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Research Paper

Stabilization and Improved *in Vivo* Performance of Amorphous Etoricoxib using Gelucire 50/13

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Purpose. Amorphous drugs have gained importance because of their advantageous biopharmaceutical properties; however, their stabilization remains a challenge. The purpose of this work was to stabilize the amorphous form of etoricoxib (ET) by using a low excipient/drug ratio to improve drug dissolution and thus bioavailability.

Methods. The effect of Gelucire and polyvinylpyrrolidone (PVP) on stabilization and bioavailability of amorphous etoricoxib (AET) was studied. X-ray powder diffractometry, differential scanning calorimetry, and scanning electron microscopy were used to study the physical state of the drug. Dissolution studies were performed for melt granules of AET with Gelucire 50/13 (MG-AET) and solid dispersion with PVP (SDP) to differentiate dissolution performance. A stability study on samples was conducted for 3 months to evaluate the physical state of the drug and its dissolution in the formulation. The *in vivo* performance of the optimized and stable formulation of ET was evaluated in rat.

Results. Dissolution of MG-AET was significantly improved as compared to AET and SDP. Both factors, amorphization of drug and melt granulation with lipid, seemed to be important for improving dissolution. Stability data revealed that MG-AET was significantly advantageous for AET stabilization, whereas PVP was not. The amount of Gelucire required for the stabilization of one part of AET was 0.5 part (by weight), whereas even 1.5 part (by weight) of PVP failed to elicit the same result. The superior *in vivo* performance of MG-AET has been attributed to the altered physiochemical properties of AET and the presence of lipid in the system.

Conclusion. Gelucire can stabilize AET and improve its biopharmaceutical performance at a low excipient/drug ratio and may provide a better alternative to conventional stabilizers such as PVP.

KEY WORDS: amorphous; bioavailability; Gelucire 50/13; melt granulation; solid dispersion.

INTRODUCTION

Amorphous drugs have recently gained significant importance because of their advantageous biopharmaceutical properties. Although there are many reports describing methods of preparation and application of the amorphous form, it is equally important to note that devitrification of amorphous drugs has limited their applications to a great extent. To date, several attempts have been made to obtain and stabilize drugs in the amorphous state. Solid dispersions (SDs) with various polymers such as poly(vinylpyrrolidone) (PVP), hydroxypropylmethylcellulose, hydroxypropylcellulose (1,2), and silicates such as calcium silicate, silicon dioxide, magnesium aluminosilicate (Neusilin®) (3,4), cyclodextrins (5), and lipids (6) have been reported. These SDs were obtained by using various techniques such as melt quenching, solvent evaporation, spray drying, milling, etc. Among these techniques, spray drying is the most suitable technique for scale-up.

Polymer/drug ratios required to stabilize the amorphous form are significantly high (6), which limit their applications because of problems in the design of final dosage forms such as tablets or capsules. Problems such as failure to disintegrate, sticking to punches, etc., are often encountered (7). Moreover, the amount of solvent required to dissolve drug and polymer increases significantly with the increase in polymer content, which may affect process economy. Complete amor-phization of curcumin was reported to occur at a curcumin/PVP ratio of 1:7 parts by weight, with a significantly high amount of the solvent required for processing (8). A high amount of hydrophilic polymers may also increase the availability of moisture, which may aid devitrification.

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ABBREVIATIONS: AET, amorphous etoricoxib; AUC, area under curve; BA, bioavailability; C_{max}, maximum concentration; ET, etoricoxib; HPLC, high-pressure liquid chromatography; MG-AET, melt granulation of AET with lipid; MG-CET, melt granulation of crystalline ET with lipid; PVP, polyvinylpyrrolidone; SD, solid dispersions; SDL, solid dispersion with lipid; SDP, solid dispersion with PVP; T_g, glass transition temperature; T_{max}, time at which maximum concentration is reached; ΔH, heat of melting.

Recently, Weuts *et al.* (9) reported a spray-drying technique for obtaining loperamide-PEG 6000 solid dispersion. However, the processing temperature had to be maintained low because of the presence of PEG, which caused the formation of a product that contained some proportions of a crystalline drug. This residual crystallinity in the product was responsible for the faster devitrification and deterioration in the dissolution profile on storage. Passerini *et al.* (10) reported the formation of ultrasound-assisted spray congealed carbamazepine-Gelucire 50/13 particles. However, the amount of lipid required in the formulation was significantly high. Thus, taking into consideration the problems related to the use of polymers in spray-dried solid dispersions, an attempt was made to stabilize the spray-dried amorphous drug *via* melt granulation using a low Gelucire 50/13:drug ratio.

Etoricoxib (ET) is a novel selective cyclooxygenase-2 inhibitor administered orally as an analgesic and antiinflammatory drug. The chemical structure of ET is shown in Fig. 1. It is an off-white crystalline powder, relatively insoluble in water, and freely soluble in alkaline aqueous solutions. Improvements in the apparent solubility and/or dissolution rate of a poorly water-soluble drug through the formation of an amorphous state may lead to an enhancement of its bioavailability (BA).

In the present study, amorphous ET (AET) and solid dispersions with PVP K-30 [solid dispersion with PVP (SDP)] and Gelucire 50/13 [solid dispersion with lipid (SDL)] were prepared by spray drying. AET was further subjected to melt granulation with Gelucire 50/13 to obtain granules (MG-AET). Physicochemical characterization of the dispersions and melt granules was performed on freshly prepared samples as well as on stability samples using scanning electron microscopy (SEM), X-ray diffraction (XRD) study, differential scanning calorimetry (DSC), and dissolution study. The stable formulation was further evaluated for *in vivo* performance in comparison to neat ET.

MATERIALS AND METHODS

Materials

ET was obtained as a gift from Unichem Laboratories Ltd. (Mumbai, India). Gelucire® 50/13 (Stearoyl Macrogolglycerides EP, Gattefosse, France) and PVP (BASF, Ludwigshafen, Germany) were supplied by Colorcon India (Mumbai, India) and Get-Rid Pharmaceuticals Pvt. Ltd. (Pune, India), respectively. All other chemicals were of analytical grade.

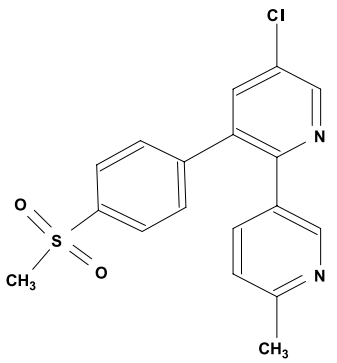

Fig. 1. Chemical structure of etoricoxib.

Preparation of Amorphous ET

Etoricoxib was dissolved in methylene chloride (10% w/v). The clear solution was spray-dried using a spray drier (Jay Instruments & Systems, Mumbai, India) under the following set of conditions: flow rate, 10 ml/min; inlet temperature, 90°C; outlet temperature, 70–75°C; aspiration −300 mm WC; and atomization air pressure, 2 kg/cm^2. The resulting solid powder was placed in a vacuum dryer for 24 h to remove the residual solvent.

Preparation of SDs

Etoricoxib, in combination with Gelucire 50/13 (SDL) or PVP (SDP) (1:0.5, 1:1, and 1:1.5 parts by weight), was dissolved in methylene chloride (7–10% w/v). The clear solution was spray-dried using a spray drier as described above, except for inlet temperature (40–65°C) in the case of Gelucire. The resulting solid was placed in a vacuum dryer for 24 h to remove the residual solvent.

Preparation of Granules

Granules of crystalline ET (MG-CET) and AET (MG-AET) were prepared using the melt granulation technique. The drug/lipid ratios used to prepare the granules were 1:0.5 and 1:1 parts by weight. Lipid was melted at 60°C. To obtain the solid mass, either CET or AET was added to the molten lipid, which was then mixed well and cooled to room temperature. The mass was passed through 510-μm sieve to obtain uniform-sized granules.

Characterization

Samples of AET, SDP, MG-CET, and MG-AET were subjected to characterization immediately after their preparation based on the following parameters.

Thermogravimetric Analysis

To calculate the amount of residual methylene chloride in the spray-dried drug and solid dispersions, thermogravimetrical analyses were performed using TA-60WS Thermalgravimetric analyzer (Shimadzu Corporation, Japan). Samples (approximately 30–40 mg) were heated in platinum crucible in nitrogen atmosphere and the loss of weight as a function of temperature was recorded.

Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) studies were performed using Mettler-Toledo DSC 821^e (Mettler Toledo, Switzerland) instrument equipped with an intracooler. Indium/zinc standards were used to calibrate the DSC temperature and enthalpy scale. The samples were hermetically sealed in an aluminum pan and heated at a constant rate of 10°C/min over a temperature range of 25–170°C. The inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50 ml/min. Sample weights were in the range of 5 to 10 mg.

X-ray Powder Diffraction

X-ray powder diffraction (XRPD) patterns were recorded on X-ray diffractometer (PW 1729, Philips, The Netherlands). The samples were irradiated with monochromatized Cu Kα radiation (1.542 °A), and analyzed between 2 and 50 °2θ at ambient temperature. The voltage and current used were 30 kV and 30 mA, respectively. The range and chart speed were 5×10^{-3} CPS and 10 mm/°2θ, respectively.

Scanning Electron Microscopy

Samples were mounted on a double-faced adhesive tape and sputtered with thin gold–palladium layer using sputter coater unit (VG-Microtech, UK), and surface topography was analyzed with a Cambridge Stereoscan S120 scanning electron microscope (Cambridge, UK).

Dissolution Studies

Dissolution studies (in triplicate) were carried out using USP 24 type II dissolution test apparatus (TDP-06P; Electrolab, India) with an agitation speed of 100 rpm in phosphate buffer (pH 6.8) maintained at 37 ± 0.2°C. At appropriate time intervals, aliquots were withdrawn and replaced with a fresh dissolution medium. After filtration through Whatman filter paper no. 41, the concentration of ET was determined spectrophotometrically at 232.2 nm with suitable dilutions. Analysis of data was done using PCP-Disso V3 software (Poona College of Pharmacy, Pune, India).

Molecular Modeling

All molecular modeling studies were performed on Intel Pentium IV 1.8 GHz computer running Windows 2000 using Molecular Operating Environment (MOE) 2004.03 software (MOE 2004.03, Chemical Computing Group Inc., Montreal, Canada). All the molecules were constructed using MOE molecular builder. Polymers, lipids, and drug molecules were constructed; partial charges were calculated using MMFF94 and minimized. Etoricoxib molecules were placed randomly in the network of polymer chains and the system was minimized to reduce the steric clashes between the drug and polymer. The drug–polymer complex was subjected to *in vacuo* molecular dynamics simulations at 300 K using NVT ensemble for 200 ps after equilibrating for 50 ps. The frames were collected every 500 fs. The dynamics trajectories were then analyzed.

Stability Study

The stability of samples was monitored up to 3 months at ambient temperature and relative humidity (30°C/65% RH). Periodically, samples were removed and characterized for dissolution and the presence of crystallinity using DSC and XRPD.

Bioavailability Study

Rat has been reported (11) as a suitable animal model for assessing the intestinal absorption of drugs in humans. Thus, rat as an animal model was selected for the present study. All studies were approved by the Institutional Animal Ethics Committee of Poona College of Pharmacy (Pune, India), and were conducted under the provisions of the approved protocol.

Experimental Procedure

Bioavailability (BA) of MG-AET (stable formulation) was determined in comparison with CET in healthy albino rats (Wistar strain) of either sex, each weighing between 200 and 250 g. Animals were fasted overnight prior to dosing. Water was allowed *ad libitum*. The animals were randomly divided into two groups of four animals each. BA was assessed after single oral dosing of sample (60 mg/kg) in the aqueous suspension form (prepared just before dosing). After mild anesthetization of animals, serial blood samples (1 ml each) were collected using capillaries by retro orbital puncture, at predetermined time intervals (0,1, 2, 3, 4, 10, and 24 h). Plasma was separated by centrifugation (3,000 rpm, 4°C, 15 min) and stored at −40°C until further study.

Assay of Plasma Concentration

Plasma (0.5 ml) was transferred to stopper test tube, to which 200 µl of internal standard solution (Celecoxib, stock solution 10 µg/ml) was added. The sample was mixed by vortexing for 5 min, followed by deproteinization and extraction of ET and celecoxib using 10 ml of diethyl ether by vortex mixing for 5 min. The mixture was then centrifuged at 3,000 rpm for 5 min. The resulting supernatant was separated and evaporated to dryness at 40°C in vacuum evaporator. The residue was reconstituted with 500 µl of mobile phase. The reconstituted solution was filtered through a 0.45-µ membrane filter and analyzed via the HPLC method reported by Mullangi *et al.* (12) with suitable modifications.

The HPLC system specifications were as follows: pump, PU-1580 (JASCO, Japan); injector, auto sampler (AS-1555; JASCO); column, RP C_{18}, 250 × 4.6 mm (Kromasil®100, 5 µm; Flexit Jour Lab. Pvt. Ltd., Pune, India); detector, UV/visible (UV-1575; JASCO). Data acquisition and analysis was carried out using Borwin/HSS 2000 software (LG 1580-04; JASCO). The chromatographic conditions were as follows: mobile phase, 0.01 M potassium dihydrogen *ortho*-phosphate (pH 3.2) and acetonitrile (30:70, v/v); flow rate, 1.5 ml/min; wavelength, 232 nm.

The calibration curves of ET covered a concentration range of 0–25 µg/ml. The ratio of peak area of ET/celecoxib was used for quantification of plasma samples.

Pharmacokinetic Analysis

The pharmacokinetic parameters viz. C_{max} and t_{max} were determined based on the plasma concentration data. $AUC_{0-24\ h}$ was determined as the area under the plasma concentration–time curve using the trapezoidal rule. The differences in C_{max} and $AUC_{0-24\ h}$ between the neat drug and MG-AET were statistically analyzed by Student's t test at the $p < 0.01$ level of significance.

RESULTS AND DISCUSSION

The optimization of parameters for spray drying was carried out on the basis of % yield. Batches of AET and SDP were processed at relatively higher inlet temperature as compared to SDL, taking into consideration the melting point of Gelucire. The yield was 80–85% for both AET and SDP with 92–94% w/w ET content. Regarding SDL, the product could not be obtained even at the lowest proportion of lipid (1:0.5) and the lowest possible temperature (30°C) because of the drying chamber sticking to the wall, indicating limitation of spray drying. Therefore AET, SDP, and MG-AET were characterized further. In literature, the spray-freezing technique has been reported to allow dispersion of drugs in Gelucire or other lipids, but such a technique lacks commercial feasibility (13). The amount of organic solvent in the dried particles was below the detection limit of TGA (<0.05% w/w).

Dissolution profiles of ET, AET, SDP (1:1, 1:1.5), MG-CET, and MG-AET (1:0.5, 1:1) in phosphate buffer (pH 6.8) are shown in Fig. 2. AET showed a significant increase in dissolution rate (51% in 60 min) compared to ET (35% in 60 min). Dissolution profiles for SDP (1:1) and SDP (1:1.5) did not show any significant difference, but the amount dissolved was significantly high (78%) compared to AET. The dissolution profiles of MG-CET (1:0.5) showed that melt granulation with Gelucire resulted in a significant increase in dissolution. MG-CET showed 77% whereas MG-AET showed 93% drug dissolution in 60 min. Although Gelucire increased the dissolution rate of drugs, increase in the amount of Gelucire did not have any significant effect. No significant difference was observed in the dissolution profile of MG-AET 1:0.5 and 1:1 ratios. Melt granulation of crystalline drug led to improvement in dissolution from 35% (ET) to 77% (MG-CET) in 60 min. The percent dissolution was further increased to 93% when the amorphous drug was subjected to melt granulation. The dissolution showed by MG-CET (1:0.5) was even significantly higher than that shown by AET and was comparable to that of SDP (1:1.5). This clearly indicated that Gelucire played an important role in improving the dissolution rate of drugs.

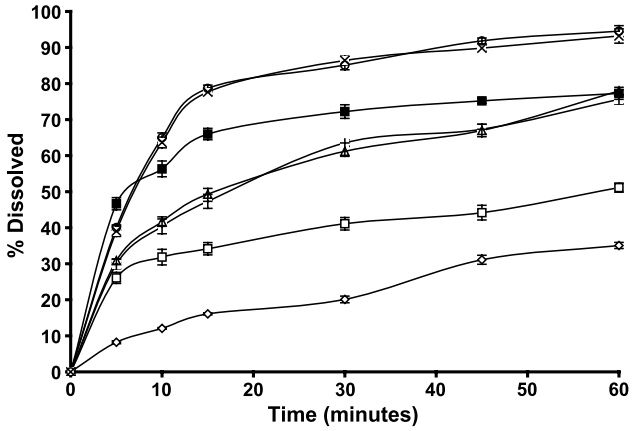

Fig. 2. *In vitro* dissolution profile of initial samples. ET (◇); AET (□); SDP, 1:1 (+); SDP, 1:1.5 (△); MG-CET, 1:0.5 (■); MG-AET, 1:0.5 (×); MG-AET, 1:1 (○).

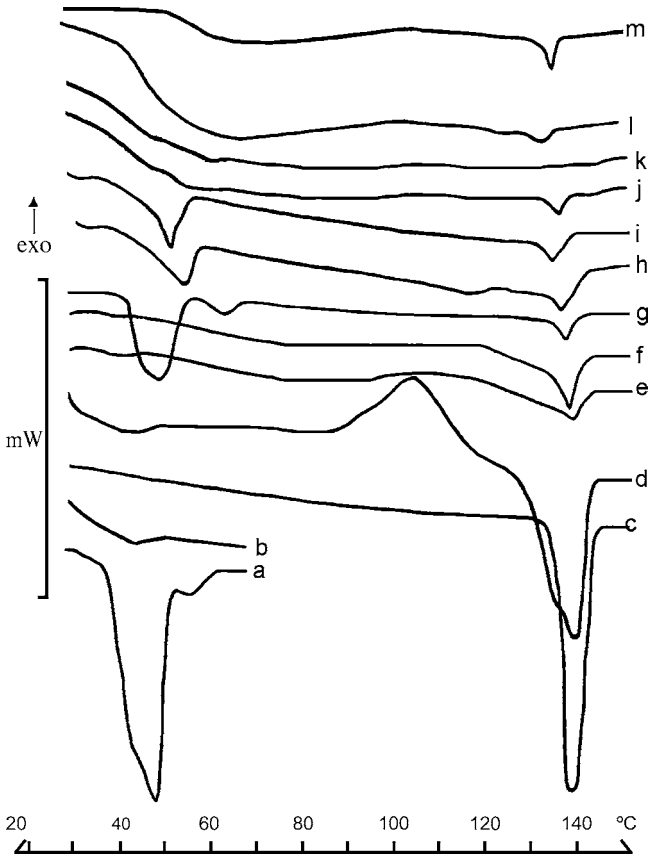

Fig. 3. DSC curves of initial and stability samples of ET. Gelucire 50/13 (a); AET showing T_g (b); ET (c); AET, initial (d); AET, 1 month (e); AET, 3 months (f); MG-AET 1:0.5, initial (g); MG-AET 1:0.5, 1 month (h); MG-AET 1:0.5, 3 months (i); SDP 1:1, initial (j); SDP 1:1.5, initial (k); SDP 1:1.5, 1 month (l); SDP 1:1.5, 3 months (m).

Compared to amorphization, melt granulation with Gelucire was superior in improving dissolution, which might be attributed to the highly hydrophilic environment provided by Gelucire. This result confirms the observation of Weuts *et al.* (9). Because there was no significant difference in the amount dissolved in MG-AET ratios of 1:0.5 and 1:1, the former was subjected to further characterization.

The DSC thermograms of initial and stability samples are shown in Fig. 3. Etoricoxib showed melting endotherm at 139°C (ΔH = 82.68 J/g). Amorphous ET showed change in heat capacity at 42°C, which indicates T_g, followed by recrystallization exotherm at 108°C and melting endotherm at 138°C. Thermograms of SDP (1:1) failed to show T_g and a melting endotherm was observed at 139°C. However, the thermogram characteristic of the amorphous form was exhibited by SDP (1:1.5). This indicated that a complete amorphization of 1 part of drug required 1.5 parts of the PVP; therefore SDP (1:1.5) was used for further studies.

Devitrification of drug was studied using DSC and XRPD along with dissolution studies over a period of 3 months. The XRPD patterns of ET, AET, SDP, MG-AET, and stability samples at different time periods are shown in Fig. 4. The diffraction peaks at 16.4, 18.2, 22.6, 24.1, and 28.8 °2θ were the characteristic peaks of crystalline ET. Among these peaks, 16.4, 18.2, and 28.8 °2θ were considered to be the important

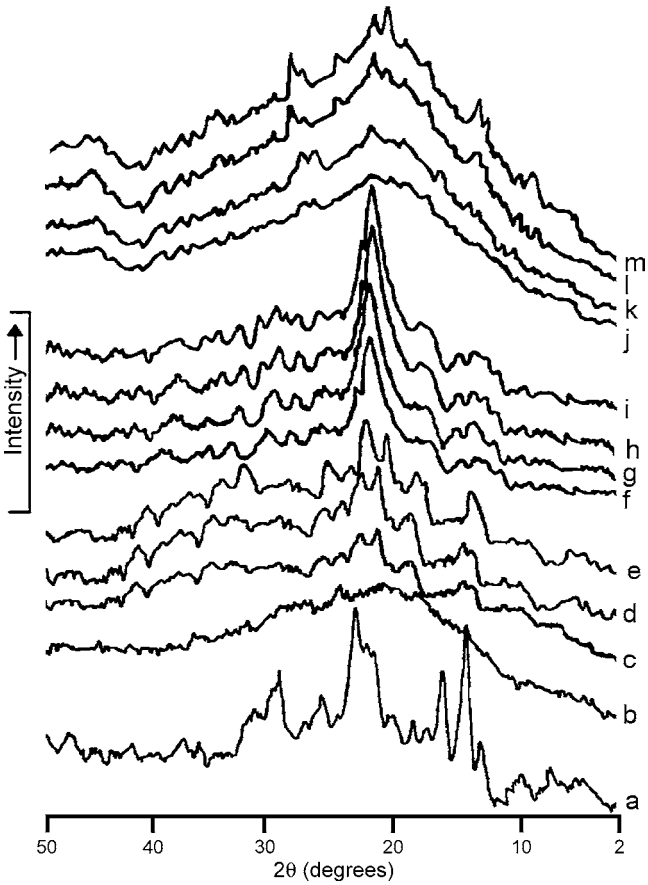

Fig. 4. XRPD diffraction pattern of initial and stability samples of ET. ET (a); AET, initial (b); AET, 10 days (c); AET, 1 month (d); AET, 3 months (e); MG-AET 1:0.5, initial (f); MG-AET 1:0.5, 10 days (g); MG-AET 1:0.5, 1 month (h); MG-AET 1:0.5, 3 months (i); SDP 1:1.5, initial (j); SDP 1:1.5, 10 days (k); SDP 1:1.5, 1 month (l); SDP 1:1.5, 3 months (m).

peaks for stability evaluation because these peaks appeared first, when the samples started to recrystallize. Peaks at 22.6, 24.1 °2θ were somewhat identical with the Gelucire 50/13 peaks (14). The hump in the XRPD pattern indicated complete conversion of ET to amorphous form (Fig. 4b). The SEM microphotographs also showed the absence of ET crystals (Fig. 5). Similarly, DSC studies showed characteristic thermograms of the amorphous form (Fig. 3). The XRPD patterns of AET stability samples showed crystallinity in the 10-day stability sample that subsequently increased on storage. The DSC pattern of the 1-month stability AET sample showed glass transition at 34°C, followed by melting peak at 138°C, which indicated partial conversion of amorphous form during stability. The 3-month stability sample showed the absence of T_g with melting endotherm at 138°C (Fig. 3f). This clearly indicated that the amorphous state of AET was not stable as such.

Figure 4f–i and j–m shows the XRPD pattern for MG-AET and SDP, respectively. The XRPD pattern of MG-AET showed characteristic peaks at 19.26 and 23.5 °2θ attributed to Gelucire 50/13. MG-AET showed the absence of ET peaks, which indicated that melt granulation did not affect the physical state of AET. An insignificant increase in the peak intensity was observed in the 3-month stability sample, which did not affect the ET dissolution. The DSC pattern of MG-AET showed broad melting peak of Gelucire 50/13 at 51°C, followed by a small melting peak at 138°C. The heat of melting (ΔH = 7.8 J/g) of this peak was significantly lower in comparison to ET (Fig. 3g). The T_g peak might have been overlapped with the melting peak of the lipid (15). Many studies, in which the amount of lipid was higher than the drug substance, reported that drugs dissolved in the molten lipid and thus there was an absence of drug melting peak (10). The appearance of the melting peak might be attributable to the conversion from an amorphous to a crystalline state in the DSC. Reports also suggested that when the melt was maintained for more than 3 min, crystal growth occurred as a result of the plasticizing effect (15). In contrast, crystalline nifedipine at a low concentration in solid dispersion did not show any characteristics of the crystalline nifedipine. One of the reason could be that nifedipine might have been converted to a metastable amorphous form, or might have dissolved in the matrix system to form a solid solution, or might exist in a microcrystalline form in the system (14). The solid dispersion of the cinnarizine in Gelucire 50/13, showed no melting peak of cinnarizine at a low concentration (≤30% w/w). Therefore, DSC seems to be unsuitable for determining the degree of crystallinity for such systems (16). To explain the presence of small endothermic peak in MG-AET at 138°C, the DSC of MG-CET (1:0.5) was performed. The DSC thermograms showed that some portions of the drug was dissolved in the molten lipid, but the remaining crystalline form has given the melting peak (ΔH = 65.12 J/g) comparable with ET.

T_g at 45°C, the absence of melting in DSC data, and the presence of hump in XRPD pattern suggested the complete conversion of ET to the amorphous form with PVP (SDP 1:1.5). During stability, the presence of peaks in XRPD and melting peak in DSC indicated that PVP did not have a stabilizing ability in this case (Fig. 3). This might be because of the absence of hydrogen bonding between ET with PVP. The interaction study was carried out with molecular modeling and is discussed further. Although PVP could not establish hydrogen bonding with ET for stabilization, it was assumed that the PVP would stabilize the amorphous form in SDP by antiplasticizing property (17).

The dissolution profiles of the AET and stability samples are shown in Fig. 6. The dissolution of AET has slightly improved as compared to ET. This might be due to the formation of small agglomerates of the spray-dried powder as a result of static charges. On storage, dissolution of AET decreased but was always higher than that of the crystalline form, indicating that there was an incomplete transformation from amorphous to crystalline form. The XRPD and DSC data supported this incomplete transformation of AET to crystalline form. Dissolution of SDP (1:1.5) was significantly improved compared to AET; however, it was still lower than that of MG-AET. Similar to AET, the dissolution of SDP decreased on storage; this might be due to the conversion of AET to a crystalline form (Fig. 7).

The dissolution of MG-AET improved significantly compared to that of AET and SDP (Fig. 2). Here the improvement in dissolution was attributed to two factors: the presence of amorphous form in the granules and the hydro-

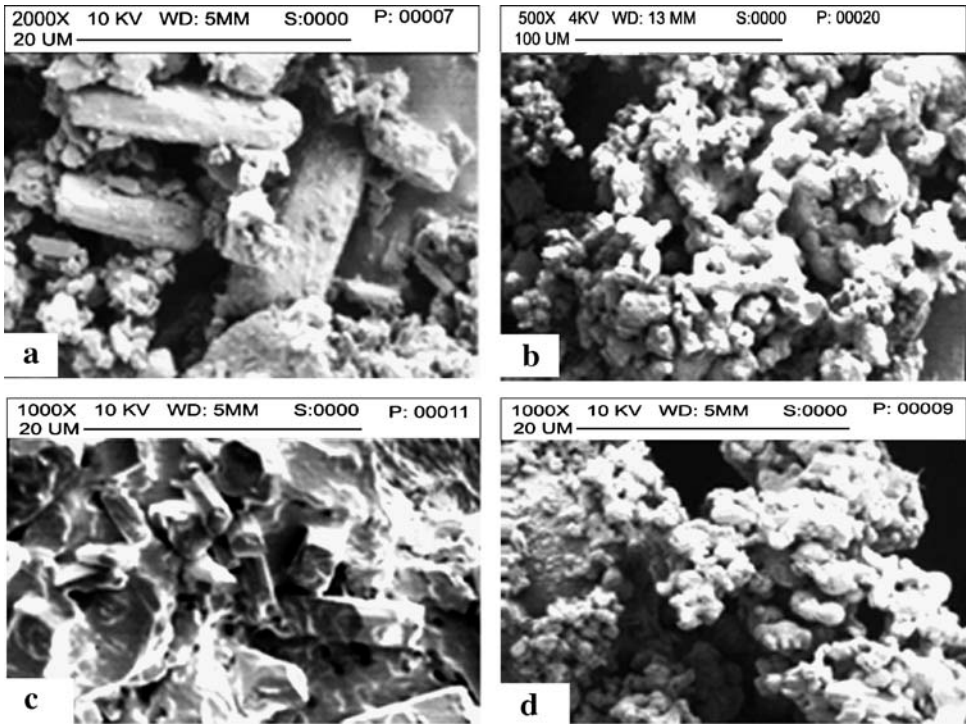

Fig. 5. SEM microphotographs of different formulations of ET. ET (a), AET (b), MG-CET (c), MG-AET (d).

philicity of lipid. No significant differences were found between the dissolution profiles of MG-AET on storage for 3 months. This indicated that the amorphous form of the ET was stable in MG-AET. Stabilization of the amorphous form in MG-AET might be attributed to the formation of hydrogen bond between the drug and lipid, and the immobilization of the drug in the system.

Molecular modeling studies confirmed the lack of hydrogen bonding between PVP and ET. The dynamics trajectories showed other polar interactions between the amide group of PVP and the pyridine (N) of ET, but to a smaller extent. The possibility of hydrogen bonding for amorphous form stabilization was completely ruled out. Hence, the only mechanism assumed for stabilization was the antiplasticizing property of PVP. The dynamics trajectories for ET and Gelucire confirmed hydrogen bonding between the –S=O group of ET and the –OH group of Gelucire (Fig. 8). The configuration obtained from the dynamics trajectories also showed the formation of a complex structure surrounding the ET molecules, which prevented the mobility of molecules and was thus responsible for the amorphous drug stabilization.

MG-AET was expected to exhibit a better bioavailability over neat ET because of its greater dissolution rate. The HPLC method and extraction process were well validated. The ratio of AUC of ET to celecoxib concentration was linear. A summary of pharmacokinetic parameters and plasma

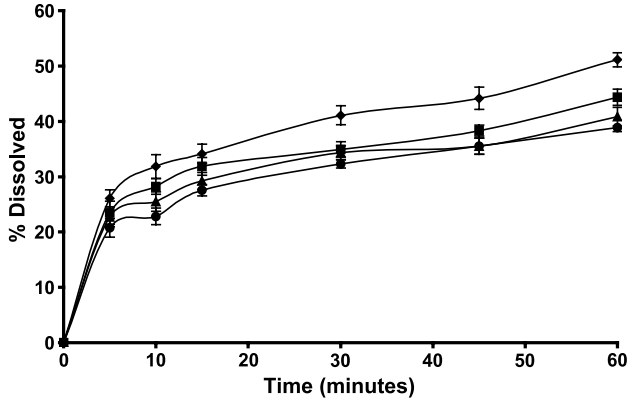

Fig. 6. *In vitro* dissolution profile of AET stability samples. Initial (♦), 10 days (■), 1 month (▲), 3 months (●).

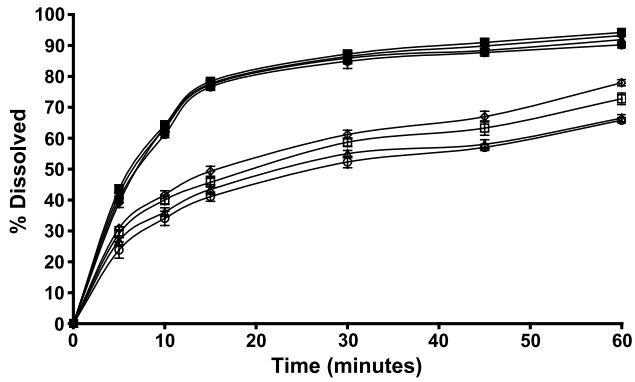

Fig. 7. *In vitro* dissolution profile of SDP and MG-AET stability samples. MG-AET 1:0.5, initial (♦); MG-AET 1:0.5, 10 days (■); MG-AET 1:0.5, 1 month (▲); MG-AET 1:0.5, 3 months (●); SDP 1:1.5, initial (◇); SDP 1:1.5, 10 days (□); SDP 1:1.5, 1 month (△); SDP 1:1.5, 3 months (○).

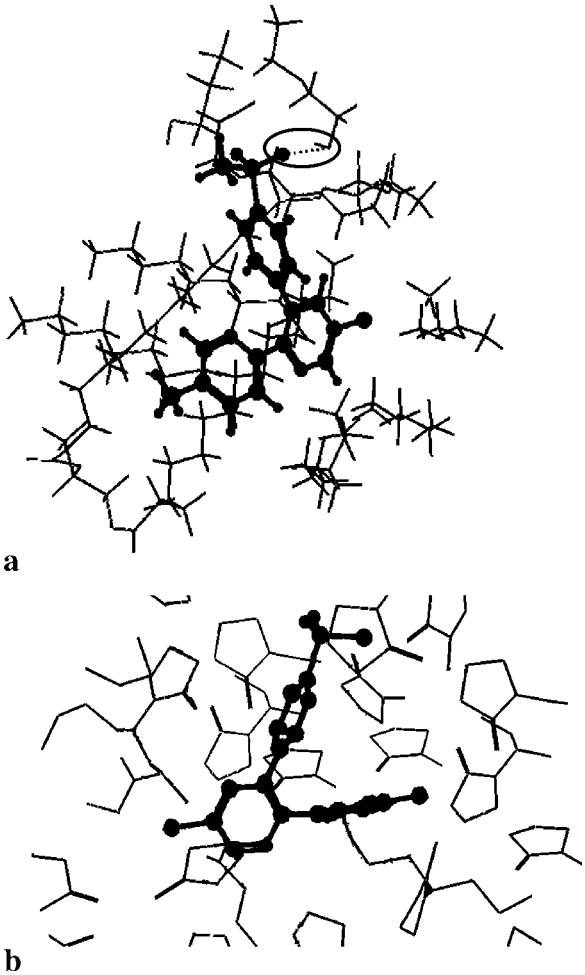

Fig. 8. Stereo view showing the interaction between the etoricoxib-Gelucire (a) and etoricoxib-PVP (b). Etoricoxib is represented by the ball-and-stick model, whereas Gelucire and PVP are represented by the stick model. The dotted line (encircled) represents the hydrogen bonding between the $-SO_2$ group of etoricoxib and –OH group of Gelucire.

concentration-*vs.*-time curves of ET and MG-AET after oral administration to rat are shown in Table 1 and Fig. 9, respectively. The ET plasma concentration from MG-AET was significantly higher than that of the neat drug for up to 24 h. Both the C_{max} and $AUC_{0-24\ h}$ of MG-AET values were approximately twofolds greater than those of the neat drug, indicating the remarkable improvement in oral absorption of ET when administered in amorphous form with lipids. This was in agreement with an earlier report (18).

Table 1. Pharmacokinetic Parameters of ET and MG-AET after Oral Dose in Rat

Pharmacokinetic parameters	ET	MG-AET
C_{max} (μg/ml)*	9.64 ± 1.07	17.35 ± 1.17
T_{max}	2	1
$AUC_{0-24\ h}$ (μg/hr/ml)	102.48 ± 3.95	171.06 ± 15.18

Mean ± SD, $n = 4$, $p < 0.01$, $^*p < 0.001$.

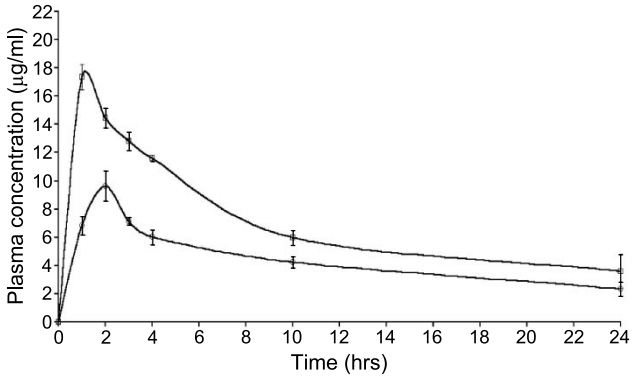

Fig. 9. A representative plasma concentration vs. time profile after an oral dose. ET (○), MG-AET (□), mean ± SD, $n = 4$.

CONCLUSION

Concerning melt granulation technique for poorly water-soluble drugs with low Gelucire/drug ratio is a potentially useful technique for improving dissolution and thus bioavailability. Apart from improvements in dissolution and bioavailability, such a system also promises stabilization of the amorphous form of the drug. This approach also leads to the possibility of further processing Gelucire to be formulated in dosage forms such as tablets. In this investigation, solid dispersions with PVP has shown limited success in stabilizing the amorphous form. Melt granulation with lipids can be further exploited for enzyme stabilization and for BCS class IV drug formulations.

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REFERENCES

1. Y. Yokoi, E. Yonemochi, and K. Terada. Changes in surface properties by granulation and physicochemical stability of granulated amorphous cefditoren pivoxil with additives. *Int. J. Pharm.* **280**:67–75 (2004).
2. A. A. Ambike, K. R. Mahadik, and A. Paradkar. Stability study of amorphous valdecoxib. *Int. J. Pharm.* **282**:151–162 (2004).
3. T. Watanabe, N. Wakiyama, F. Usui, M. Ikeda, T. Isobe, and M. Senna. Stability of amorphous indomethacin compounded with silica. *Int. J. Pharm.* **226**:81–91 (2001).
4. M. K. Gupta, Y.-C. Tseng, D. Goldman, and R. H. Bogner. Hydrogen bonding with adsorbent during storage governs drug dissolution from solid dispersion granules. *Pharm. Res.* **19**:1663–1672 (2002).
5. J. Li, Y. Guo, and G. Zografi. The solid-state stability of amorphous quinapril in the presence of β-cyclodextrins. *J. Pharm. Sci.* **91**:229–243 (2002).
6. F. Damian, N. Blaton, R. Kinget, and G. Van den Mooter. Physical stability of solid dispersions of the antiviral agent UC-781 with PEG 6000, Gelucire 44/14 and PVP K30. *Int. J. Pharm.* **244**:87–98 (2002).

7. J. Akbuga, A. Gursoy, and F. Yetimoglu. Preparation and properties of tablets prepared from furosemide-PVP solid dispersion systems. *Drug Dev. Ind. Pharm.* **14**:2091–2108 (1988).
8. A. Paradkar, A. A. Ambike, B. K. Jadhav, and K. R. Mahadik. Characterization of Curcumin–PVP solid dispersion obtained by spray drying. *Int. J. Pharm.* **271**:281–286 (2004).
9. I. Weuts, D. Kempen, G. Verreck, A. Decorte, K. Heymans, J. Peeters, M. Brewster, and G. Van den Mooter. Study of the physicochemical properties and stability of solid dispersions of loperamide and PEG6000 prepared by spray drying. *Eur. J. Pharm. Biopharm.* **59**:119–126 (2005).
10. N. Passerini, B. Perissutti, M. Moneghini, D. Voinovich, B. Albertini, C. Cavallari, and L. Rodriguez. Characterization of carbmazepin–Gelucire 50/13 microparticles prepared by a spray congealing process using ultrasound. *J. Pharm. Sci.* **91**:699–707 (2002).
11. Y. H. Zhao, M. H. Abraham, J. Le, A. Hersey, C. N. Luscombe, G. Beck, B. Sherborne, and I. Cooper. Evaluation of rat intestinal absorption data and correlation with human intestinal absorption. *Eur. J. Med. Chem.* **38**:233–243 (2003).
12. R. Mullangi, R. R. Kallem, R. K. Bhamidipati, R. N. V. S. Mamidi, and N. R. Srinivas. HPLC method for determination of DRF-4367 in rat plasma: validation and its application to pharmacokinetics in Wistar rats. *Biomed. Chromatogr.* **18**:576–580 (2004).
13. M. Emas and H. Nyqvist. Methods of studying aging and stabilization of spray-congealed solid dispersions with carnauba wax. 1. Microcalorimetric investigation. *Int. J. Pharm.* **197**: 117–1271 (2000).
14. S. R. Vippagunta, K. A. Maul, S. Tallvajhala, and D. W. J. Grant. Solid state characterization of nifedipine solid dispersions. *Int. J. Pharm.* **236**:111–123 (2002).
15. D. Law, S. L. Krill, E. A. Schmitt, J. J. Fort, Y. Qiu, W. Wang, and W. R. Porter. Physicochemical considerations in the preparation of amorphous ritonavir—poly(ethylene glycol) 8000 solid dispersions. *J. Pharm. Sci.* **90**:1015–1025 (2001).
16. J. M. Gines, M. D. Veiga, M. J. Arias, and A. M. Rabasco. Elaboration and thermal study of interactions between cinnarizine and Gelucire 53/10 physical mixtures and solid dispersions. *Int. J. Pharm.* **126**:287–291 (1995).
17. G. Van den Mooter, M. Wuyts, N. Blaton, R. Busson, P. Grobet, P. Augustijns, and R. Kinget. Physical stabilization of amorphous ketoconazole in solid dispersions with polyvinylpyrrolidone K25. *Eur. J. Pharm. Sci.* **12**:261–269 (2001).
18. S. M. Khoo, C. J. H. Porter, and W. N. Charman. The formulation of halofantrine as either non-solubilizing PEG 6000 or solubilizing lipid based solid dispersions: physical stability and absolute bioavailability assessment. *Int. J. Pharm.* **205**:65–78 (2000).