ELSEVIER

International Journal of Pharmaceutics 108 (1994) 101–107

international journal of pharmaceutics

Physical characteristics and dissolution kinetics of solid dispersions of ketoprofen and polyethylene glycol 6000

María Victoria Margarit *, Inés Carmen Rodríguez, Antonio Cerezo

Department of Pharmacy and Pharmaceutical Technology, School of Pharmacy, University of Granada, E-18071 Granada, Spain

(Received 30 November 1993; Accepted 24 January 1994)

Abstract

The formation of solid dispersions is an effective method of increasing the dissolution rate of poorly soluble drugs, and hence, of improving their bioavailability. We used the dissolution method to prepare solid dispersions of ketoprofen and polyethylene glycol 6000 (PEG 6000), and compared the dissolution kinetics of the dispersions with physical mixtures and pure drug. Physicochemical characteristics were determined by X-ray diffractometry and differential scanning calorimetry. Drug/polymer mixtures containing up to 50% ketoprofen formed eutectic compounds. The results of dissolution kinetics studies showed that PEG 6000, when used as a carrier for solid dispersions, increased the dissolution rate of ketoprofen. The $t_{80\%}$ of dissolution for pure drug (88.5 min) decreased to 1.9, 4.0 and 22.5 min, respectively, in solid dispersions containing 10:90, 50:50 and 90:10 proportions of ketoprofen/PEG 6000. We conclude that the 10:90 solid dispersion displays the best dissolution kinetics of those tested.

Key words: Solid dispersion; X-ray diffractometry; DSC; Dissolution kinetics

1. Introducction

Diverse factors are involved in increasing the dissolution rate of drugs, e.g., increased wettability, drug/carrier ratio, and physical structure of the dispersion, among others (Ford, 1986). Many recent reviews have dealt with the formation of solid dispersions of poorly soluble drugs with different water soluble, pharmacologically inert carriers as a means of increasing the dissolution rate (Goldberg et al., 1965; Chiou and Riegelman, 1971; Hajratwala, 1974; Puisieux and Henry, 1981; Kreuter, 1983; Vila Jato et al., 1983, 1984; Ford, 1986). This approach improves the bioavailability of the drug when absorption is limited by solubility.

This mechanism works because of the reduced particle size in solid dispersions. Under optimal circumstances, the particle is reduced to molecular size, and yields a solid-state solution within the carrier.

At a normal gastric pH of 1.2, the solubility of ketoprofen (0.051 mg ml^{-1}) is low and pH-dependent (Herzfeldt and Rümmel, 1983). We de-

* Corresponding author. Tel: +34-58-243900; Fax: +34-58-243900.

SSDI 0378-5173(94)00043-5

signed the present study to improve the solubility and dissolution rate of this drug by preparing solid dispersions in polyethylene glycol 6000 (PEG 6000). The physical characteristics of the drug/carrier combinations were determined by differential scanning calorimetry (DSC) with X-ray diffractometry, and dissolution kinetics were then measured. The results were compared with those obtained for pure ketoprofen and physical mixtures prepared to match the proportions used in solid dispersions.

2. Materials and methods

2.1. Materials

Ketoprofen (Rhône-Poulenc, Madrid), PEG 6000 (Hoechst, Frankfurt) and analytical grade 96% ethanol were used.

2.2. Sample preparation

Solid dispersions (SD) containing different percentage proportions of drug/PEG 6000 (Table 1) were prepared according to the dissolution method described by Chiou and Riegelman (1971). Alcohol was used as the solvent, and evaporated in an oven at 30°C. Desiccation was completed in a vacuum oven until constant weight was achieved, and the resulting solids were pulverized and sieved to obtain the granulometric fraction (0.15–0.20 mm) with a mean particle size of 0.175 mm. Solid dispersions containing 30:70 and 40:60 proportions of drug/PEG 6000 took the form of a white, plastic solid which could not be pulverized, obviating X-ray analysis and dissolution kinetic studies of the powdered form.

Physical mixtures (PM) were prepared by homogenizing the two components in the proportions shown in Table 1.

Table 1
Composition and melting point of bynary mixture of ketoprofen and polyethylene glycol 6000

Composition (%)		Melting point (°C)	
Ketoprofen/PEG 6000		PEG 6000	Ketoprofen
–	100	63.63	–
10	90	61.00	–
20	80	59.57	–
30	70	62.00	–
40	60	55.63	–
50	50	51.33	–
60	40	51.17	75.10
70	30	51.70	84.37
80	20	49.97	90.10
90	10	49.20	94.30
100	–	–	95.13

2.3. X-ray diffraction studies

X-ray diffraction patterns of powdered samples were obtained with a Rigaku-Miniflex Ca 2005 apparatus equipped with a nickel filter, using CuKα radiation. The rate was 2° at 2θ/min over a range of 5–40°.

2.4. Thermal analyses

DSC (Mettler FP 80 calorimeter) was used to obtain thermograms of 5 mg samples, using a heating rate of 5°C/min over the range of 30–110°C. Phase diagrams of the binary ketoprofen/PEG 6000 mixtures were obtained at peak transition temperature.

2.5. Dissolution kinetics

Samples in the form of powder were studied in an automated, closed-circuit system. The device was loaded with 2500 ml deionized water at 37 ± 0.5°C as the solvent, and pumped through a continuous flow chamber of a spectrophotometer (Perkin Elmer 124) set at 261 nm to record the cumulative absorbance/time curves. The presence of PEG 6000 did not interfere with measurements of ketoprofen.

All assays were performed by placing a sample of powdered pure ketoprofen (100 mg) or ketoprofen, in the form of SD or PM containing amounts of drug equivalent to 100 mg, on the surface of the dissolution medium. The cut-off point for the assays was extended to 180 min, however, after 60 min ketoprofen dissolved slowly in all samples, reaching an asymptotic peak. The

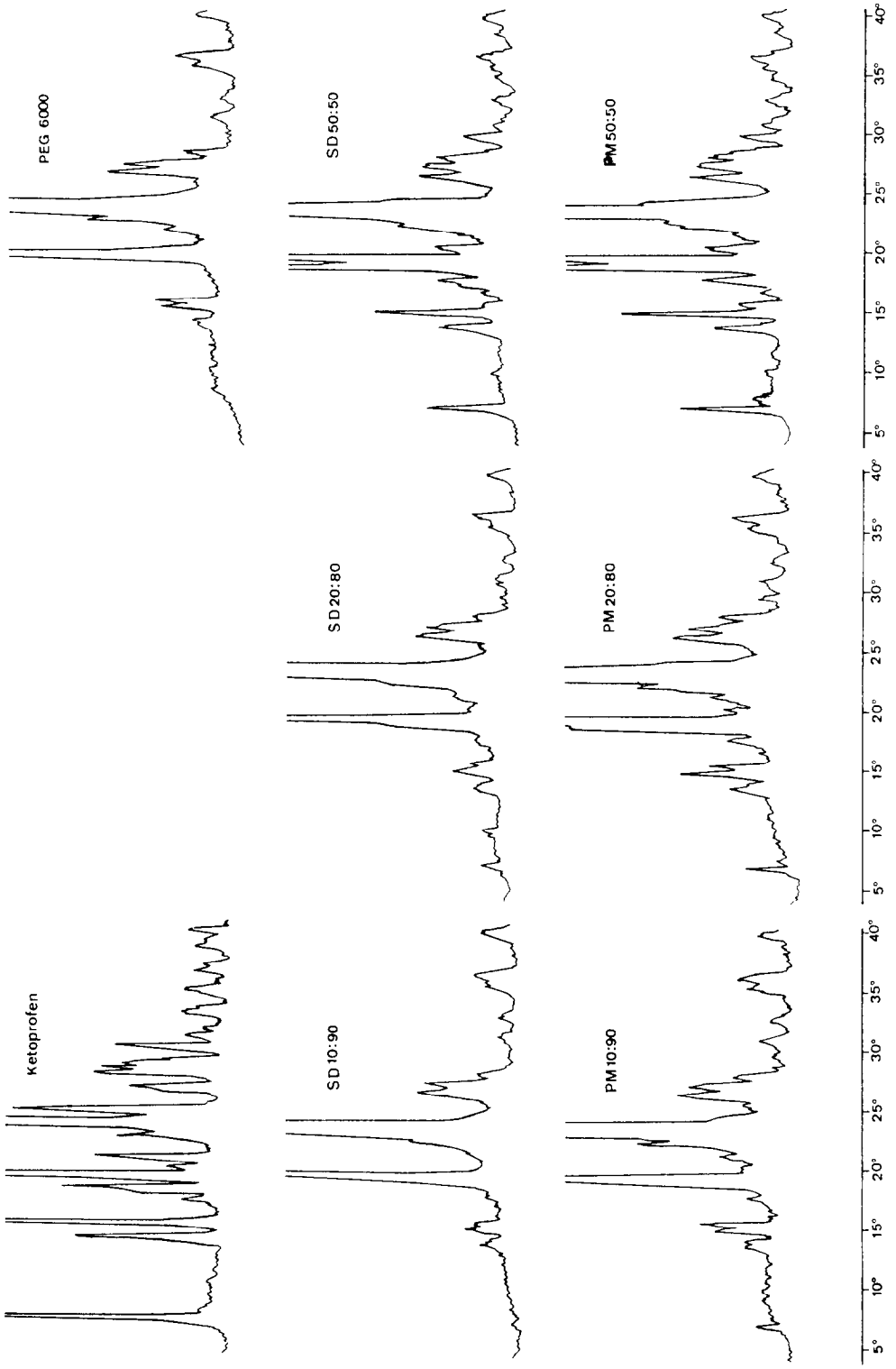

Fig. 1. X-ray diffractograms of binary 10:90, 20:80 and 50:50 mixtures of ketoprofen and PEG 6000.

figures therefore illustrate the concentrations attained during the first 60 min only.

Dissolution kinetics were determined from the mean of five determinations by fitting the experimental data to logarithmic (first order) and cube root functions to obtain rectilinear plots of dissolution rates.

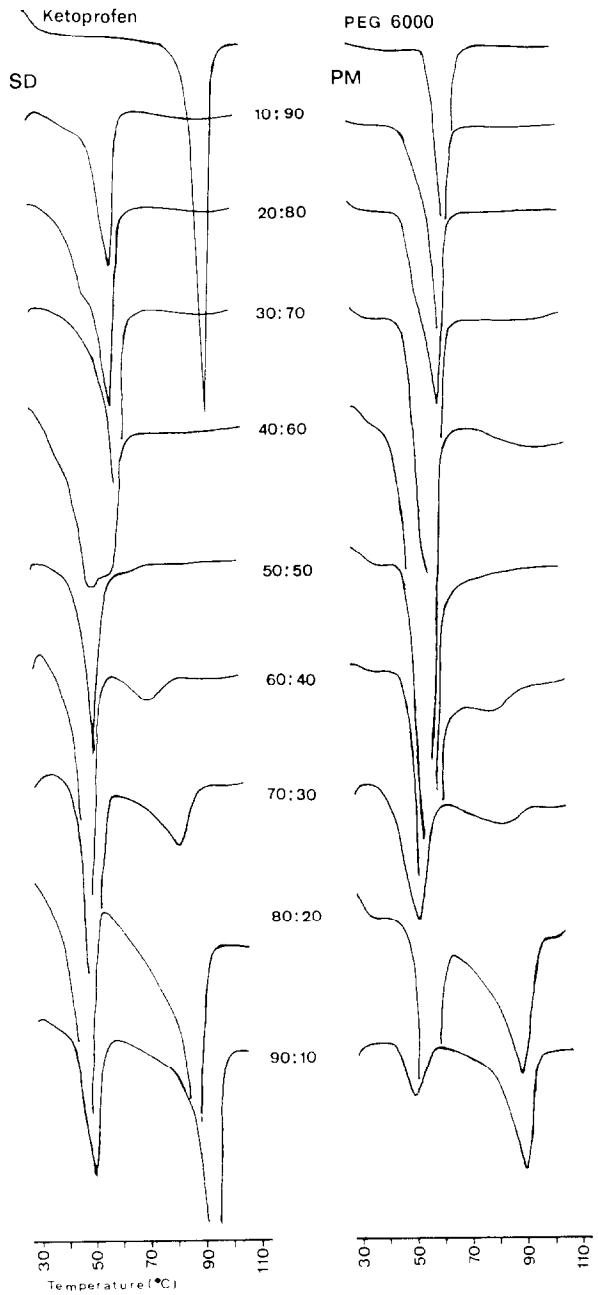

Fig. 2. Thermograms of ketoprofen and PEG 6000 in solid dispersions and physical mixture.

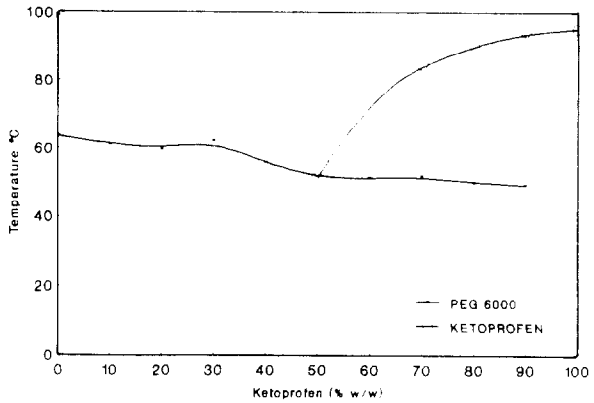

Fig. 3. Phase diagram of solid dispersions of ketoprofen and PEG 6000.

3. Results and discussion

3.1. X-ray diffraction patterns

The peaks in the X-ray diffractograms (Fig. 1) reflected, in number and height, the relative content of the drug and carrier used in the mixtures. In SD with low proportions of drug (10:90 and 20:80), the ketoprofen peaks were masked. In 50:50 combinations and those containing a larger proportion of ketoprofen, PEG 6000 lost its masking effect, and the diffractograms for SD and PM showed superimposable peaks for the drug and carrier. Fig. 1 illustrates the results only for ketoprofen contents of up to 50%. As noted in section 2, diffractograms were not obtained for 30:70 and 40:60 dispersions.

3.2. Thermal analyses

Thermograms for ketoprofen and PEG 6000 alone, SD and PM are given in Fig. 2. The DSC curves of each component gave a single endothermal peak for the melting of ketoprofen (95.13°C) and PEG 6000 (63.63°C). One or two endothermal peaks were obtained from SD and PM, de-

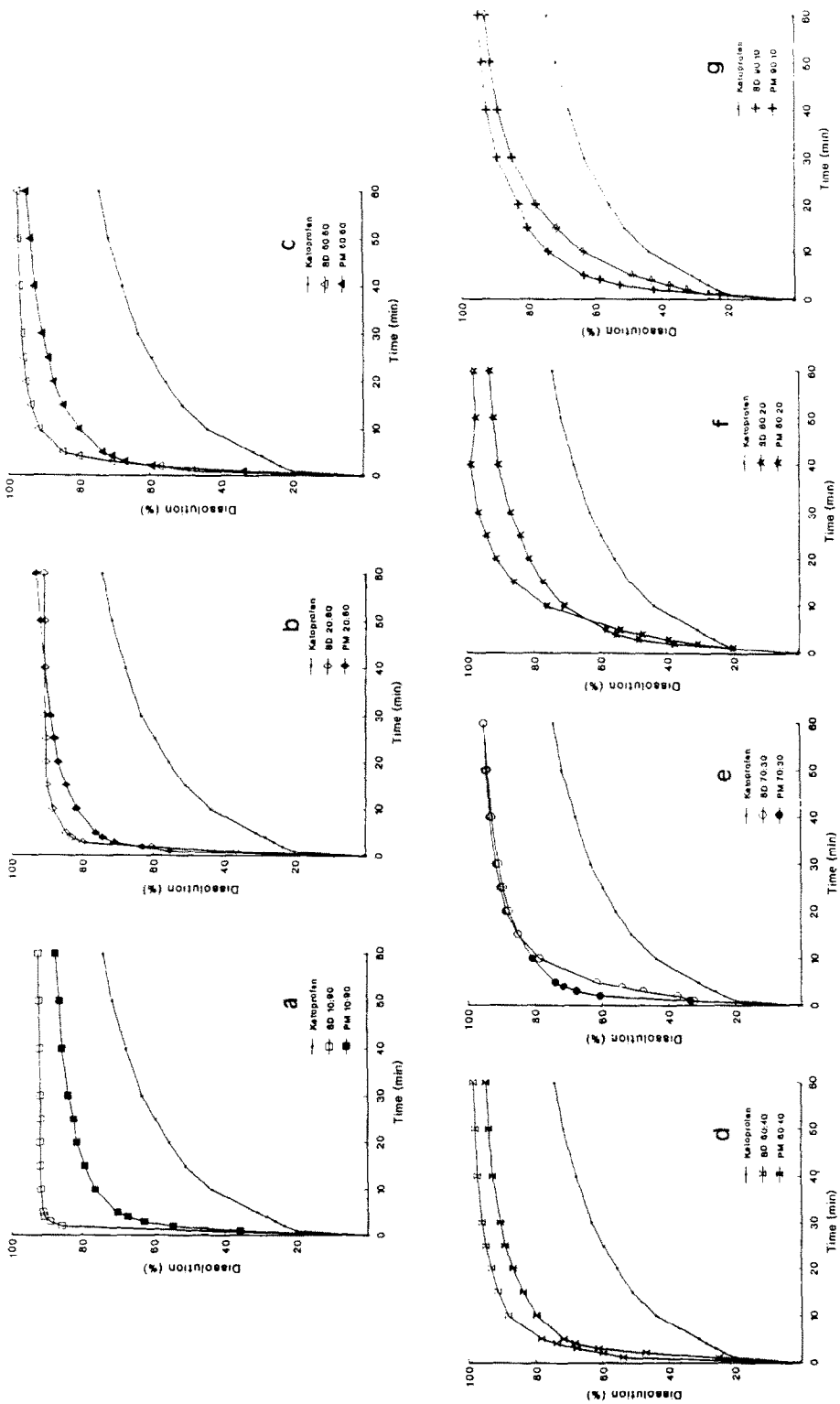

Fig. 4. Dissolution kinetics of ketoprofen in solid dispersions and physical mixtures.

pending on the proportion of drug to polymer (Table 1).

At proportions of ketoprofen above 50% (60:40 and 90:10), the thermograms showed two endothermal peaks: the low-temperature peak reflected melting of PEG 6000, while the endotherm for ketoprofen shifted progressively with increasing proportions of the drug.

Diminishing ketoprofen content (50:50 and 10:90) led to the disappearance of the drug's fusion endotherm, with a single endothermal peak representing melting of PEG 6000, and a shift in peak temperature toward the melting point of the polymer. Loss of the endothermal peak for ketoprofen melting was associated with solubilization of the drug in melted PEG 6000.

Physical mixtures the drug and polymer (Fig. 2) displayed a thermal behavior similar to that of the corresponding SD, suggesting that there was no chemical interaction between ketoprofen and PEG 6000. This was confirmed by the X-ray diffraction results.

The phase diagram (Fig. 3) constructed from the peak melting point (Table 1) was typical of a monotectic system, taking the form of a simple eutectic diagram. One of the liquid branches had disappeared, and the branch illustrating the component of lower melting point (PEG 6000) had been replaced with the eutectic compound in samples containing up to 50% ketoprofen. The liquid branch remained essentially unchanged as ketoprofen content increased, indicating that the drug was solubilized in liquid PEG 6000. Once the polymer reached its melting point (63.63°C), it was able to dissolve its own weight in ketoprofen (50:50 samples).

This type of system is also typical of SD of testosterone (Hoelgaard and Moller, 1975), griseofluvin, tolbutamide (Rabinder et al., 1980), and diflunisal (Najib and Suleiman, 1989), among other substances.

3.3. Dissolution kinetics

Our study of the dissolution kinetics of the SD and PM was based on experimental data of concentrations recorded during the first 30 min of the assays ($n = 11$), as dissolution was 90% or better in most SD and PM after this time. When the data were fitted to first order and cube root functions, and subjected to linear regression analysis, the dissolution process was found to reflect first order kinetics, with a significant correlation coefficient at $p < 0.001$. The exception was the 10:90 DS, which reached asymptotic concentration (91.09%) within 5 min, hence the dissolution kinetics could not be determined. That PEG 6000 accelerated the solubilization of ketoprofen is shown in Fig. 4a–g, which illustrates the dissolution curves for pure ketoprofen, and for the drug in SD and PM. After 30 min, 63.26% of the drug had dissolved; this concentration reached 84.06–90.81% in PM and 84.90–96.72% in DS. The drug generally dissolved more rapidly in SD; the exception was the 90:10 combination, in which the high proportion of ketoprofen in the binary mixture impeded ultrafine crystallization within the carrier, and the dissolution of PEG 6000 released an excess of ketoprofen particles, slowing dissolution.

The dissolution rates of eutectic mixtures at 10:90, 20:80 and 50:50 were faster than in other samples. Ketoprofen forms a dispersion of small particles in the soluble carrier, which, in contact with the dissolution medium, gives rise to a fine suspension of readily dissolved ketoprofen: the greater the number of particles in the dispersion, the faster dissolution occurs. The $t_{80\%}$ values calculated by interpolation on the dissolution

Table 2
Dissolution kinetics of ketoprofen in solid dispersions and physical mixtures

Composition (%) Ketoprofen/ PEG 6000	$y = a - bx$ ($n = 11$)							
	Solid dispersions				Physical mixtures			
	a	b	r_{exp}	$t_{80\%}$ (min)	a	b	r_{exp}	$t_{80\%}$ (min)
10:90	–	–	–	1.9	3.93	0.049	0.85	17.2
20:80	3.58	0.059	0.76	3.2	3.73	0.054	0.85	8.6
50:50	3.72	0.098	0.91	4.0	3.90	0.064	0.90	10.0
60:40	3.82	0.092	0.94	5.4	4.02	0.069	0.92	10.6
70:30	4.19	0.080	0.96	11.4	3.89	0.065	0.90	9.3
80:20	4.43	0.111	0.99	12.0	4.22	0.062	0.95	18.5
90:10	4.32	0.058	0.98	22.5	4.16	0.067	0.95	15.0

Ketoprofen reference ($n = 11$): $y = 4.41 - 0.029x$, $r_{exp} = 0.97$, $t_{80\%} = 88.5$ min.

curve (Table 2) were 1.9, 3.2 and 4 min for the 10:90, 20:80 and 50:50 DS, respectively; these times were much shorter than the $t_{80\%}$ of 88.5 min for pure ketoprofen.

The phase diagram shows that SD of ketoprofen/PEG 6000 obtained by the dissolution method form simple eutectic mixtures displaying monotectic behavior. The carrier PEG 6000 effectively improves ketoprofen solubilization, with 10:90 solid dispersions showing the best dissolution kinetics.

Acknowledgement

We thank Ms Karen Shashok for translating the original manuscript into English.

References

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

Ford, J.L., The current status of solid dispersions. *Pharm. Acta Helv.*, 61 (1986) 69–88.

Goldberg, A.H., Gibaldi, M. and Kanig, J.L., Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures: I. Theorical considerations and discussion of the literature. *J. Pharm. Sci.*, 54 (1965) 1145–1148.

Hajratwala, B.R., Dissolution of solid dispersion systems. *Aust. J. Pharm. Sci.*, NS3 (1974) 101–110.

Herzfeldt, C.D. and Rümmel, R., Dissociation constants, solubilities and dissolution rates of some selected nonsteroidal antiinflammatories. *Drug Dev. Ind. Pharm.*, 9 (1983) 767–793.

Hoelgaard, A. and Moller N., Solid dispersion systems of testosterone. *Arch. Pharm. Chemi Sci. Ed.*, 3 (1975) 34–47.

Kreuter, J., Solid dispersion and solid solution. In Breimer, D.D. and Speiser, P. (Eds), *Topics in Pharmaceutical Sciences*, Elsevier, Amsterdam, 1983, pp. 359–370.

Najib, N.M. and Suleiman, M.S., Characterization of a diflunisal polyethylene glycol solid dispersion system. *Int. J. Pharm.*, 51 (1989) 225–232.

Puisieux, F. and Henry, S., Les dispersions solides. *Labo-Pharma Probl. Tech.*, 305 (1981) 11–20.

Rabinder, K., Grant, D.J.W. and Eaves, T., Comparison of polyethylene glycol and polyoxyethylene stearate as excipients for solid dispersion systems of griseofulvin and tolbutamide: I. Phase equilibria. *J. Pharm. Sci.*, 69 (1980) 1317–1321.

Vila Jato, J.L., Blanco, J. and Alonso, M.J., Las dispersiones sólidas: Interés biofarmacéutico (I). *Pharm. Clin.*, 1 (1983) 264–278.

Vila Jato, J.L., Blanco, J. and Alonso, M.J., Las dispersiones sólidas: Interés biofarmacéutico (II). *Pharm. Clin.*, 1 (1984) 29–43.