increase in wet mass torque with an increase in liquid content, reaching to its maximum value, and then decreasing as larger volumes of binder are used. The addition of lactose caused a reduction in the mean line torque of avicel from 0.943 to 0.327 Nm. In addition, the binder ratio (amount of water added for the wet massing) was found to be noticeably reduced from 1.33 mL/g in the case of avicel alone to 1 mL/g in the presence of lactose. Therefore, the formula of Avicel 7:3 Lactose was selected as pellet base.

The volume weighted mean particle size and the $d(0.1)$, $d(0.5)$ and $d(0.9)$ values of different pellet formulae loaded with FM (as determined by laser diffractometry) are listed in Table 2. Generally, the produced pellets showed a size range from 1084 to 1233 μm. In addition, pellet formulations containing FM solid dispersions (especially the formula containing Pluronic solid dispersion) are slightly smaller in size than those of untreated FM. Also, the smaller span values reported for all pellet formulations express their sphericity.

Scanning electron micrographs of FM pellets are displayed in Fig. 6. The prepared pellets were rounded and intact in shape, except those prepared from untreated FM, which were not completely spherical. All pellet formulations had smooth surfaces even the formula that was prepared from untreated drug. This might be due to a certain solubility of FM in the pellet binder liquid (water) during extrusion/spheronization processes.

(Mahrous et al., 2010) showed that more hydrophilic polymer when mixed with Avicel, produced a wet mass having the lowest mean torque value, that, in turn, reflects on the easy extrusion of wet mass resulting in pellets with less rough surfaces. Also, (Law and Deasy, 1997) reported that the use of hydrophilic polymers with Avicel favored more spherical and smooth pellets.

3.4. In vitro dissolution of FM from pellet formulations

FM:Gelucire 50/13 (1:3) and FM:Pluronic F-127 (1:3) solid dispersions were selected to be formulated as pellets and compared to the untreated FM in terms of FM dissolution rate. The in vitro dissolution profile of FM from pellets containing different formulas is shown in Fig. 7. The in vitro drug release from the pellet formulations is slightly slower than that from the powdered solid dispersion during the first dissolution period. This might be attributed to the compactness of the pellets caused by the extrusion of the formulation in the presence of the sphere forming agent (avicel) and the binder liquid; water. Untreated FM showed a very slow in vitro dissolution rate from the prepared pellets, in which only 29% of the loaded drug dissolved after 120 min. In contrast, the pellet formulations containing FM:Gelucire 50/13 (1:3) and FM:Pluronic F-127 (1:3) solid dispersions showed a noticeable enhancement in the drug dissolution rate, in which about 78% and 94% of the incorporated FM were released within the first 15 min from pellets containing FM:Gelucire 50/13 (1:3) and FM:Pluronic F-127 (1:3) solid dispersions, respectively. It is worthy to mention that pellets containing either Gelucire or Pluronic solid dispersions showed complete burst within 30 min of the dissolution period resulting in complete drug release. These results are in accordance with (Jachowicz et al., 2000), who showed that the release of ketoprofen from pellets containing solid dispersion was greater than from pellets of the drug alone, in which after 2 h of dissolution, 74.71% of ketoprofen was dissolved from pellets containing ternary solid dispersion, whereas only 20.32% was dissolved from pellets containing untreated ketoprofen.

The results revealed that pellets containing FM-Pluronic F-127 solid dispersion were superior to those containing FM-Gelucire 50/13 solid dispersion in improving the drug dissolution. This finding might be attributed to the slightly smaller size of the pellets containing Pluronic solid dispersion, Table 1. In addition, Pluronic F127 has a higher HLB value of 22 (Barreiro-Iglesias et al., 2003) compared to Gelucire, whose HLB value is 13 (El-Badry and Fathy, 2006). Therefore, the higher hydrophilicity of Pluronic might be responsible for the enhancement of FM dissolution from its solid dispersion compared to Gelucire.

4. Conclusion

This study showed that the hydrophilic polymers (Gelucire 50/30 or Pluronic F127) could be utilized as solid dispersion

carriers in the formation of FM pellets. The extent of the dissolution improvement of the drug using these carriers was attributed to the difference in hydrophilicity. The higher hydrophilicity of Pluronic F127 (represented by its higher HLB value) made it to be better than Gelucire 50/30 in improving FM dissolution.

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References

Abdul-Fattah, A.M., Bhargava, H.N., 2002. Preparation and in vitro evaluation of solid dispersions of halofantrine. Int. J. Pharm. 235, 17–33.

Ainaoui, A., Ouriemchi, E.M., Bidah, D., El-Amrani, M.K., Vergnaud, J.M., 1997. Process of drug release with oral dosage forms with lipidic Gelucire matrix. J. Polym. Eng. 17, 245–257.

Ainaoui, A., Vergnaud, J.M., 1998. Modeling the plasma drug level with oral sustained release forms with lipidic Gelucire. Int. J. Pharm. 169, 155–162.

Alexandridis, P., Hatton, T.A., 1995. Poly(ethylene oxide)–poly(propylene oxide)–poly(ethylene oxide) block-copolymer surfactants in aqueous-solutions and at interfaces-thermodynamics, structure, dynamics, and modeling. Colloids Surf., A 96, 1–46.

Barreiro-Iglesias, R., Alvarez-Lorenzo, C., Concheiro, A., 2003. Poly(acrylic acid) microgels (carbopol® 934)/surfactant interactions in aqueous media part I: nonionic surfactants. Int. J. Pharm. 258, 165–177.

Bechgaard, H., Nielsen, G.H., 1978. Controlled-release multiple-units and single-unit doses. A literature review. Drug Dev. Ind. Pharm. 4, 53–67.

Burks, T.F., 1995. Therapy of acid peptic diseases. In: Munson, P.L., Mueller, R.A., Breese, G.R. (Eds.), Principles of Pharmacology: Basic Concepts and Clinical Applications. Chapman and Hall, International Thomson Publishing Company, New York, USA, pp. 1063–1073.

Cavallari, C., Rodriguez, L., Albertini, B., Passerini, N., Rosetti, F., Fini, A., 2005. Thermal and fractal analysis of diclofenac/Gelucire 50/13 microparticles obtained by ultra-sound-assisted atomization. J. Pharm. Sci. 94, 1124–1134.

Chen, P.C., Park, Y.J., Chang, L.C., Kohane, D.S., Bartlett, R.R., Langer, R., et al, 2004. Injectable microparticle-gel system for prolonged and localized lidocaine release. I. In vitro characterization. J. Biomed. Mater. Res., Part A 70, 412–419.

Chiappetta, D.A., Sosnik, A., 2007. Poly(ethylene oxide)–poly(propylene oxide) block copolymer micelles as drug delivery agents: improved hydro solubility, stability and bioavailability of drugs. Eur. J. Pharm. Biopharm. 66, 303–317.

Chiou, W.L., Riegelman, S., 1971. Pharmaceutical applications of solid dispersion systems. J. Pharm. Sci. 60, 1281–1302.

Craig, D.Q.M., 2002. The mechanisms of drug release from solid dispersions in water-soluble polymers. Int. J. Pharm. 231, 131–144.

Douroumis, D., Bouropoulos, N., Fahr, A., 2007. Physicochemical characterization of solid dispersions of three antiepileptic drugs prepared by solvent evaporation method. J. Pharm. Pharmacol. 59, 645–653.

Dumortier, G., Grossiord, J.L., Agnely, F., Chaumeil, J.C., 2006. A review of Poloxamer 407 pharmaceutical and pharmacological characteristics. Pharm. Res. 23, 2709–2728.

El-Badry, M., Fathy, M., 2005. Properties of solid dispersions of piroxicam in pluronic F-98. J. Drug Delivery Sci. Technol. 14, 199–205.

El-Badry, M., Fathy, M., 2006. Enhancement of the dissolution and permeation rates of meloxicam by formation of its freeze-dried solid dispersions in polvvinylpyrrilidone k-30. Drug Dev. Ind. Pharm. 32, 41–150.

El-Badry, M., Fetih, G., Fathy, M., 2009. Improvement of solubility and dissolution rate of indomethacin by solid dispersions in Gelucire 50/13 and PEG 4000 Saudi. Pharm. J. 17, 219–230.

El-Badry, M., 2011. Physicochemical characterization and dissolution properties of meloxicam-Gelucire 50/13 binary systems. Sci. Pharm. 79, 375–386.

Eskilson, C., 1985. Controlled release by microencapsulation. Manuf. Chem. 56, 33–39.

Ford, J.L., Rubinstein, M.H., 1978. Phase equilibria and dissolution rate of indomethacin-polyethylene glycol 6000 solid dispersions. Pharm. Acta Helv. 53, 93–98.

Hassan, M.A., Suleiman, M.S., Najib, N.M., 1990. Improvement of the in vitro dissolution characteristics of famotidine by inclusion in b-cyclodextrin. Int. J. Pharm. 58, 19–24.

Islam, M.S., Narurkar, M.M., 1993. Solubilization, stability and ionization behaviour of famotidine. J. Pharm. Pharmacol. 45, 682–686.

Jachowicz, R., Nürnberg, E., Pieszczek, B., Kluczykowska, B., Maciejewska, A., 2000. Solid dispersion of ketoprofen in pellets. Int. J. Pharm. 206, 13–21.

Kadar, D., 1998. Histamine and antihistamines. In: Roberts, E.A. (Ed.), Mediators and modifiers of tissue responses. In: Kalant, H., Roschlau, W.H.E. (Eds.), Principles of Medical Pharmacology. Oxford University Press, Oxford, pp. 400–408, 551–560.

Law, M.F.L., Deasy, P.B., 1997. Use of canonical and other analyses for the optimization of an extrusion-spheronization process for indomethacin. Int. J. Pharm. 146, 1–9.

Lynne, S., Zografi, G., 1997. Spectroscopic characterization of interaction between PVP and indomethacin in amorphous molecular dispersions. Pharm. Res. 14, 1691–1698.

Mahrous, G.M., Ibarhim, M.A., El-Badry, M., Al-Anazi, F.K., 2010. Indomethacin sustained release pellets prepared by extrusion/spheronization. J. Drug Delivery Sci. Technol. 20, 119–125.

Newa, M., Bhandari, K.H., Oh, D.H., Kim, Y.R., Sung, J.H., Kim, J.O., et al, 2008. Enhanced dissolution of ibuprofen using solid dispersion with Poloxamer 407. Arch. Pharm. Res. 31, 1497–1507.

Page, C.P., Curtis, M.J., Sutter, M.C., Walker, M.J.A., Hoffman, B.B., 1997. Integrated Pharmacology. Mosby Inc., London, p. 306–310.

Ricci, E.J., Lunardi, L.O., Nanclares, D.M.A., Marchetti, J.M., 2005. Sustained release of lidocaine from Poloxamer 407 gels. Int. J. Pharm. 88, 235–244.

Sandberg, A., Ragnarsson, G., Jonsson, U.E., Sjogren, J., 1988. Design of a new multiple-unit controlled-release formulation of metoprolol–metoprolol CR. Eur. J. Clin. Pharmacol. 33, S3–S7.

Sethia, S., Squillante, E., 2004. Solid dispersion of carbamazepine in PVP K30 by conventional solvent evaporation and supercritical methods. Int. J. Pharm. 272, 1–10.

Sutananta, W., Craig, D.Q.M., Newton, J.M., 1994. The effects of ageing on the thermal behavior and mechanical properties of pharmaceutical glycerides. Int. J. Pharm. 111, 51–62.

Suzuki, H., Sunada, H., 1997. Comparison of nicotinamide, ethylurea and polyethylene glycol as carriers for nifedipine solid dispersion systems. Int. J. Pharm. 45, 1688–1693.

Thybo, P., Kristensen, J., Hovgaard, L., 2007. Characterization and physical stability of tolfenamic acid-PVP K30 solid dispersions. Pharm. Dev. Technol. 12, 43–53.

Yassin, A.B., Alanazi, F.K., El-Badry, M., Alsarra, I.A., Barakat, N.S., 2009. Preparation and characterization of spironolactone-loaded Gelucire microparticles using spray-drying technique. Drug Dev. Ind. Pharm. 35, 297–304.

Yoshioka, M., Hancock, B.C., Zografi, G., 1995. Inhibition of indomethacin crystallization in poly(vinylpyrrolidone) coprecipitate. J. Pharm. Sci. 84, 983–986.

Zhang, L., Parsons, D.L., Navarre, C., Kompella, U.B., 2002. Development and in-vitro evaluation of sustained release Poloxamer 407 (P407) gel formulations of ceftiofur. J. Control. Release 85, 73–81.