

Preparation and Characterization of Etoricoxib Solid Dispersions Using Lipid Carriers by Spray Drying Technique

Submitted: October 26, 2004; Accepted: April 15, 2005; Published: October 19, 2005

Bhaskar Chauhan,¹ Shyam Shimpi,¹ and Anant Paradkar¹

¹Department of Pharmaceutics, Bharati Vidyapeeth Deemed University, Poona College of Pharmacy, Erandwane, Pune-411038, Maharashtra, India

ABSTRACT

The basic objectives of this study were to prepare and characterize solid dispersions of poorly water-soluble drug etoricoxib using lipid carriers by spray drying technique. The properties of solid dispersions were studied by diffuse reflectance infrared Fourier transform spectroscopy (DRIFTS), differential scanning calorimetry (DSC), hot-stage microscopy (HSM), radiograph powder diffraction (XRPD), and dissolution studies. The absence of etoricoxib peaks in XRPD profiles of solid dispersions suggests the transformation of crystalline etoricoxib into an amorphous form. In the HSM examination of solid dispersions, the dissolution of drug in the lipid carriers was observed, which was also confirmed by the absence of etoricoxib peak in DSC curves of solid dispersions. The DRIFTS spectra revealed the presence of hydrogen bonding in solid dispersions. The *in vitro* dissolution test showed a significant increase in the dissolution rate of solid dispersions as compared with pure etoricoxib, spray-dried etoricoxib, and physical mixtures of drug with lipid carriers. Therefore, the dissolution rate of poorly water-soluble drug etoricoxib can be significantly enhanced by the preparation of solid dispersions using lipid carriers by spray drying technique.

KEYWORDS: spray drying, Gelucire, solid dispersion, amorphous

INTRODUCTION

Various techniques for the improvement of the dissolution rate of poorly water-soluble drugs include micronization,¹ formation of inclusion complexes with cyclodextrin,² formation of amorphous drug,³ and formation of solid dispersions with hydrophilic carriers.⁴⁻⁸ The most commonly used hydrophilic carriers for solid dispersions include polyvinylpyrrolidone,^{5,6} polyethylene glycols,⁹ colloidal

silicon dioxide,¹⁰ and lipids, such as polyglycolized glycerides (Gelucire).¹¹⁻¹³ The solvent evaporation,¹² melt adsorption,¹⁴ fusion,¹¹ spray drying,⁵ spray freezing,¹⁵ spray congealing,¹⁶ melt extrusion,¹⁷ and supercritical fluid precipitation¹⁸ are the techniques reported for the preparation of solid dispersions.

Recently, many workers reported solid dispersions using polyglycolized glycerides (Gelucire) by fusion and solvent evaporation techniques.¹¹⁻¹³ Polyglycolized glycerides are available with a range of properties depending on their hydrophilic lipophilic balance (HLB) over the range of 1 to 18 and melting point between 33° and 70°C.^{19,20} The carbamazepine solid dispersions with Gelucire 50/13 have shown that crystallinity reduction and wetting with hydrophilic lipid are the main mechanisms responsible for an increase in the dissolution rate.²¹ Preparation of solid dispersions by conventional spray drying with polyglycolized glycerides has been problematic. The sticky and tacky mass of polyglycolized glycerides is obtained by a conventional spray drying technique. The spray drying technique for polyglycolized glycerides has been designed with its combination high-melting lipids to overcome this problem.

Etoricoxib (5-chloro-2-[6-methyl pyridin-3-yl]-3-[4-methylsulfonylphenyl] pyridine) is a novel, selective second-generation cyclooxygenase-2 inhibitor administered orally as an analgesic and antiinflammatory drug.^{22,23} The chemical structure of etoricoxib is shown in Figure 1. It is an off-white crystalline powder, relatively insoluble in water, and freely soluble in alkaline aqueous solutions. Therefore, improvements in solubility and/or dissolution rate of poorly water-soluble drugs may be achieved through the formation of solid dispersions.

In the present study, a spray drying technique has been used to prepare solid dispersions with lipid carriers, mainly polyglycolized glycerides (Gelucire 50/13) and high-melting lipids, namely, Compritol (atomized glyceryl dibehenate) or Sterotex K NF (hydrogenated cottonseed oil). Solid dispersions and pure etoricoxib in the form of spray-dried powder were characterized in comparison with pure drug and corresponding physical mixtures in the same ratios by diffuse reflectance infrared Fourier transform spectroscopy (DRIFTS), differential scanning calorimetry (DSC), hot-stage microscopy (HSM), radiograph powder diffraction (XRPD), and *in vitro* drug release.

Corresponding Author: Anant Paradkar, Bharati Vidyapeeth Deemed University, Poona College of Pharmacy, Erandwane, Pune-411038, Maharashtra, India; Tel: +91-20-25437237; Fax: +91-20-25439383; E-mail: arparadkar@rediffmail.com

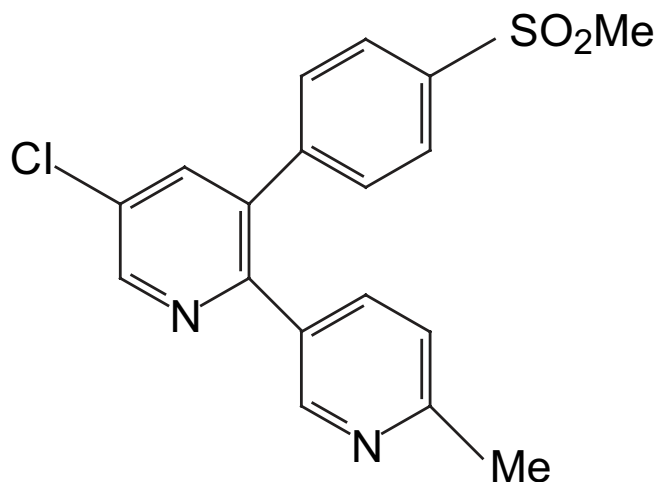


Figure 1. Chemical structure of etoricoxib.

MATERIALS AND METHODS

Etoricoxib was obtained as a gift sample from Unichem Ltd (Mumbai, India). Gelucire 50/13 (Stearoyl Macroglycerides EP, solid pastilles, HLB = 13, lot: 32582) and Compritol 888 ATO (atomized glyceryl dibehenate, free-flowing white-yellow powder, m.P = 59.3 to 70.5°C, HLB = 02, lot: 26775) were generous gifts from Gattefossé (St Priest, Cedex, France). Sterotex K NF (hydrogenated cottonseed oil, free-flowing white solid powder, m.P = 58 to 62°C, HLB = 1.5, lot: 051M3) was supplied by Abitec Corp (Janesville, WI). All of the other chemicals were of analytical grade.

Preparation of Solid Dispersions and Physical Mixtures

Samples of etoricoxib, as such or in combination with Gelucire 50/13 and Sterotex K NF 1:1:0.5 by weight or Gelucire 50/13 and Compritol 1:1:0.5 by weight were dissolved in dichloromethane to obtain clear solutions. Spray drying of these solutions were conducted using a laboratory-scale spray dryer (Jay Instruments & Systems Pvt Ltd, Mumbai, India) under the following set of conditions: inlet temperature, 50°C; outlet temperature, 44°C; feed rate, 4 to 6 mL/min; atomization air pressure, 2 kg/cm²; and aspiration, -300 mm water column. Physical mixtures of drug with Gelucire 50/13 and Sterotex K NF or Gelucire 50/13 and Compritol in the same ratios of 1:1:0.5 (w/w) were prepared by mixing thoroughly for 5 minutes in a mortar until a homogeneous mixture was obtained. All of the samples were passed through a fine mesh (150 µm) and stored in desiccated environment until additional study.

Drug Content and Percent Yield

Solid dispersions equivalent to 60 mg of etoricoxib were weighed accurately and dissolved in a suitable quantity of

methanol. The solutions were filtered through a membrane filter (0.45 µm). The drug content was determined at 232.4 nm by UV spectrophotometer (V-530, JASCO, Kyoto, Japan) after suitable dilution. Analysis of data were done using Disso v 2.08 software.²⁴ The percentage yield of each formulation was also calculated.

Saturation Solubility

To evaluate the increase in solubility of etoricoxib after spray drying (with or without lipid carriers) or only by the presence of lipid excipients (physical mixtures), saturation solubility measurements were conducted. The known excess (approximately 10 mg) of etoricoxib was added to 10 mL of phosphate buffer (pH 6.8). Samples were rotated at 20 rpm in a water bath (37 ± 0.5°C) for 48 hours. The samples were then filtered, suitably diluted, and analyzed by UV spectrophotometer at 232.4 nm.

Residual Solvent Content and Moisture Determination

To calculate the amount of moisture and residual dichloromethane in the spray-dried etoricoxib and solid dispersions, a combination of Karl Fischer titration (MATC-D Karl Fischer Titrator, Veego, Mumbai, India) and thermal gravimetric analysis was performed by heating a weighed amount of the sample in a nitrogen atmosphere from 25 to 70°C at the rate of 2°C/min (TGA-50, Shimadzu Corp, Kyoto, Japan).

DRIFTS

The DRIFTS spectra of pure etoricoxib, spray-dried etoricoxib, physical mixtures, and solid dispersions were obtained, after appropriate background subtraction, using an FTIR spectrometer (FTIR-8400, Shimadzu Corp) equipped with a diffuse reflectance accessory (DRS-8000, Shimadzu Corp) and a data station. About 2 to 3 mg of the sample was mixed with dry potassium bromide, and the sample was scanned from 4,000 to 400 cm⁻¹.

DSC

DSC studies were conducted using a Mettler-Toledo DSC 821^e instrument equipped with an intracooler (Mettler-Toledo, Greifensee, Switzerland). Indium/zinc standards were used to calibrate the DSC temperature and enthalpy scale. The samples were hermetically sealed into pierced aluminum pans and heated at a constant rate of 10°C/min over a temperature range of 25 to 170°C. Inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50 mL/min.

HSM

HSM of solid dispersions and physical mixtures were conducted using Mettler-Toledo FP82HT hotstage (Greifensee, Switzerland) assembled on a Leica DMLP polarizing microscope equipped with a Leica MPS-30 camera (Leica, Bensheim, Germany). A small amount (2-4 mg) of sample was placed on a glass slide with a coverglass and heated at 3°C/min. Changes in the samples morphology were noted as a function of temperature.

XRPD

The XRPD patterns were recorded on a radiograph diffractometer (PW 1729, Philips, Eindhoven, The Netherlands). The samples were irradiated with monochromatized Cu K α radiation (1.542° A) and analyzed between 2 and 50° (2 θ). The voltage and current used were 30 kV and 30 mA, respectively. The range and the chart speed were 5 \times 10³ CPS and 10 mm/° (2 θ), respectively.

Dissolution Rate

The dissolution studies were performed using a US Pharmacopeia 24 type II dissolution test apparatus (Electrolab TDT-06P, Mumbai, India). The samples equivalent to 60 mg etoricoxib were placed in a dissolution vessel containing 900 mL of phosphate buffer (pH 6.8) maintained at 37 \pm 0.5°C and stirred at 100 rpm. Samples were collected periodically and replaced with a fresh dissolution medium. After filtration through Whatman filter paper no. 41, a concentration of etoricoxib was determined spectrophotometrically at 232.4 nm. Data were analyzed by PCP-Disso software.

RESULTS AND DISCUSSION

The sticky and tacky mass was obtained in the cyclone of spray drier when only Gelucire 50/13 and etoricoxib solution was spray dried. Whereas solid dispersions along with Compritol or Sterotex K NF showed good flow properties with yields of 70% to 73% wt/wt. The drug content in solid dispersions was found to be 97% to 98.7%. The moisture content in the spray-dried etoricoxib, solid dispersion of etoricoxib with Gelucire 50/13 and Compritol, and solid dispersion of etoricoxib with Gelucire 50/13 and Sterotex K NF were found to be 0.43%, 0.63%, and 0.091% w/w, respectively. The dichloromethane residual content in the spray-dried etoricoxib, solid dispersion of etoricoxib with Gelucire 50/13 and Compritol, and solid dispersion of etoricoxib with Gelucire 50/13 and Sterotex K NF were found to be 0.031%, 0.053%, and 0.083% w/w, respectively. Therefore, the spray drying method used in this study appears applicable for the preparation of solid dispersions without affecting drug content. Etoricoxib has

Table 1. Saturation Solubility of Different Formulations of ETO* Tested in Phosphate Buffer (pH 6.8) at 37 \pm 0.5°C

Type of Formulation	Saturation Solubility ($\mu\text{g/ml}$) [†]
Pure Etoricoxib	77.16 \pm 0.523
Spray-Dried Etoricoxib	109.13 \pm 0.811
PM ETO + Gel + Sterotex	123.23 \pm 0.801
PM ETO + Gel + Comp	120.61 \pm 0.996
SD ETO + Gel + Sterotex	165.08 \pm 0.769
SD ETO + Gel + Comp	160.15 \pm 0.555

*ETO, Etoricoxib; Gel, Gelucire 50/13; Comp, Compritol; PM, physical mixture; SD, solid dispersion.

[†]Mean \pm SD; *n* = 3.

pH-dependent solubility. During in vitro drug release and solubility measurements, the change in pH may hamper the results. So to maintain the pH constant, phosphate buffer (pH 6.8) was used. Pure etoricoxib was characterized by 77.17 $\mu\text{g/mL}$ of saturation solubility. All of the test samples showed an increase in drug solubility (Table 1). Physical mixtures showed higher saturation solubility as compared with pure etoricoxib and spray-dried etoricoxib. It might be attributable to an improvement of wetting of drug particles and localized solubilization by the lipid carriers.

The DRIFT spectra of etoricoxib, spray-dried etoricoxib, physical mixtures, and solid dispersions are shown in Figure 2. The DRIFT spectra of pure etoricoxib showed characteristic peaks at 1,596.9 cm^{-1} (C = N stretching vibration); 1,431 cm^{-1} , 1,300 cm^{-1} , 1,141.8 cm^{-1} , and 1,085.8 cm^{-1} (S = O stretching vibrations); and 840.9 cm^{-1} , 775.3 cm^{-1} , and 638 cm^{-1} (C-Cl stretching vibration), respectively. In the case of spray-dried etoricoxib, a slight shift in S = O stretching vibrations (1,305.5 cm^{-1} , 1,147.6 cm^{-1} , and 1,090.8 cm^{-1}) and C-Cl stretching vibration (846.6 cm^{-1} , 780.4 cm^{-1} , and 653.8 cm^{-1}) peaks were observed with the presence of an additional peak at 3,344.3 cm^{-1} (O-H stretching vibration). It might be the possibility of intermolecular hydrogen bonding between adjunct etoricoxib molecules. The spectra of physical mixtures were equivalent to the spectra obtained by the addition of lipid carriers and crystalline drug spectrum. This indicated that no interaction occurred with a simple physical mixing of drug and lipid carriers. This was additionally confirmed by XRPD patterns of physical mixtures. The DRIFT spectrum of solid dispersion of etoricoxib with Gelucire 50/13 and Compritol showed significant broadening O-H stretching vibrations peak characteristic for lipid carriers (large band between 3,650 cm^{-1} and 3,150 cm^{-1} for free O-H stretching vibration of the COOH groups) and S = O stretching vibration (1,141.1 cm^{-1}) characteristic of etoricoxib. Similarly, the spectrum of solid dispersion of etoricoxib with Gelucire 50/13 and Sterotex K NF revealed a slight shift and slight

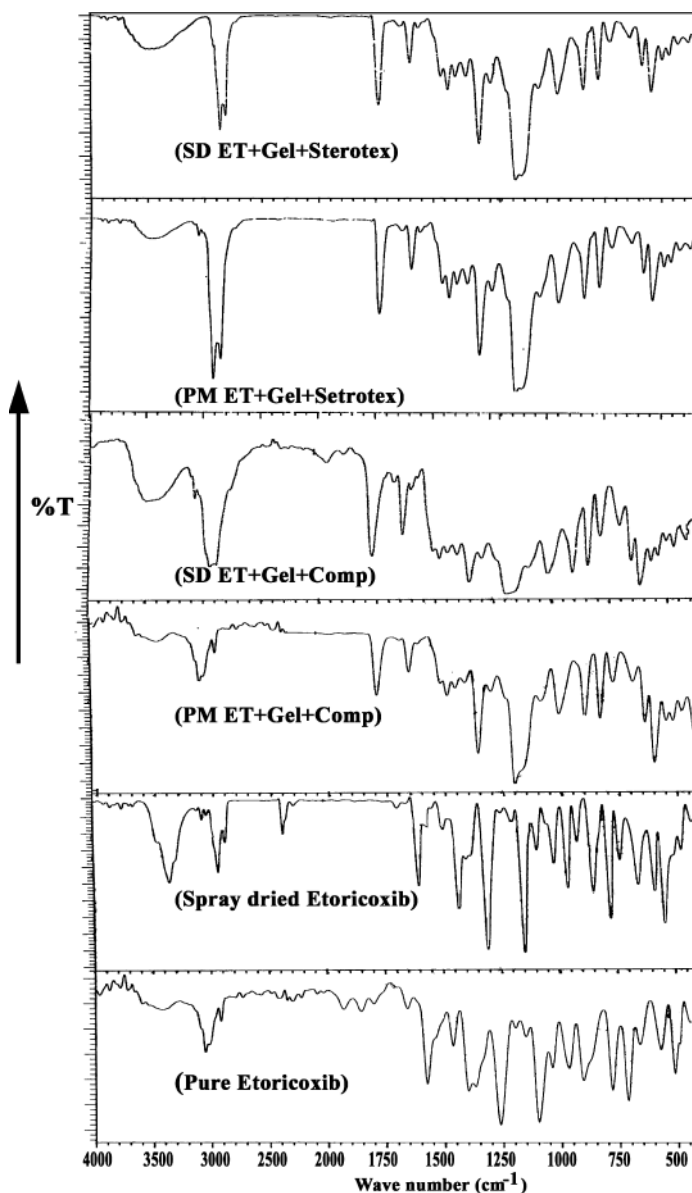


Figure 2. DRIFT spectras of etoricoxib. ET, etoricoxib; Gel, Gelucire 50/13; Comp, Compritol; PM, physical mixture; SD, solid dispersion.

broadening of S = O ($1,146.1 \text{ cm}^{-1}$) stretching vibration peaks of etoricoxib and O-H stretching vibration peak ($3,650 \text{ cm}^{-1}$ and $3,110 \text{ cm}^{-1}$) characteristic for lipid carriers. These observations might show the possibility of intermolecular hydrogen bonding via the S = O group of etoricoxib and OH of lipid carriers.

The DSC thermograms of pure etoricoxib, spray-dried etoricoxib, physical mixtures, solid dispersions, and solid dispersions without etoricoxib are represented in Figure 3. The DSC thermogram of crystalline etoricoxib showed a single peak endotherm at 139.15°C , which was ascribed to drug melting. The DSC thermogram of spray-dried etoricoxib showed a shallow endotherm at 40.8°C , indicating glass transition temperature, recrystallization peak at 105°C , shoulder at 110 and 130°C , and a melting peak at

139°C . This confirmed the transformation of crystalline etoricoxib into an amorphous etoricoxib. The shoulder at 110 and 130°C might show the possibility of hydrates or polymorphs, and so forth. Similar observations have been reported for the glassy state of celecoxib, which readily crystallizes when heated at $10^\circ\text{C}/\text{min}$.²⁵ The physical mixture of etoricoxib with Gelucire 50/13 and Compritol exhibited a large, broad endotherm in the region of 31.1 to 40.54°C , corresponding with the melting of Gelucire 50/13, and a smaller broad endotherm in the region of 59.3 to 70.5°C , corresponding with the melting of Compritol, whereas the endotherm of etoricoxib was completely absent. DSC thermograms of solid dispersions of etoricoxib with Gelucire 50/13 and Compritol were very similar to that of the physical mixture of etoricoxib with Gelucire 50/13 and Compritol. Similarly, the physical mixture of etoricoxib with Gelucire 50/13 and Sterotex K NF exhibited a first endotherm in the region of 33 to 41.1°C , ascribed to the melting of Gelucire 50/13, and a second endotherm in the region of 58 to 62°C , corresponding with the melting of Sterotex K NF, whereas the endotherm of etoricoxib was completely absent. DSC thermograms of solid dispersions of etoricoxib with Gelucire 50/13 and Sterotex K NF were very similar to that of the physical mixture of etoricoxib with Gelucire 50/13 and Sterotex K NF, except for a shoulder endotherm at 53°C in the solid dispersions of etoricoxib with Gelucire 50/13 and Sterotex K NF. It appears that the glass transition temperature and

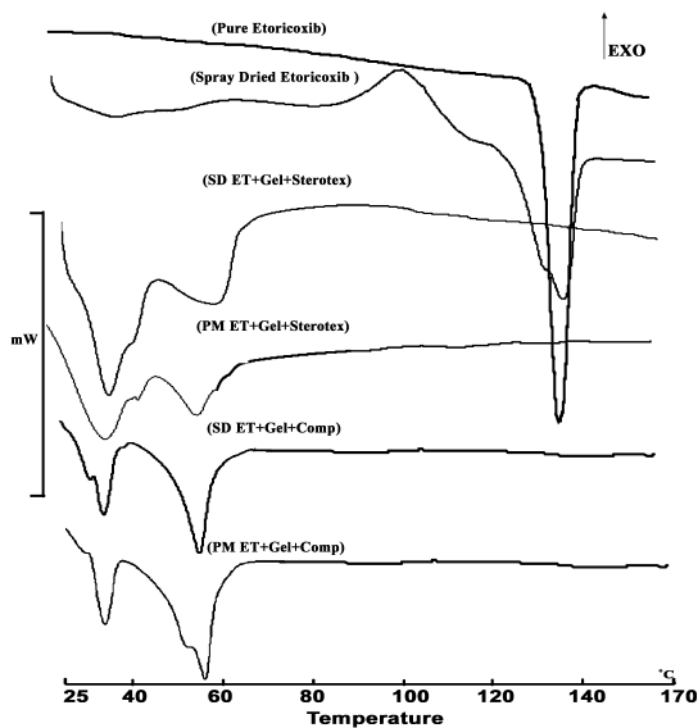


Figure 3. Differential scanning calorimetry thermograms of etoricoxib. ET, etoricoxib; Gel, Gelucire 50/13; Comp, Compritol; PM, physical mixture; SD, solid dispersion.

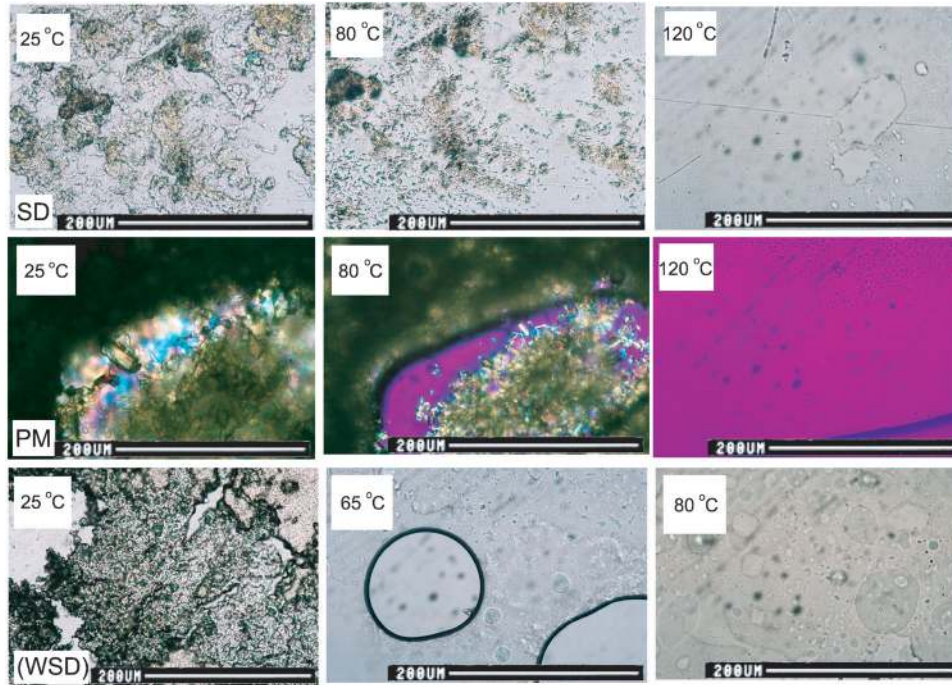


Figure 4. HSM photomicrographs of etoricoxib, Gelucire 50/13, and Compritol at original magnification at $\times 200$. PM, physical mixture; SD, WSD, solid dispersion without etoricoxib.

melting peak of lipids were merged. The melting peak of etoricoxib in both physical mixtures and solid dispersions were absent. It was because of the dissolution of etoricoxib in the lipid carriers, which was additionally supported by HSM examination. Similar observations have been reported for carbamazepine-Gelucire 50/13 microparticles.²⁶ However, the similarity of physical mixtures and solid

dispersions in the DSC thermograms also indicated the dissolution of the drug into the molten lipid carriers at temperatures $>100^{\circ}\text{C}$ during the DSC scan. The above hypothesis has been additionally clarified by HSM analysis.

The hot stage microscopic examination of the solid dispersions without etoricoxib showed that complete melting of the lipid carriers occurs at 80°C (Figures 4A and 5A) with

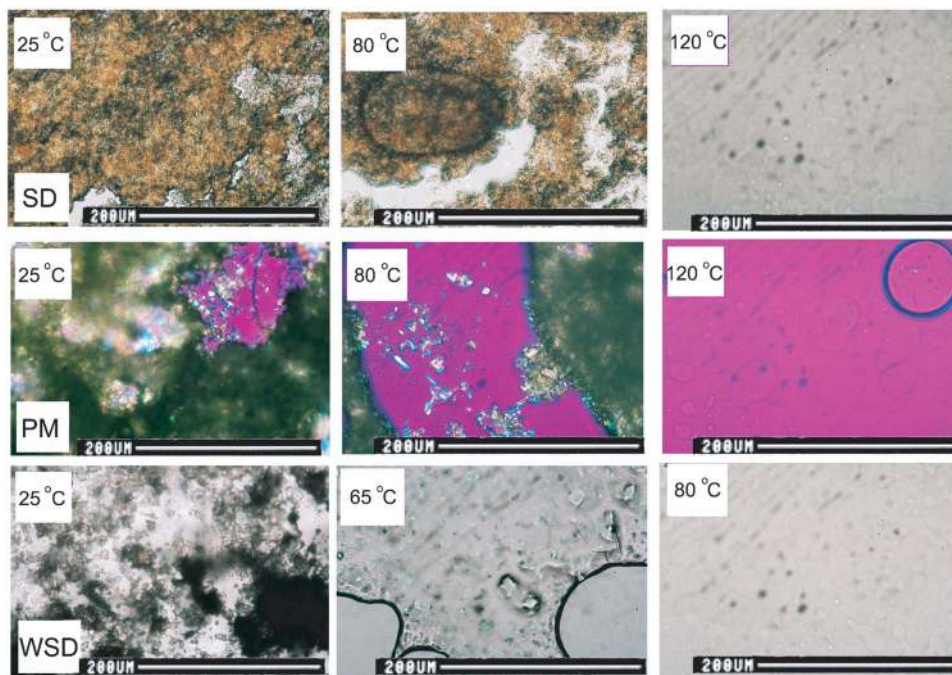


Figure 5. HSM photomicrographs of etoricoxib, Gelucire 50/13, and Sterotex at original magnification at $\times 200$. PM, physical mixture; SD, WSD, solid dispersion without etoricoxib.

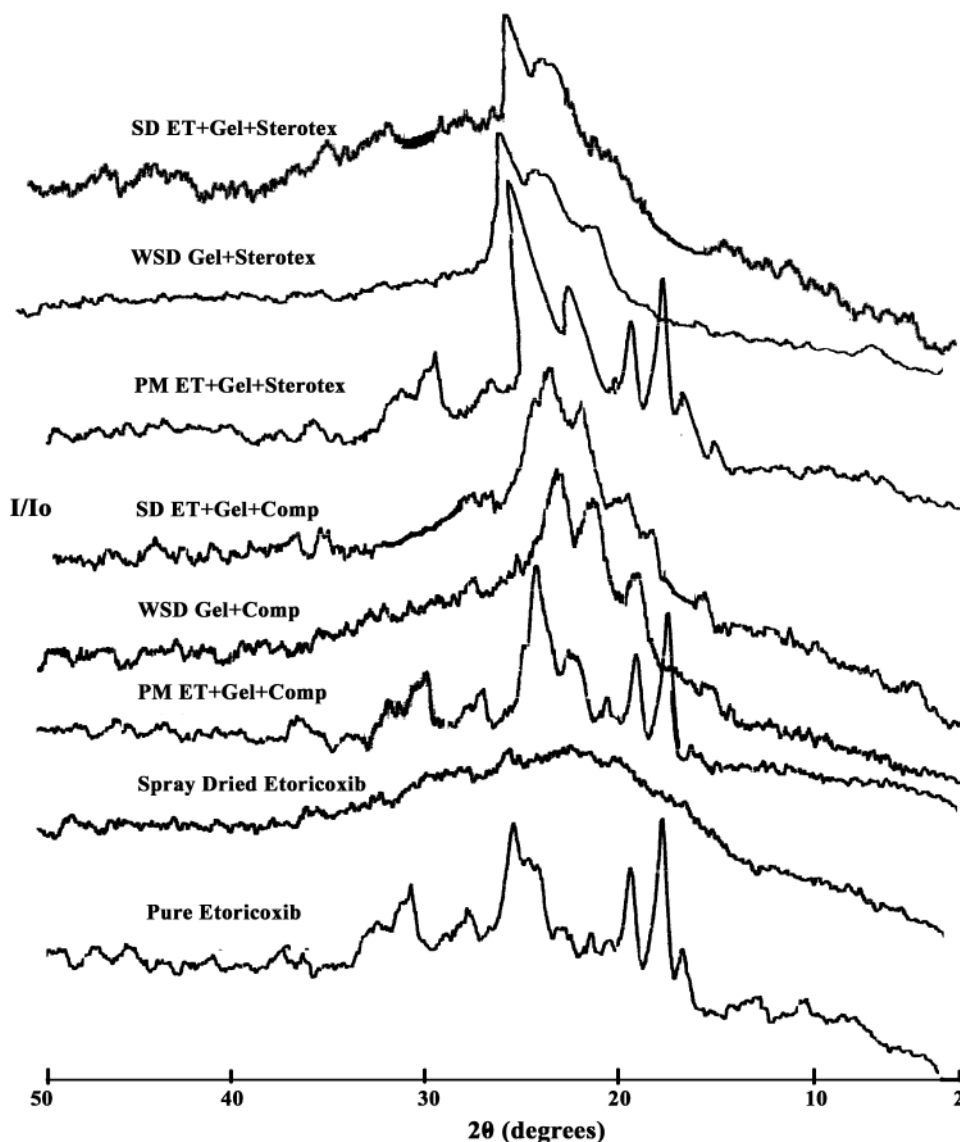


Figure 6. Radiograph powder diffraction patterns etoricoxib. ET, etoricoxib; Gel, Gelucire 50/13; Comp, Compritol; PM, physical mixture; SD, solid dispersion; WSD, solid dispersion without etoricoxib.

out birefringence. In the hot stage microscopic examination of physical mixtures (Figures 4B and 5B) or solid dispersions (Figures 4C and 5C), we observed the birefringence of drug in the molten lipid carriers. After heating up to 80°C, etoricoxib was easily recognized as tiny particles dispersed throughout the molten lipid carriers. The hot stage microscopic examination of physical mixtures showed more birefringence as compared with respective solid dispersions. It was attributable to the decrease of crystallinity of etoricoxib during spray drying. The birefringence was completely absent at 120°C; that is, the drug dissolved completely into molten lipid carriers at 120°C. These results confirmed that the disappearance of etoricoxib melting endotherm in the DSC thermograms of physical mixtures and solid dispersions were attributable to dissolution of the drug into the molten lipid carriers.

The XRPD patterns of pure etoricoxib showed numerous distinctive peaks in the region of 10 to 36° (2θ) (17, 18.2, 24.2, 29.2 [2θ]) that indicated the crystalline nature of etoricoxib (Figure 6), whereas a halo pattern was seen in XRPD of spray-dried etoricoxib (Figure 6). It showed broad and diffuse maxima attributable to the relatively random arrangement of the constituent molecules, which produced poorly coherent scatters. These patterns were quite distinct from those produced by the crystalline etoricoxib. This confirmed the transformation of crystalline etoricoxib into an amorphous etoricoxib and was also supported by DSC results. The XRPD patterns of solid dispersions without etoricoxib showed the typical peaks for triglycerides, observed in the region of 19.1 and 23.3° (2θ) (Figure 6), called short spacing.^{26,27} The XRPD pattern of physical mixtures showed the presence of characteristics of etoricoxib

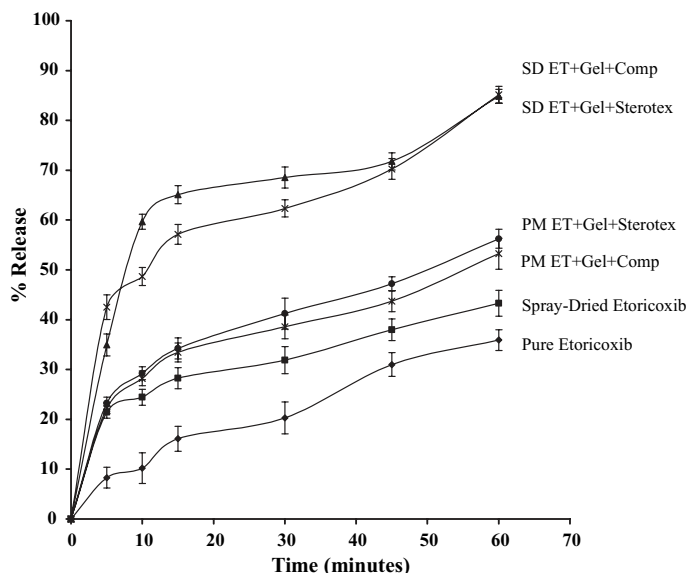


Figure 7. Comparative dissolution profiles of different formulations of Etoricoxib. Each point refers to mean \pm SD ($n = 3$). ET, etoricoxib; Gel, Gelucire 50/13; Comp, Compritol; PM, physical mixture; SD, solid dispersion.

peaks except for the etoricoxib peak at 24.2 (Figure 6). The disappearance of the etoricoxib peak at 24.2 in physical mixtures might be a result of attenuation of a signal in the presence of excipients or preferential orientation. The presence of etoricoxib peaks in the physical mixtures indicating that in the physical mixture of etoricoxib was present in the crystalline form as confirmed by the DRIFTS results. The XRPD patterns of solid dispersions also showed typical lines for triglycerides but lack of etoricoxib peaks at 17, 18.2, and 29.2 (2θ) (Figure 6). It confirmed that etoricoxib was present in the partial amorphous form in the solid dispersions. The presence of typical lines for triglycerides in solid dispersions and solid dispersions without etoricoxib of XRPD patterns showed that the spray drying technique did not modify the original polymorphic form of the carriers.

Dissolution profiles of crystalline etoricoxib, spray-dried amorphous etoricoxib, solid dispersions, and physical mixtures in phosphate buffer (pH 6.8) are shown in Figure 7. Amorphous etoricoxib showed a significant increase in the dissolution rate as compared with etoricoxib. The amount dissolved in 60 minutes was 43.3% for amorphous etoricoxib, whereas it was only 35.9% for crystalline etoricoxib. All of the physical mixtures and solid dispersion samples showed improved dissolution of etoricoxib over the pure etoricoxib. The dissolution from spray-dried etoricoxib and physical mixtures are similar at the 5-minute time point. Differences exist in the extent of dissolution (53% to 57% dissolution of etoricoxib in 60 minutes for physical mixtures). It might be attributed to an improvement of wet-

ting of drug particles and localized solubilization by the lipid carriers in the diffusion layer. Solid dispersions showed almost similar drug release profiles (84% to 85% in 60 minutes). Within first 5 minutes, the solid dispersions exhibited a higher burst release of etoricoxib. The increase in dissolution of etoricoxib from the solid dispersions might be attributed to factors such as a reduction in the particle size of the drug in the matrix, increase in the surface area, reduced crystallinity, and an increase in the solubility of the drug in the presence of the lipid carriers.^{28,29} Similar observations have been reported for solid dispersions of naproxen in polyethylene glycols and nifedipine in Gelucire 50/13 with pluronic F68.^{30,31}

CONCLUSION

It may be concluded that solid dispersions of the purely water-soluble drug etoricoxib were successfully prepared by spray drying using lipid carriers. DRIFT spectroscopy revealed the possibility of H-bonding interactions in solid dispersions, which was also supported by DSC and XRPD observations. The in vitro dissolution test showed a significant increase in the dissolution rate of solid dispersions as compared with pure etoricoxib, spray-dried etoricoxib, and physical mixtures of drug with lipid carriers. Therefore, the dissolution rate of the poorly water-soluble drug etoricoxib can be significantly enhanced by the preparation of solids using lipid carriers by the spray drying technique.

ACKNOWLEDGMENTS

Anant Paradkar and Bhaskar Chauhan are thankful to University Grant Commission and Council of Scientific and Industrial Research, New Delhi, India, for providing financial support in the form of a major research project and Senior Research Fellowship, respectively. The authors are thankful to Gattefossé (St Priest, Cedex, France), Colorcon (Goa, India), and Abitec Corp (Jenesville, WI) for the gift samples.

REFERENCES

- Gupta MK, Vanwert A, Bogner RH. Formation of physically stable amorphous drugs by milling with Neusilin. *J Pharm Sci.* 2003;92:536-551.
- Cavallari C, Abertini B, Gonzalez-Rodriguez ML, Rodriguez L. Improved dissolution behaviour of steam-granulated piroxicam. *Eur J Phar Biopharm.* 2002;54:65-73.
- Corrigan OI. Thermal analysis of spray dried products. *Thermochim Acta.* 1995;248:245-258.
- Chiou WL, Riegelman S. Pharmaceutical applications of solid dispersion systems. *J Pharm Sci.* 1971;60:1281-1302.
- Ambike AA, Mahadik KR, Paradkar A. Stability study of amorphous valdecoxib. *Int J Pharm.* 2004;282:151-162.

6. Paradkar A, Ambike AA, Jadhav BK, Mahadik KR. Characterization of curcumin—PVP solid dispersion obtained by spray drying. *Int J Pharm.* 2004;271:281-286.
7. Van den Mooter G, Wuyts M, Blaton N, et al. Physical stabilisation of amorphous ketoconazole in solid dispersions with polyvinylpyrrolidone K25. *Eur J Pharm Sci.* 2001;12:261-269.
8. Jung J, Yoo S, Lee S, Kim K, Yoon D, Lee K. Enhanced solubility and dissolution rate of itraconazole by a solid dispersion technique. *Int J Pharm.* 1999;187:209-218.
9. Doshi DH, Ravis WR, Betageri GV. Carbamazepine and polyethylene glycol solid dispersion preparation, invitro dissolution, and characterization. *Drug Dev Ind Pharm.* 1967;23:1167-1176.
10. Takeuchi H, Nagira S, Yamamoto H, Kawashima Y. Solid dispersion particles of tolbutamide prepared with fine silica particles by the spray-drying method. *Powder Technology.* 2004;141:1187-1195.
11. Abdul-Fattah AM, Bhargava HN. Preparation and in vitro evaluation of solid dispersions of halfantrine. *Int J Pharm.* 2002;235:17-33.
12. Damian F, Blaton N, Naesens L, et al. Physicochemical characterization of solid dispersions of the antiviral agent UC-781 with polyethylene glycol 6000 and Gelucire 44/14. *Eur J Pharm Sci.* 2000;10:311-322.
13. Pozzi F, Longo A, Lazzarini C, Carezzi A. Formulations of Ubidecarenone with improved bioavailability. *Eur J Pharm Biopharm.* 1991;37:243-246.
14. Gupta MK, Tseng YC, Goldman D, Bogner RH. Hydrogen bonding with adsorbent during storage governs drug dissolution from solid-dispersion granules. *Pharm Res.* 2002;19:1663-1672.
15. Hu J, Rogers TL, Brown J, Young T, Johnston KP, Williams RO 3rd. Improvement of dissolution rates of poorly water soluble APIs using novel spray freezing into liquid technology. *Pharm Res.* 2002;19:1278-1284.
16. Fini A, Rodriguez C, Cavallari C, Albertini B, Passerini N. Ultrasound-compacted and spray-congealed indomethacin/polyethyleneglycol systems. *Int J Pharm.* 2002;247:11-22.
17. Brietenbach J, Berndl G, Neumann J, Rosenberg J, Simon D, Zeidler J. Solid dispersion by integrated melt extrusion system. *Proc Control Rel Soc.* 1998;804-805.
18. Sethia S, Squillante E. Solid dispersion of carbamazepine in PVP K30 by conventional solvent evaporation and supercritical methods. *Int J Pharm.* 2004;272:1-10.
19. Aïnaoui A, Vergnaud JM. Modelling the plasma drug level with oral controlled release forms with lipidic Gelucire. *Int J Pharm.* 1998;169:155-162.
20. Sheu MT, Hsia AHO. Polyglycolized saturated glycerides as carrier and enhancer for drug penetration. *Chin Pharm J.* 2001;53:107-111.
21. Passerini N, Perissutti B, Moneghini M, et al. Characterization of carbamazepine-Gelucire 50/13 microparticles prepared by a spray-congealing process using ultrasounds. *J Pharm Sci.* 2002;91:699-707.
22. Agrawal NGB, Porras AG. Dose proportionality of oral etoricoxib, a highly selective cyclooxygenase-2 inhibitor, in healthy volunteers. *J Clin Pharmacol.* 2001;41:1106-1110.
23. Rodrigues AD, Halpin RA, Geer LA, et al. Absorption, metabolism, and excretion of etoricoxib, a potent and selective cyclooxygenase-2 inhibitor, in healthy male volunteers. *Drug Metab Dispos.* 2003;31:224-232.
24. Ketkar AR, Patil VB, Paradkar AR. Computer aided exploratory data analysis model fitting for dissolution kinetics. Fourth International Symposium on Advances in Technology and Business Potential of New Drug Delivery System. Mumbai, India: Controlled Release Society Indian Chapter, 2002;62.
25. Paradkar AR, Chauhan B, Yamamura S, Pawar AP. Preparation and characterization of glassy celecoxib. *Drug Dev Ind Pharm.* 2003;29:739-744.
26. Persutti B, Rubessa F, Princivalle F. Solid dispersions of carbamazepine with gelucire 44/14 and 50/13. *STP Pharm Sci.* 2000;10:479-484.
27. Hamdani J, Moës AJ, Amighi K. Physical and thermal characterisation of Precirol and Compritol as lipophilic glycerides used for the preparation of controlled-release matrix pellets. *Int J Pharm.* 2003;260:47-57.
28. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. *Eur J Pharm Biopharm.* 2000;50:47-60.
29. Serajuddin ATM. Solid dispersions of poorly water-soluble drugs: early promises, subsequent problems, and recent breakthroughs. *J Pharm Sci.* 1999;88:1058-1066.
30. Mura P, Manderioli A, Bramanti G, Ceccarelli L. Properties of solid dispersions of naproxen in various polyethylene glycols. *Drug Dev Ind Pharm.* 1996;22:909-916.
31. Vippagunta SR, Maul KA, Tallavajhala S, Grant DJW. Solid-state characterization of nifedipine solid dispersions. *Int J Pharm.* 2002;236:111-123.