ELSEVIER

International Journal of Pharmaceutics 118 (1995) 221–227

international journal of pharmaceutics

Formulation studies of a poorly water-soluble drug in solid dispersions to improve bioavailability

Pai-Chang Sheen *, Vinod K. Khetarpal, Christina M. Cariola, Colin E. Rowlings

Rhône-Poulenc Rorer Central Research, 500 Arcola Road, Collegeville, PA 19426, USA

Received 8 April 1994; revised 13 October 1994; accepted 14 November 1994

Abstract

To improve the bioavailability of a poorly water-soluble drug, RP 69698 (**1**), solid dispersion formulations were investigated in beagle dogs. The formulations were prepared by a melting method with water-soluble carriers in which **1** is highly soluble. When incorporated into a solid dispersion formulation composed of polyethylene glycol (PEG) 3350, Transcutol and Labrasol, the bioavailability of **1** was determined to be 11.8%. This represented about 2-fold improvement over 6% bioavailability observed previously with an aqueous suspension of the drug in 0.5% methylcellulose. When the formulation contained only Labrasol, in which **1** was completely solubilized, the bioavailability of **1** was 12.9%. Addition of a surfactant, polysorbate 80, at a strength of 10% to the dispersion with PEG 3350 and Labrasol as carriers increased the bioavailability of **1** from 11.8 to 27.6%. This result was attributed to the ability of the surfactant to increase the wettability and spreadability of the drug in a solubilized state once released in the gastrointestinal medium. Increase in the concentration of the surfactant did not further increase the bioavailability of **1**. DSC and powder XRD data demonstrated that the major fraction of drug was dissolved in the carrier. A possible explanation for the maximum achievable bioavailability of about 25% with solid dispersion preparation may be that once released, a significant fraction of drug may precipitate in the GI tract. Re-solubilization of the precipitated drug for the absorption is likely to be difficult due to its very low aqueous solubility.

Keywords: Leukotriene B_4 antagonist; Solid dispersion; DSC ; Powder X-ray diffraction; Bioavailability

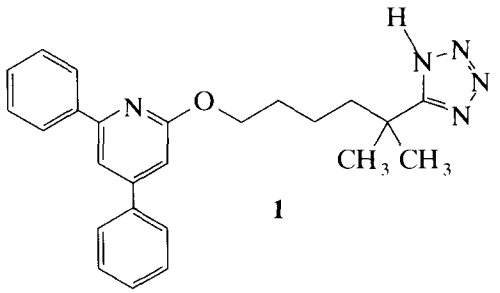
1. Introduction

The use of solid dispersions of drugs in water-soluble carriers, in which the drugs are highly soluble, to increase the dissolution rate and bioavailability of poorly soluble drugs has been studied extensively (Chiou and Riegelman, 1971; Ford, 1986). This technique provides a means of reducing particle size to nearly a molecular level. As the soluble carrier dissolves, the insoluble drug is exposed to the dissolution medium as very fine particles for quick dissolution and absorption. As a part of a new drug development pro-

* Corresponding author.

SSDI 0378-5173(94)00366-1

gram, we have investigated the possible use of this technique to improve the bioavailability of a poorly soluble drug, 2-[[5-methyl-5-(1H-tetrazol-5-yl)hexyl]oxy]-4,6-diphenylpyridine (RP 69698; **1**). This compound is a novel leukotriene B_4 antagonist, with very low water solubility (< 1 μg/ml).



1

In the dog, the bioavailability of **1** was only 6% when given as a suspension in 0.5% methylcellulose (Khetarpal et al., 1994). Also, when **1** was incorporated into a lactose matrix capsule and administered to dogs at a dose of 50 mg/kg, its bioavailability was only 2% (Khetarpal and Cariola, unpublished data). Because of the low bioavailability of **1** from either suspension or lactose matrix capsule, it is difficult to study preclinical safety and subsequent clinical efficacy.

This investigation was designed to select a suitable water-soluble or miscible carrier system for a solid dispersion formulation of **1**. The carriers were selected and formulation approaches were utilized to increase the solubility of **1** in the formulation. Incorporation of a surfactant, polysorbate 80, into the matrix was studied and the bioavailability of **1** in dog was examined. An optimum concentration of polysorbate 80 in the solid dispersion formulation was determined from the bioavailability data. The solubility of **1** in the lead formulation was examined using differential scanning calorimetry (DSC) and powder X-ray diffraction.

2. Experimental

2.1. Materials

Compound **1** (Mol. Wt 413.5; m.p. 158°C) was produced by the Medicinal Chemistry Department of Rhône-Poulenc Rorer Central Research, Collegeville, PA. The water solubility of **1** (< 1 μg/ml) was determined by equilibrium solubility technique at 25°C and assayed by HPLC using fluorescence detection (McKean, R., personal communication). Polyethylene glycol 3350, NF (PEG 3350) and polyethylene glycol 400, NF (PEG 400) were received from Union Carbide, Danbury, CT. Labrasol® (a defined combination of mono-, di- and triglyceride and mono- and di-fatty acid, C8–C10, esters, which has an HLB value of 14; it is an oily liquid and soluble in water), Transcutol® (a diethylene glycol monoethyl ether; it is an oily liquid and soluble in water) and Gelucire® 44/14 (a mixture of glyceryl and PEG 1500 esters of fatty acids; it has melting point of 44°C and an HLB value of 14) were obtained from Gattefosse Corp., Westwood, NJ. These Gattefosse excipients are all derived from vegetable oil and, therefore, are well tolerated by the body. Polysorbate 80, NF was received from ICI America, Wilmington, DE.

2.2. Carrier screening procedure

In order to select carriers which would lend themselves to a more detailed investigation, an initial screening procedure was developed based on the drug solubility in the carriers in the liquid state (Table 1). 2 g of carrier was placed into a test tube. The tube was immersed into a temperature-controlled silicon bath at 70–75°C. The solid carriers liquefied at this elevated temperature. 20-mg increments of **1** were added and the mix-

Table 1
Solubility (mg/g) of RP 69698 in various water-soluble carriers at 70°C

Gelucire 44/14	PEG 400	PEG 3350	Polysorbate 80	Transcutol	Labrasol
< 10	40–50	40–50	10–20	80–90	80–90

Table 2
RP 69698 formulations

Formulation no.	mg/capsule [a]			
	1	2	3	4
RP 69698	50	50	50	25
Polyethylene glycol 3350, NF	325		290	302.5
Transcutol	125			
Labrasol	200	650	290	302.5
Polysorbate 80, NF			70	70
	700	700	700	700

[a] In size no. 0 gelatin capsules.

ture was constantly stirred with a micro spatula until complete solubilization occurred. The procedure was continued until no further solubilization of the drug was achieved. The solubility was determined by calculating the sum of increments prior to the last one which could not be completely dissolved.

2.3. Preparation of capsules

On the basis of results obtained in the carrier screening, the first set of capsules were prepared for a bioavailability study in the dogs, according to the formulations shown in Table 2. Additional formulations, as listed in Table 3, were prepared for a second bioavailability evaluation. Each vehicle was melted in a small beaker immersed in a silicon oil bath maintained at 70–75°C. The drug was dissolved in the liquid vehicle by constant stirring with a micro spatula. The resultant solution was manually pipetted into the bottom halves of no. 0 hard gelatin capsules, and then the upper halves of the shells were replaced. The solutions inside the capsules solidified at room temperature. The fill weight of each capsule was 700 mg. With the exception of one formulation which contained 25 mg of **1**, all other formulations contained 50 mg of drug. The same method was used to prepare the Labrasol solution capsules.

2.4. Thermal analyses

A Perkin Elmer DSC 7 thermal analyzer was used to obtain thermograms at a heating rate of 10°C/min over the temperature range 30–170°C. The samples ranged in weight from 2.1 to 5.7 mg and were sealed inside crimped aluminum pans.

2.5. Powder X-ray diffraction

The powder X-ray diffraction (XRD) patterns of **1** and PEG 3350, Formulation 3 and a placebo solid dispersion matrix (formulation 3 without **1**) were determined using a Philip PW 1710 automatic diffractometer, with monochromatized CuKα radiation. The samples were analyzed between 2θ angles of 2 and 62°.

2.6. Oral bioavailability study in dogs

Eight beagle dogs weighing 9–10 kg were used for the study. In the first study, the bioavailability of **1** from each formulation as listed in Table 2 was determined in four dogs. A partial cross-over study design was used. The dogs were fasted overnight and food was returned 4 h post-dose. For formulations 1–3, a dose of approx. 10 mg/kg was obtained by administering two capsules to

Table 3
RP 69698 formulations

Formulation no.	mg/capsule [a]			
	5 [b]	6	7	8
RP 69698	50	50	50	50
Polyethylene glycol 3350, NF	290	255	290	290
Transcutol				290
Labrasol	290	255	220	
Polysorbate 80, NF	70 (10%)	140 (20%)	210 (30%)	70 (10%)
	700	700	700	700

[a] In size no. 0 gelatin capsules.
[b] Same formulation as formulation 3.

each dog. For formulation 4, the intended dose of 10 mg/kg was obtained by giving four capsules to each dog. Blood samples (approx. 3 ml) were taken at 0 (pre-dose), 0.25, 0.5. 1, 1.5, 2, 3, 4, and 6 h post-dose. Plasma was separated by centrifugation and frozen until analyzed. In the second study, a similar protocol was followed to evaluate the second set of formulations from Table 3; two capsules were administered to each of the four dogs.

2.7. *Analysis of drug in plasma samples*

On the day of analysis, plasma was thawed and analyzed for **1** according to a specific HPLC method (Khetarpal et al., 1994). A 0.5 ml aliquot of plasma containing an internal standard was deproteinized with acetonitrile followed by extraction with hexane/ethyl acetate (4:1, v/v) at pH 5.0. The extract was dried and reconstituted with mobile phase and a portion was injected on to the HPLC column. The analysis was performed on a C18 column, using a mobile phase comprised of 48% acetonitrile and 52% pH 6.1 sodium acetate buffer. The eluent was monitored at 258 nm. The concentration of **1** in plasma samples was based on peak area ratios and extrapolation from standard curves.

3. Results and discussion

The physiologically inert and easily water-soluble carriers as listed in Table 1 were selected for the drug solubility evaluation. If the melted drug and vehicle are immiscible their solid-state interaction will be negligible (McGinity and Coffin, 1990). Therefore, the solubility screening was performed to determine the solid-state interaction of the drug and carriers. With the exception of Gelucire 44/14 and Polysorbate 80, the solubilities of **1** in these carriers were more than 40 mg/g. Labrasol and Transcutol are liquids and have higher solvent powers for **1** than PEGs. Both Labrasol and Transcutol formed a homogeneous liquid with PEG 3350 when fused and produced an uniform solid mass when cooled to ambient temperature. To take advantage of the greater solvent power for **1**, the mixed systems containing combination of these solvents were pursued. The drug was found to be easily dissolved into the hot melts of these formulations shown in Tables 2 and 3. When the molten drug solutions were cooled, the solute **1** appeared to be trapped within the matrix.

The cooling rate of the hot melt can influence the physical state of solid obtained and the drug particle size of crystal formed (Vadnere, 1990). The melted mixture is usually cooled rapidly to entrap the drug particles in as a fine state as possible. This would result in fast dissolution after the drug particles are released from the soluble matrix (McGinity and Coffin, 1990). However, to follow the practical production setting, the filled capsules were cooled to ambient temperature without chilling. Microscopic examination showed that most of the drug remained dissolved in the vehicles. Only a few very fine crystals of **1** (< 3 μm) in the solid dispersions were observed under a microscope after 3 months of aging at ambient temperature.

Due to the low solubility of **1**, no dissolution data were generated for the capsules. The capsules eroded within 10 min in water at 37°C, and produced a cloudy solution.

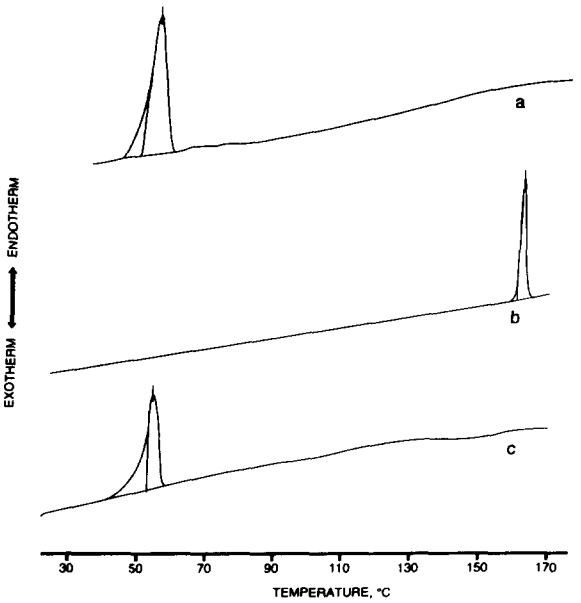


Fig. 1. DSC scans of (a) placebo, (b) **1**, and (c) formulation 3.

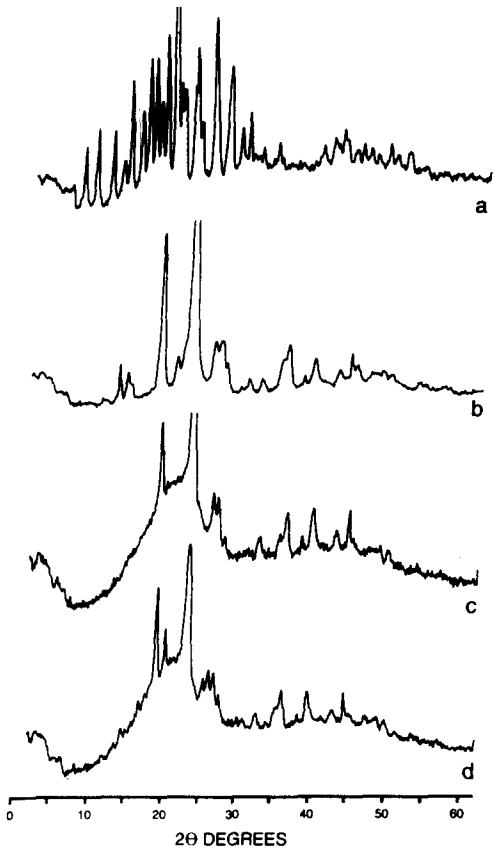


Fig. 2. Powder XRD patterns of (a) **1**, (b) PEG 3350, (c) placebo, and (d) formulation 3.

DSC testing is particularly useful in determining the solubility of a drug in a polymeric carrier (Sjokvist et al., 1991; Fernandez et al., 1992). The carrier matrix and **1** have single-peak thermograms with melting peaks at 53.6 and 163.8°C, respectively. The thermograms of the solid dispersion showed the characteristic peak of the carrier matrix, without drug peak indicating that the drug was completely dissolved in the carrier (Fig. 1).

The powder XRD patterns of **1**, PEG 3350, placebo (formulation 3 minus drug) and solid dispersion (formulation 3) are illustrated in Fig. 2. The diffraction spectra of pure **1** showed that the drug was highly crystalline in nature as indicated by numerous distinctive peaks. PEG 3350 exhibited two high-intensity peaks at 19.2 and 23.4°. The spectra of the placebo carrier showed all characteristic diffraction lines of PEG 3350. The lack of distinctive peak of **1** in the solid dispersion demonstrated that a high concentration of **1** dissolved in the carrier in the solid state (McGinity et al., 1984; Save and Venkitachalam, 1992).

Table 4 gives the bioavailability parameters such as the mean (±S.D.) maximum plasma concentration (C_{max}), time to reach maximum plasma concentration (T_{max}), area under the plasma concentration vs time curve (AUC) and an estimate of bioavailability obtained for each formulation. The bioavailability was estimated from the dose-adjusted ratio of AUC obtained following capsule administration and that determined after intravenous administration in the previous study (Khetarpal et al., 1994). The mean plasma concentration vs time curves obtained for each formulation are plotted in Fig. 3.

The bioavailability of **1** from formulation 1 was estimated to be about 11.8%, which is higher than that obtained with aqueous 0.5% methylcel-

Table 4
Bioavailability of RP 69698 in the dog following treatment with various capsule formulations at a dose of 10 mg/kg

Parameter	Formulation no.							
	1	2	3	4	5	6	7	8
C_{max} (μg/ml)	2.35 ± 0.84	2.07 ± 1.21	6.38 ± 2.61	6.41 ± 4.01	3.68 ± 2.54	2.91 ± 1.09	5.20 ± 3.83	3.88 ± 3.12
T_{max} (h)	0.62 ± 0.25	0.62 ± 0.25	0.50 ± 0.00	0.62 ± 0.25	0.62 ± 0.25	0.62 ± 0.25	0.88 ± 0.48	0.62 ± 0.25
AUC (0–24 h) (μg h ml^{-1})	2.95 ± 0.75	3.23 ± 2.14	6.90 ± 2.27	7.71 ± 4.25	5.56 ± 2.70	5.24 ± 3.00	7.58 ± 2.36	5.04 ± 2.11
Bioavailability [a] (%)	11.78 ± 2.98	12.91 ± 8.55	27.61 ± 9.08	30.82 ± 17.01	22.23 ± 10.78	20.97 ± 6.25	30.33 ± 9.45	20.18 ± 8.45

[a] Calculation based on dose-adjusted ratios of AUCs obtained for capsule formulation in this study vs that obtained for i.v. administered drug (AUC for i.v. dose of 2.5 mg/kg = 6.25 μg h ml^{-1}) in a previous pharmacokinetic study (Khetarpal et al., 1994)

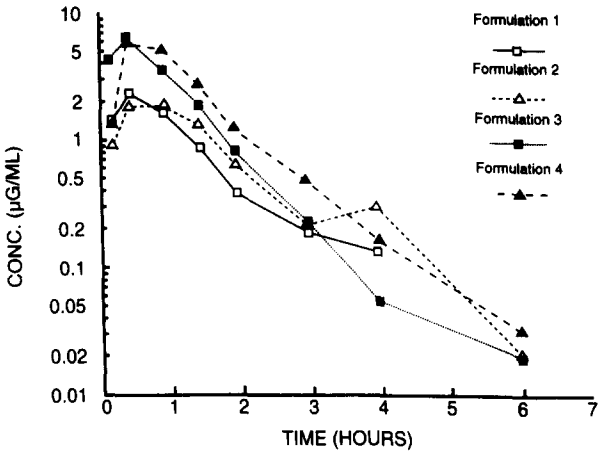


Fig. 3. Mean plasma concentration vs time curves obtained in dogs following administration of capsule formulations 1–4.

lulose suspension of the drug in the previous study (Khetarpal et al., 1994). Formulation 2 was designed to determine the bioavailability of **1** from the solution. The bioavailability of the drug was estimated to be about 12.9%, which represents no improvement over the bioavailability from formulation 1 despite the fact that the drug was completely solubilized in Labrasol. The lack of any improvement may be due to the precipitation of the drug in the gastrointestinal medium. Re-solubilization of the drug is not likely to occur due to its very low aqueous solubility.

Formulation 3 contains 10% of polysorbate 80 and no Transcutol. The bioavailability of the drug from this formulation was estimated to be about 27.6%. The solubility of the drug in polysorbate 80 is very low (Table 1). This is equivalent to less than 1.4 mg of the drug in 70 mg of the surfactant in the solid dispersion formulation. Therefore, the increase in bioavailability of 2–6% from lactose matrix and suspension to 27.6% from formulation 3 can not be attributed to the surfactant alone. It is contended, however, that this increase is due to the ability of the surfactant to increase the wettability of precipitated drug and spreadability of the drug in the solubilized state once released in the gastrointestinal medium.

The bioavailability of **1** from formulation 4 which contains 25 mg of drug was estimated to be about 30.8%. The slight increase in bioavailability over formulation 3 may be due to the greater fraction of drug that was molecularly dissolved in the carriers for quicker dissolution in the fluid. Sjokvist et al. (1991) have found that an increase in the drug content normally retards the dissolution rate.

Since the formulation containing 10% polysorbate 80 increased the bioavailability of **1** substantially, an additional study was conducted to compare the bioavailability of the drug from the formulations having different concentrations of the surfactant (Table 3). In addition, the effect of

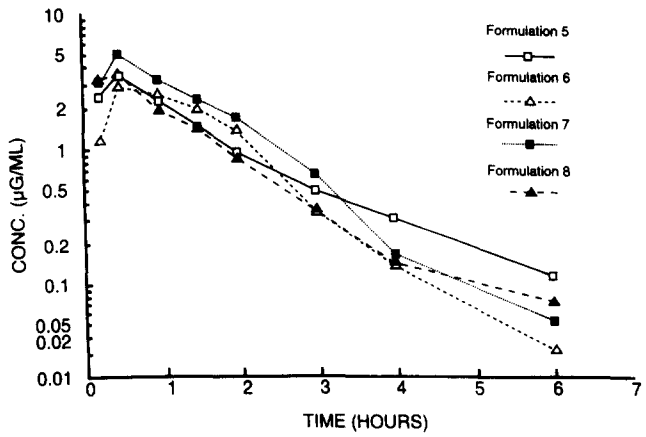


Fig. 4. Mean plasma concentration vs time curves obtained in dogs following administration of capsule formulations 5–8.

replacing Labrasol with Transcutol in the formulation containing 10% polysorbate 80 was also tested. The results of bioavailability evaluation are shown in Table 4.

The bioavailability of **1** from formulation 5 was about 22%, which is less than the original result of 28%. This may be attributed to inter-animal and/or experimental variability. Formulation 6 with 20% polysorbate 80 gave an estimate of about 21%, which showed no apparent improvement over formulation 5. Formulation 7 (30% polysorbate 80) showed slightly higher bioavailability (30%) than both formulations 5 and 6. However, in view of the variability observed within this experiment and those of the previous one, it is difficult to ascribe much significance to this improvement. The bioavailability from formulation 8, which differed from formulation 5 in that Labrasol was replaced by Transcutol, was similar to that determined for formulation 5. The mean plasma concentration vs time curve obtained from formulations 5–8 are plotted in Fig. 4.

Based on the data generated from the studies, it appears that bioavailability of **1** from solid dispersion capsules formulation containing 10% of polysorbate 80 is expected to be around 25%. This value represents an overall average of bioavailability estimates obtained for **1** from the formulations containing 10% polysorbate 80. In general, inter-individual variability was quite high for bioavailability from all formulations; the coefficient of variation (CV) values ranged between 25 and 66%. Because higher concentration of the surfactant in the formulation did not lead to unambiguous improvement in bioavailability and also for safety concerns for using high level of polysorbate 80, 10% may represent the optimum limit for this surfactant in the solid dispersion capsule formulation.

In conclusion, the bioavailability of poorly water-soluble **1** was increased from the water-soluble carriers. It was further improved by the addition of a surfactant. The optimum concentration of the surfactant in the solid dispersion formulations was determined to be 10% based on the bioavailability data. This study also demonstrates strategies that were followed in the development of a formulation of a very poorly water-soluble drug.

Acknowledgements

The authors are grateful to Professor J.K. Guillory, College of Pharmacy, University of Iowa for conducting powder XRD analysis. We also wish to thank Drs G.J. Alcorn and J.A. Ziemniak for their encouragement during the course of this investigation.

References

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

Fernandez, M., Rodriguez, I.C., Margarit, M.V. and Cerezo, A., Characterization of solid dispersions of piroxicam-polyethylene glycol 4000. *Int. J. Pharm.* 84 (1992) 197–202.

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

Khetarpal, V.K., Cariola, C.M., Collina, S.J. and Ziemniak, J.A., Assay of RP 69698, a novel LTB_4 antagonist, in plasma by HPLC and its application for characterizing pharmacokinetics of the drug in dogs. *J. Liq. Chromatogr.*, 17 (1994) 329–346.

McGinity, J.W., Maincent, P. and Steinfink, H., Crystallinity and dissolution rate of tolbutamide solid dispersions prepared by the melt method. *J. Pharm. Sci.*, 73 (1984) 1441–1444.

McGinity, J.W. and Coffin, M.D., Cooling processes and congealing. In Swarbrick, J. and Boylan, J.C. (Eds), *Encyclopedia of Pharmaceutical Technology*, Dekker, New York, Vol. 3, 1990, pp. 315–335.

Save, T. and Venkitachalam, P., Studies on solid dispersions of nifedipine. *Drug Dev. Ind. Pharm.*, 18 (1992) 1663–1679.

Sjokvist, E., Nystrom, C. and Alden, M., Physicochemical aspects of drug release: XIII. The effect of sodium dodecyl sulphate additions on the structure and dissolution of a drug in solid dispersions. *Int. J. Pharm.*, 69 (1991) 53–62.

Vadnere, M.K., Coprecipitates and melts. In Swarbrick, J. and Boylan, J.C. (Eds), *Encyclopedia of Pharmaceutical Technology*, Dekker, New York, Vol. 3, 1990, pp. 337–352.