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Enhanced release of solid dispersions of etodolac in polyethylene glycol☆

Yalçın Özkan *, Nazan Doğanay, Necati Dikmen, Aşkın Işımer

Department of Pharmaceutical Technology, Gülhane Military Medical Academy, 06018, Etlik, Ankara, Turkey

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Abstract

This work examines the release of etodolac from various molecular weight fractions of polyethylene glycol (PEG) solid dispersions. Solid dispersions of etodolac were prepared in different molar ratios of drug/carrier by using solvent and melting methods. The release rate of etodolac from the resulting complexes was determined from dissolution studies by use of USP dissolution apparatus 2 (paddle method). The physical state and drug:PEG interaction of solid dispersions and physical mixtures were characterized by X-ray diffraction (XRD), infrared spectroscopy (IR) and differential scanning calorimetry (DSC). The dissolution rate of etodolac is increased in all of the solid dispersion systems compared to that of the pure drug and physical mixtures. The solid dispersion compound prepared in the molar ratio of 1:5 by the solvent method was found to have the fastest dissolution profile. The physical properties did not change after 9 months storage in normal conditions.

Keywords: Etodolac; Solid dispersion; Polyethylene glycol; Dissolution

1. Introduction

Drug dissolution from a solid dispersion is influenced by various factors such as the technology employed to prepare the dispersion, proportion and properties of the carrier used, pH of the dissolution medium, temperature, and surface properties of the solid dispersion particles. In general, the main interest in such systems has been focused on attempts to increase the dissolution rates of hydrophobic drugs by incorporating them in a water-soluble polymer matrix [1].

The use of solid dispersions to increase the dissolution rate and the bioavailability of poorly water-soluble drugs is now well-established [2–5]. Solid dispersions represent a useful pharmaceutical technique for increasing the dissolution, absorption and therapeutic efficacy of drugs in dosage forms. An important factor influencing the properties of such solid dispersions is the method of preparation and the type of the carrier used. The solid dispersion of one or more active ingredients in an inert carrier or matrix in the solid state can be prepared by the solvent, melting or solvent-melting methods [1].

The most commonly used carriers are long-chain polymers such as polyethylene glycols (PEGs). These hydrophilic carriers have been shown to increase the dissolution rate of many drugs [3,6,7].

Etodolac [(1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-6]indol-1-yl)acetic acid] is a nonsteroidal anti-inflammatory agent; it is an inhibitor of prostaglandin synthetase. It is used in rheumatoid arthritis, usually at an oral dose of 200 mg twice daily; up to 600 mg daily may be given if necessary. Etodolac is absorbed from the gastro-intestinal tract with peak plasma concentrations being attained about 1–2 h after ingestion [8,9]. Etodolac is poorly water soluble, and therefore its bioavailability is expected to be limited by its dissolution rate, which might be increased using solid dispersion technology.

In this work, the physicochemical properties of solid dispersions have been examined. In the present work, an attempt is made to improve the dynamic and equilibrium aqueous solubility of etodolac by dispersing it

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* Corresponding author. Fax: +90-312-323 4923.

E-mail address: yozkan@obs.gata.edu.tr (Y. Özkan)

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in PEGs. This involved the study of the possible interaction between etodolac and PEG in the solid state. Interaction in the solid state was studied by X-ray diffraction (XRD), infrared spectroscopy (IR) and differential scanning calorimetry (DSC). For the present work solid dispersions of etodolac with PEGs of different molecular weight were prepared by the solvent and melting methods. The properties of solid dispersions of etodolac at different ratios of PEGs (1:1; 1:2; 1:5) and dissolution rate profiles of etodolac from the solid dispersions are presented.

2. Experimental

2.1. Materials

Etodolac was obtained from Nobel Drug Inc (Istanbul, Turkey). Polyethylene glycols were of nominal molecular weights 3350, 6000, 10 000, 20 000 (Sigma, USA). All other reagents were of analytical grade.

2.2. Preparation of solid dispersions and physical mixtures

Solid dispersions and physical mixtures were prepared with drug:PEGs in 1:1, 1:2, 1:5, weight ratios by means of solvent and melting methods. Physical mixtures were prepared by mixing manually. The mixture was passed through a 500 μm mesh sieve.

The solid dispersions were prepared from the above-mentioned physical mixtures by the melting method [10] in an oil bath heated at 150°C. Fusion was reached in 20 min at this temperature with constant stirring by a glass agitator. Once the resultant melt was homogeneous, the melted mixture was flash-cooled on ice water. After solidification, the obtained solid was ground and sieved with a 500-μm mesh sieve.

Solid dispersions were prepared also by the solvent method. The minimum amount of methanol was added to prepared the above-mentioned physical mixtures. The solvents were removed under reduced pressure at 50°C and dried under vacuum at room temperature for 5 h. The samples were pulverized using a mortar and pestle and sieved.

2.3. X-ray diffraction studies

XRD patterns were obtained using a PW 1730 diffractometer (Philips, Holland) with CuKα radiation, collimated by a 0.08° divergence slit and a 0.2° receiving slit and scanned at a rate of 2.4° min^{-1} over the 2θ range of 5–45°.

2.4. Differential scanning calorimetry

DSC was performed on a DSC 200 Netzsch (Germany). Samples were heated in hermetically sealed aluminum pans with a heating rate of 10°C min^{-1} in the range of 20–300°C under nitrogen atmosphere.

2.5. Infrared spectroscopy

The spectra were recorded on Shimadzu IR 470 (Japan). Samples were prepared in KBr discs.

2.6. Dissolution studies

The dissolution medium consisted of 900 ml simulated gastric fluid TS prepared without pepsin [11] maintained at 37 ± 0.5°C. The USP paddle apparatus (Caleva model 7 ST, UK) fixed at 50 rpm left for dissolution tests.

Table 1
Released percentage of Etodolac from physical mixtures and solid dispersions after 45 min [a]

PEG molecular weight	% released			
	Dispersion composition (Eto:PEG)			
	Preparation method of solid dispersion	1:1	1:2	1:5
3350	Physical mixture	28.51 ± 0.12	29.92 ± 0.54	41.83 ± 0.70
	Melting method	32.19 ± 0.25	37.47 ± 0.40	43.93 ± 0.29
	Solvent method	32.20 ± 0.32	33.35 ± 0.10	44.97 ± 0.74
6000	Physical mixture	17.30 ± 0.43	23.74 ± 0.51	34.87 ± 0.18
	Melting method	28.80 ± 0.95	38.70 ± 0.07	49.05 ± 1.67
	Solvent method	25.96 ± 0.49	32.50 ± 0.72	70.58 ± 1.33
10 000	Physical mixture	24.25 ± 0.28	25.43 ± 0.88	33.08 ± 1.08
	Melting method	29.43 ± 0.03	33.40 ± 0.45	57.08 ± 0.22
	Solvent method	33.35 ± 0.67	36.06 ± 0.98	56.13 ± 0.42
20 000	Physical mixture	25.05 ± 0.76	29.70 ± 0.19	38.53 ± 0.15
	Melting method	22.00 ± 0.35	31.78 ± 0.67	51.00 ± 0.44
	Solvent method	26.50 ± 1.85	32.47 ± 0.53	50.65 ± 1.56

[a] Result represent means of replicate determinations with the standard deviation ($n = 6$).

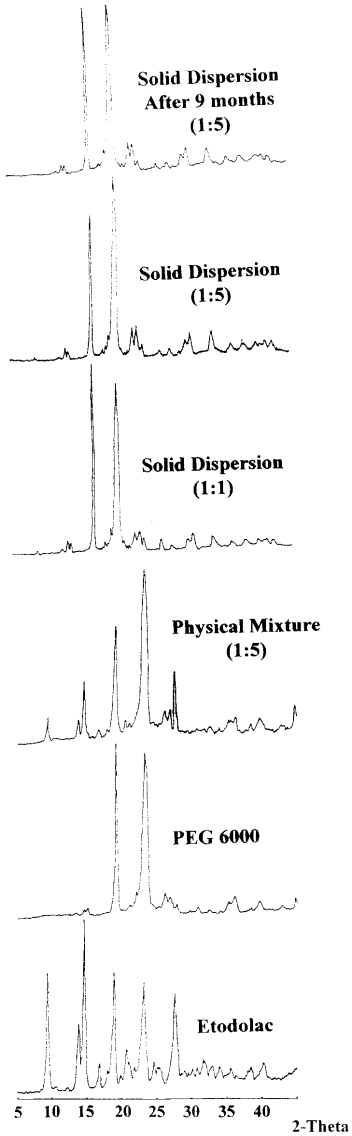

Fig. 1. X-ray diffractions of etodolac, physical mixtures and solid dispersions in PEG 6000 prepared by the solvent method.

Samples were tested with the dispersed amount method by placing 200 mg of etodolac or its equivalent in solid dispersions or physical mixtures on the surface of the dissolution medium. A 2-ml aliquot was withdrawn at appropriate time intervals, and replaced with a 2 ml of fresh dissolution medium.

The amount of etodolac was determined spectrophotometrically at 270 nm (Philips PU 8630, Holland) without interference from PEGs. Etodolac concentration was calculated and expressed as percentage of drug released from the mean of six parallel determinations. The dissolution test was carried out for 45 min.

3. Results and discussion

The solid dispersions of drug:PEGs of different molecular weight at 1:1; 1:2; 1:5 ratios were prepared and their dissolution rates and physical state properties were characterized.

Solid dispersion formulations of drug:PEGs were prepared by solvent and melting methods.

The results of the studies showed that the dissolution rate of etodolac increased markedly when present in solid dispersions in comparison with the physical mixtures and the pure drug. There were large differences between different types of solid dispersions. The amount of dissolved etodolac after 45 min dissolution were measured (Table 1). The data show that the amount of the carriers has big influence on the dissolution of the drug in etodolac:carrier system.

According to the dissolution rate studies, the best results were obtained with 1:5 molar ratio of drug: PEG 6000, prepared by the solvent method. For this reason XRD, DSC and IR figures were given for PEG 6000 prepared by the solvent method.

The XRD spectrum of the etodolac solid dispersions prepared solvent and melting method displayed similar

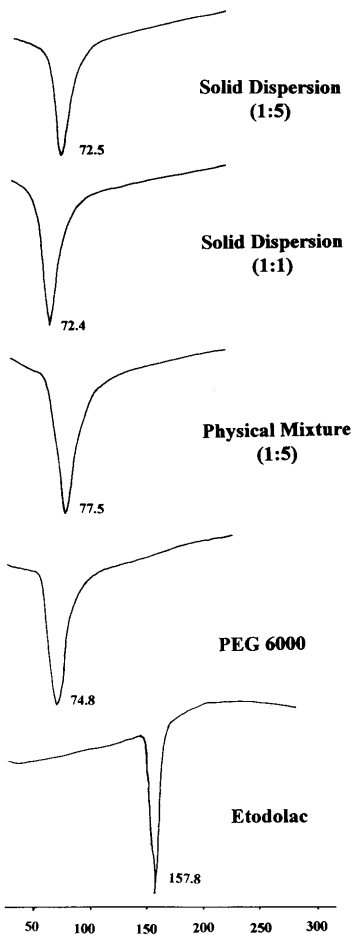

Fig. 2. DSC thermograms of etodolac, physical mixtures and solid dispersions in PEG 6000 prepared by the solvent method.

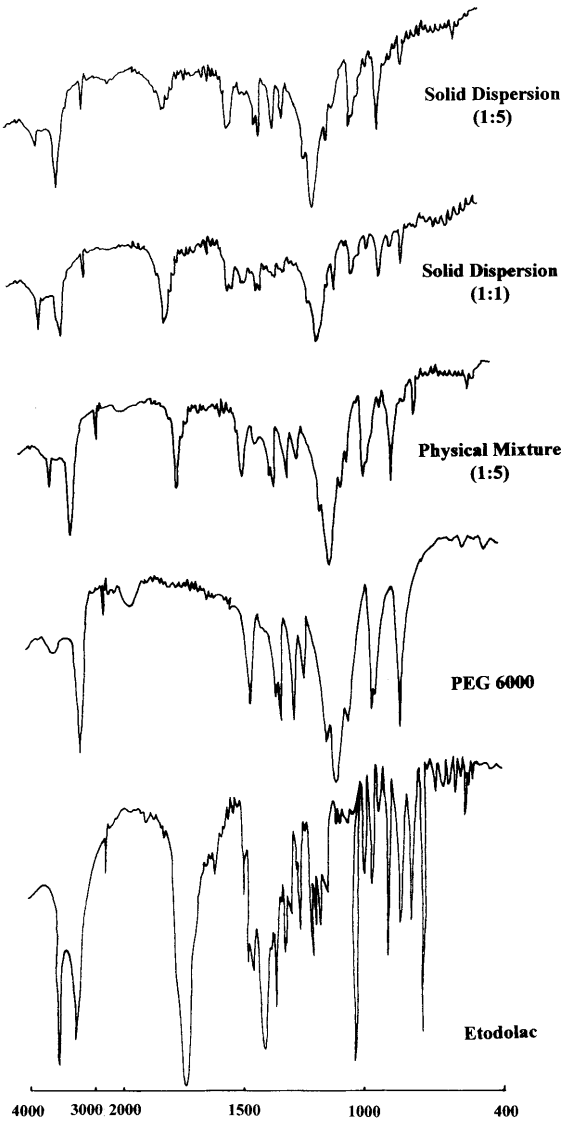

Fig. 3. IR spectrums of etodolac, physical mixtures and solid dispersions in PEG 6000 prepared by the solvent method.

characteristics. The main spectral lines of the drug and PEG 6000 were found solid dispersions with 1:5 molar ratio. The XRD patterns of etodolac PEG 6000 solid dispersions prepared by the solvent method and physical mixtures are shown in Fig. 1. Characteristic peaks of etodolac appeared at diffraction angle of 2θ at 9.51, 14.55, 16.69, 27.55°. The XRD pattern of etodolac was similar to those of physical mixtures indicating that the crystallinity of etodolac did not essentially change in the physical mixtures. This was consistent with the results obtained by other studies (i.e. IR, DSC). PEG 6000 XRD patterns are also shown in Fig. 1. Characteristic peaks of PEG 6000 appeared at diffraction angle of 2θ at 19.01, 23.55°. The XRD peaks of PEG 6000 in physical mixtures drug: PEG 6000 were similar to those in pure PEG 6000.

The reflections corresponding to the drug and PEG 6000 were also found in the solid dispersion spectrum, with smaller intensity. The relative intensity of most lines corresponding to etodolac in the solid dispersion was lower as compared to that of etodolac alone. Some characteristic peaks of etodolac disappeared (i.e. 27.55°). The XRD patterns of solid dispersions were different from those of etodolac and physical mixtures (Fig. 1).

The thermograms of the etodolac solid dispersions prepared by solvent and melting method displayed similar characteristics. The behavior of solid dispersions prepared by the solvent method is shown in Fig. 2. The pure etodolac curve shows one endothermic peak at about 157.8°C. This point corresponds to the melting

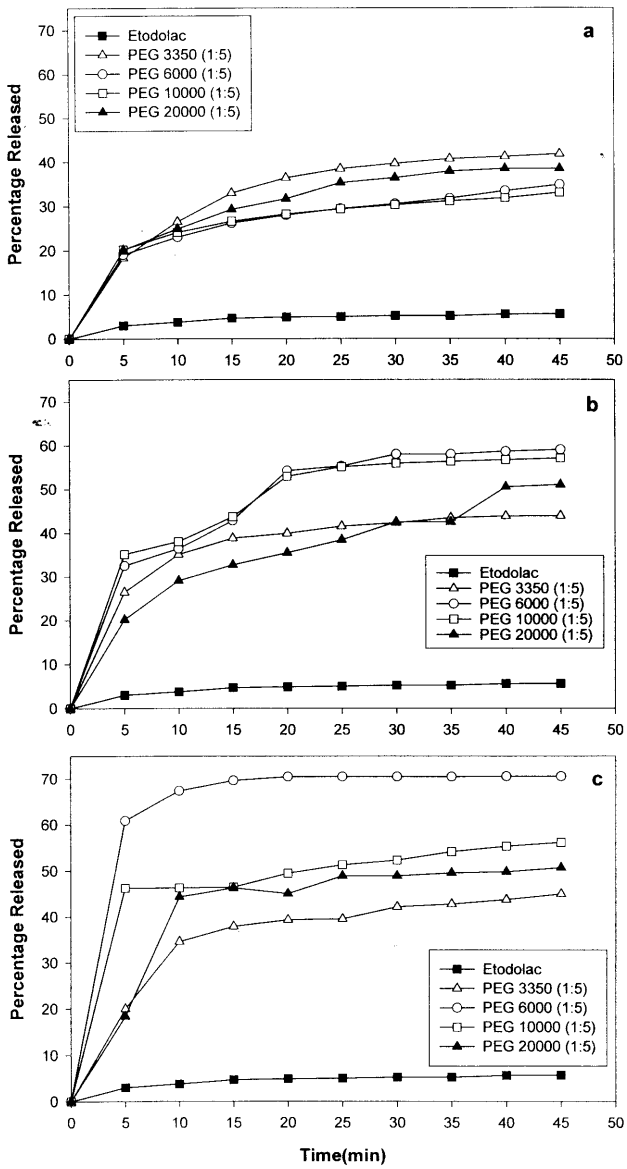

Fig. 4. Dissolution profiles of etodolac from 1:5 molar ratio of solid dispersions in different molecular weight PEGs. (a) Physical mixtures; (b) melting method; (c) solvent method.

point of etodolac. PEG 6000 also exhibits only one endothermic peak corresponding to the melting point of PEG 6000. The DSC curves of the solid dispersions show one peak. The peak value depended on the drug:polymer ratio. The DSC curves of the solid dispersions show one peak corresponding to the melting point of PEG 6000. The disappearance of the endothermic peak corresponding to the melting of etodolac is due to its solubility at lower concentration in the melted PEG 6000. Physical mixture of etodolac and PEG 6000 showed nearly the exactly same thermal behavior as the solid dispersions of the same composition. The similarities between the DSC data of the solid dispersion and physical mixture indicate the absence of chemical interaction between etodolac and PEG 6000.

The IR spectra of the drug, the polymer and the solid dispersion are shown in Fig. 3. Etodolac, which is present as ether forms, showed the C–O stretching vibration at 1037 cm^{-1}. Other characteristic bands were shown at 1740 cm^{-1} for C=O stretching vibration of the COOH group, at 3530 cm^{-1} for N–H stretching vibration of secondary amine group and at 3720 cm^{-1} for free O–H stretching vibration of the COOH group. The peak at 1115 cm^{-1} showed maximum intensity in PEG 6000. Etodolac:PEG 6000 dispersion did not modify dramatically the spectra with respect to the pure PEG 6000. The frequency of the C=O and free O–H stretching vibration of the COOH group and N–H stretching vibration of secondary amine was found considerably smaller than those of pure etodolac. C–O stretching vibration of the ether group also disappeared from the solid dispersion system (Fig. 3). These results have demonstrated that the original morphology and nature of the investigated materials changed.

The dissolution profiles of etodolac:PEGs, physical mixtures and solid dispersions which are prepared by solvent and melting methods were shown in Fig. 4.

Solid dispersions in all PEGs exhibited faster dissolution rates than pure drugs and their corresponding physical mixtures. Etodolac yielded the slowest initial dissolution rate with only about 10% of the drug dissolved in 20 min. Its hydrophobic property caused the powder to float on the surface of the dissolution medium and prevented its surface contacting the medium. As shown in Table 1, etodolac in all physical mixtures was released with quite different rates, but faster than etodolac alone. This might be caused by the surface tension lowering effect of PEGs to the medium, resulting in wetting of hydrophobic etodolac crystalline surface.

Dissolution rates for solid dispersions which are prepared by two different method were greater than those for physical mixtures and etodolac alone (Fig. 4) in all PEGs. The enhanced dissolution rate of etodolac from the solid dispersions might be due to the increase in drug wettability and the drug:PEG interactions.

The dissolution rate for solid dispersions prepared with different molecular weight PEGs are shown in Fig. 4 and Table 1. As a result of these studies, the best dissolution rate was obtained with PEG 6000.

In Fig. 5, three groups of curves can be distinguished. The first group of curves (Fig. 5a) includes the dissolution profiles of etodolac from the different ratios of physical mixtures. Differences were obtained for these three ratios at 45 min (Table 1). The second group of curves was obtained from the solid dispersions which were prepared by the melting method (Fig. 5b). The third group was obtained from the solid dispersions which were prepared by the solvent method (Fig. 5c).

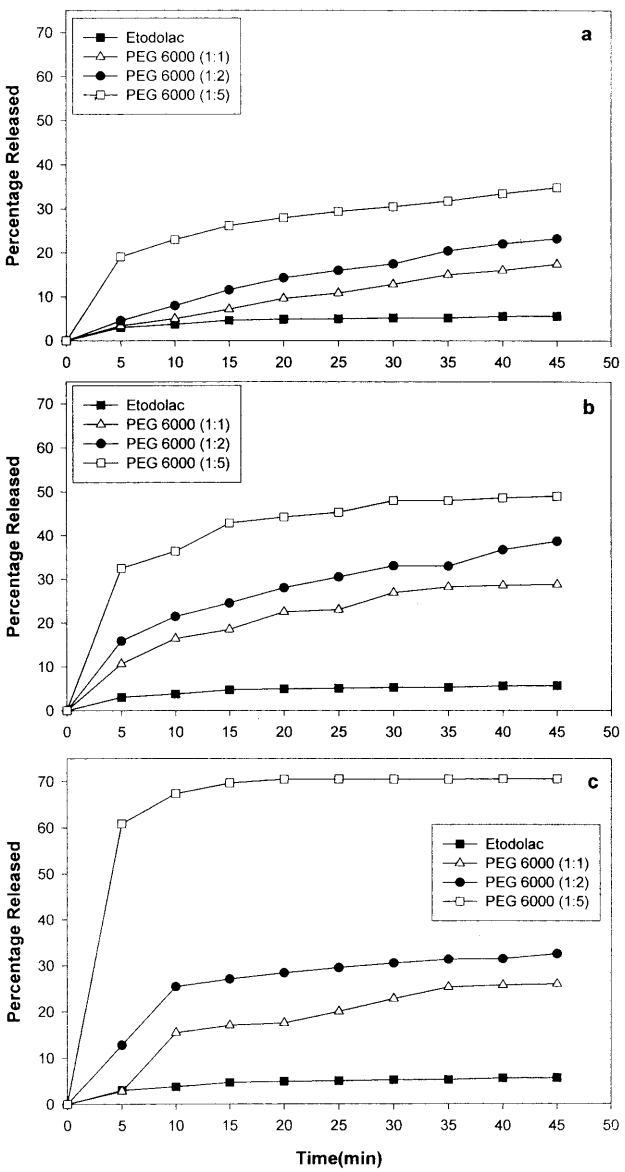

Fig. 5. Dissolution profiles of etodolac from solid dispersions in PEG 6000 with different molar ratio. (a) Physical mixtures; (b) melting method; (c) solvent method.

As shown in Fig. 5c, the drug:PEG 6000 solid dispersion with 1:5 molar ratio exhibit faster dissolution, more than 60% of the sample being dissolved within 10 min.

Due to low solubility of etodolac, its solubility after formulation of solid dispersions was investigated. The results indicated higher solubility of the drug from 1:5 molar ratio of solid dispersion than the corresponding physical mixtures and other solid dispersions (Table 1, Fig. 4)

The stability of etodolac in solid dispersions after 9 months storage was satisfactory. No changes occurred in the amorphous state of etodolac in PEG 6000 (1:5) (Fig. 1).

4. Conclusions

The present results of investigations show the suitability of PEG 6000 as the carrier for solid dispersions of etodolac. As mentioned above, this substance is widely used as a pharmaceutical excipient. In this work, it has been used as the carrier of solid dispersions, with good results. The amorphous etodolac:PEG solid dispersion was formed at different molar ratio drug to PEG molar ratio. The dissolution rates of physical mixtures were higher than that of pure drug; this being possibly caused by the increase in drug wettability. Solid dispersions exhibited higher dissolution rates than those of physical mixtures, resulting from the increase in drug wettability and drug:PEG interactions. Maximum dissolution rate was obtained with the solid dispersion containing the amorphous form of the 1:5 drug to PEG 6000 ratio. The amorphous form of etodolac found in powdered solid dispersions as demonstrated by XRD, DSC and IR may offer an explanation of better dissolution rate from solid dispersion. The proposed amorphous solid dispersion ensures good pharmaceutical availability of etodolac.

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