Available online at www.sciencedirect.com
SCIENCE DIRECT®
International Journal of Pharmaceutics 269 (2004) 251–258
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Bioavailability enhancement of a poorly water-soluble drug by solid dispersion in polyethylene glycol–polysorbate 80 mixture

Hemant N. Joshi[1], Ravindra W. Tejwani, Martha Davidovich, Vaishali P. Sahasrabudhe[2], Mohammed Jemal, Mohinder S. Bathala, Sailesh A. Varia, Abu T.M. Serajuddin[*,3]

Bristol-Myers Squibb Pharmaceutical Research Institute, New Brunswick, NJ 08903, USA

Received 30 June 2003; received in revised form 4 September 2003; accepted 5 September 2003

Abstract

Oral bioavailability of a poorly water-soluble drug was greatly enhanced by using its solid dispersion in a surface-active carrier. The weakly basic drug (pK_a ~5.5) had the highest solubility of 0.1 mg/ml at pH 1.5, <1 μg/ml aqueous solubility between pH 3.5 and 5.5 at 24 ± 1 °C, and no detectable solubility (<0.02 μg/ml) at pH greater than 5.5. Two solid dispersion formulations of the drug, one in Gelucire 44/14® and another one in a mixture of polyethylene glycol 3350 (PEG 3350) with polysorbate 80, were prepared by dissolving the drug in the molten carrier (65 °C) and filling the melt in hard gelatin capsules. From the two solid dispersion formulations, the PEG 3350–polysorbate 80 was selected for further development. The oral bioavailability of this formulation in dogs was compared with that of a capsule containing micronized drug blended with lactose and microcrystalline cellulose and a liquid solution in a mixture of PEG 400, polysorbate 80 and water. For intravenous administration, a solution in a mixture of propylene glycol, polysorbate 80 and water was used. Absolute oral bioavailability values from the capsule containing micronized drug, the capsule containing solid dispersion and the oral liquid were 1.7 ± 1.0%, 35.8 ± 5.2% and 59.6 ± 21.4%, respectively. Thus, the solid dispersion provided a 21-fold increase in bioavailability of the drug as compared to the capsule containing micronized drug. A capsule formulation containing 25 mg of drug with a total fill weight of 600 mg was subsequently selected for further development. The selected solid dispersion formulation was physically and chemically stable under accelerated storage conditions for at least 6 months. It is hypothesized that polysorbate 80 ensures complete release of drug in a metastable finely dispersed state having a large surface area, which facilitates further solubilization by bile acids in the GI tract and the absorption into the enterocytes. Thus, the bioavailability of this poorly water-soluble drug was greatly enhanced by formulation as a solid dispersion in a surface-active carrier.

Keywords: Solid dispersion; Bioavailability enhancement; Poorly soluble drug; Polyethylene glycol; Polysorbate 80

* Corresponding author. Tel.: +1-862-778-3995; fax: +1-973-781-8487.
E-mail address: abu.serajuddin@pharma.novartis.com (A.T.M. Serajuddin).
[1] Present address: Barr Laboratories, Inc., 2 Quaker Road, P.O. Box 2900, Pomona, NY 10970, USA.
[2] Present address: Pfizer Global R&D, 2800 Plymouth Road, Ann Arbor, MI 48105, USA.
[3] Present address: Novartis Pharmaceuticals Corporation, 1 Health Plaza, East Hanover, NJ 07936-1080, USA.

0378-5173/$ – see front matter © 2003 Published by Elsevier B.V.
doi:10.1016/j.ijpharm.2003.09.002

1. Introduction

For absorption to be possible from the gastrointestinal (GI) tract, achieving a solution of drug in the GI fluid is a critical requirement for a poorly water-soluble drug. Horter and Dressman (1997) defined a poorly water-soluble drug as the one whose dissolution in the GI fluid under ordinary conditions

takes a longer time than its transition through the absorption sites in the GI tract. Although salt formation, particle size reduction, etc., have commonly been used to increase dissolution rates of drugs, there are practical limitations with these techniques and the desired bioavailability enhancement may not always be achieved (Wadke et al., 1989; Serajuddin, 1999). Solid dispersion systems in which the drug is dispersed in solid water-soluble matrices either molecularly or as fine particles have also shown promising results in increasing bioavailability of poorly water-soluble drugs (Chiou and Riegelman, 1971; Ford, 1986). The commercial use of such systems has been limited primarily because of manufacturing difficulties and stability problems. Serajuddin (1999), Serajuddin et al. (1988a) and Serajuddin et al. (1990) reported that some of the manufacturing problems with solid dispersion systems may be overcome by using surface-active and self-emulsifying carriers. The carriers are melted at elevated temperatures, the drugs are dissolved in molten carriers, and the hot solutions are then filled into hard gelatin capsules. Solid plugs are formed inside capsules at room temperature, and due to the surface activity of carriers, drugs dissolve or disperse rapidly once the plugs come in contact with the GI fluid.

There are only a limited number of surface-active agents that are suitable for solid dispersion (Serajuddin, 1999). Serajuddin et al. (1990) and Morris et al. (1992) reported that mixtures of polyethylene glycol (PEG) and polysorbate 80 have potential for use as surface-active carriers. However, very few in vivo studies demonstrating bioavailability enhancement by solid dispersion in such carriers have been reported in the literature (Sheen et al., 1995). In this article, we are reporting the development of solid dispersion formulation of an experimental drug in the PEG 3350–polysorbate 80 mixture, which is amenable to large-scale manufacturing. The in vitro dissolution of the formulation was compared with that of another formulation where a proprietary surface-active carrier, Gelucire 44/14® (Gattefossé Corp., Westwood, NJ, USA), was used. Absolute oral bioavailability of drug from the solid dispersion formulation containing the mixture of PEG 3350 and polysorbate 80 was then compared in a dog model with that of a solution and a dry powder-blend capsule containing micronized drug.

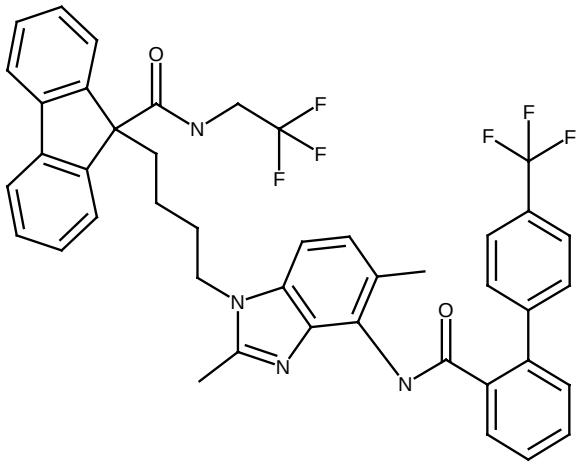

Fig. 1. Chemical structure of Compound 1.

2. Materials and methods

2.1. Materials

The structure of the experimental drug (Compound 1) is given in Fig. 1. It was obtained from Process Research and Development department at Bristol-Myers Squibb Pharmaceutical Research Institute. Compound 1 is a weak base with pK_a value of ∼5.5 and molecular weight of 754. In the crystalline state, it exists as a dihydrate. All experiments in this study refer to the free form equivalent quantities, which are adjusted for water of hydration. PEG 400, PEG 3350, polysorbate 80 and other chemicals were procured by Bristol-Myers Squibb from commercial sources and released for use in drug products. Gelucire 44/14® was supplied by Gattefossé Corp.

2.2. pH–solubility study

The effect of pH on the solubility of Compound 1 was determined at 25 ± 1°C. A suspension of drug was prepared in distilled water, and the pH of suspension was then adjusted by using either hydrochloric acid or sodium hydroxide solutions. After each adjustment of pH, the suspension was shaken for 6–10 h using a wrist action shaker, the resulting pH of the suspension was noted, and an aliquot was then filtered through a Millipore filter (0.22 μm pore) for the HPLC determination of the dissolved drug.

2.3. Dosage form development

Five different dosage forms: two capsule formulations containing solid dispersions, a capsule containing micronized drug, an oral solution and a parenteral solution were prepared. For the preparation of the solid dispersion formulations, solubility of the drug in different vehicles, such as PEG 400, PEG 1450, PEG 3350, Gelucire 44/14® and polysorbate 80 was determined. The solubility in liquid vehicles was determined at 25 ± 1 °C and that in solid vehicles was determined at 60–65 °C. Drug compatibility with vehicles was evaluated by storing the drug solutions at 60 °C for 2 weeks and subsequently analyzing samples by HPLC. The prototype formulations selected for further evaluation contained 25 or 50 mg of drug in each of the two solid dispersion vehicles: Gelucire 44/14® and PEG 3350–polysorbate 80 (3:1) mixture. The drug was dissolved in the carrier at 65 ± 5 °C, and 600 mg of the solution was then filled into each size no. 0 hard gelatin capsule either manually or by using a semi-automated filling machine (Wiley et al., 1995). Thus, a 25 mg capsule contained 575 mg of vehicle and a 50 mg capsule contained 550 mg of vehicle. After preliminary evaluation capsules were subjected to accelerated stability testing by storing them in high-density polyethylene (HDPE) bottles.

For the second capsule formulation, 50 mg of micronized drug (7–10 μm average particle size) was blended with 250 mg of a 9:1 mixture of lactose and microcrystalline cellulose. Each size no. 0 hard gelatin capsule was then filled with 300 mg of this blend.

In the oral solution, 2 mg of drug was dissolved per millilitre of a cosolvent system containing PEG 400, polysorbate 80 and aqueous 0.005N HCl in the ratio of 20:1:79 (w/w/v).

In the parenteral solution for infusion, the drug was dissolved at a concentration of 2 mg/ml in a mixture of polysorbate 80, propylene glycol and 0.008N HCl (2:40:58, w/w/v).

2.4. In vitro dissolution testing

Dissolution profiles of the capsule formulation containing micronized drug and the two capsule formulations containing solid dispersion were determined in 0.05N HCl according to the USP paddle method (50 rpm at 37 ± 0.5 °C). Aliquots of dissolution medium collected at different intervals of time (0, 5, 10, 20, 30, 45, 60, 90 and 120 min) were filtered through 0.45 μm syringe filters and analyzed. The dissolution rates of certain solid dispersion capsules were also studied in distilled water, where the aliquots were analyzed both with and without filtration; in the unfiltered state, a milky emulsion was formed.

2.5. Solubility in bile salt–lecithin solutions

Different amounts of lecithin were dissolved in a 40 mM solution of sodium taurocholate in a pH 6.8 sodium phosphate buffer (0.01 M). Excess drug was equilibrated with these lecithin solutions at 37 °C for 24 h prior to the HPLC determination of the dissolved drug.

2.6. Examination of drug crystals

A preliminary study established that a sample of solid dispersion spiked with very small amounts of crystalline material (<1%) could not be identified with powder X-ray diffractometry or differential scanning calorimetry. But such a sample could be differentiated using the following microscopy method: The solid dispersion was gently smeared over a glass slide to obtain a thin and uniform specimen. The specimen was observed at 100× magnification under a light microscope equipped with cross polarizers. Cross polarizers allow for visualization of the birefringent crystalline material in partially birefringent matrix.

2.7. HPLC analysis

A reversed-phase column (YMC-Pack, ODS-AQ-302-3, 15 cm × 4.6 mm, 5 μm), using a 55:45 (v/v) mixture of acetonitrile and aqueous trifluoroacetic acid (0.1%) as the mobile phase, was used for the HPLC analysis of Compound 1. The UV wavelength for the detector was set at 212 nm. With a flow rate of 1.2 ml/min for the mobile phase, the retention time of the drug was 11 min.

2.8. Bioavailability testing in dogs

The drug was administered to four male beagle dogs as 12.5 ml of intravenous infusion solution

(dose: 25 mg), one capsule containing micronized drug with excipients (dose: 50 mg), 50 ml of oral solution (dose: 100 mg), or two capsules containing PEG 3350–polysorbate 80 solid dispersion of drug (dose: 100 mg). A washout period of 1 week was used between two consecutive dosings. The dogs were fasted overnight before dosing and for 8 h post-dosing. Water was available as needed throughout the study. For intravenous dosing, the solution was infused at the rate of 1 ml/min using a 20-ml syringe and a Harvard infusion pump. The oral solution was administered by gavage, which was followed by 20 ml of water. The oral administration of hard gelatin capsules was followed by the administration of 10 ml of water.

Serial 3-ml blood samples were collected from each dog just prior to dose administration and at each of the following time points after the start of intravenous infusion: 6, 12.5, 15, 18 and 24 min, and 0.5, 1, 2, 4, 6, 8, 12, 24, 28 and 48 h. For the oral doses, serial blood samples were drawn just prior to dose administration and at each of the following time points: 15 min, 0.5, 1, 2, 4, 6, 8, 12, 24, 36 and 48 h. Blood was collected via the jugular vein into Vacutainer® tubes containing tripotassium EDTA as an anticoagulant. Plasma was obtained by centrifugation and stored at −20 °C.

The plasma samples were analyzed for the drug concentration by the HPLC-MS-MS method.

2.9. HPLC-MS-MS analysis of the plasma samples

The plasma samples were extracted using *t*-butyl ether (0.5–3 ml) by shaking together for 10 min and centrifuging at 3000 rpm for 10 min. The organic layer was then separated and evaporated to dryness. The residue was reconstituted quantitatively using acetonitrile (0.1 ml) and the resulting solution was injected into a BDS Hypersil column with an HP 1090L HPLC system at a flow rate of 0.3 ml/min. The effluent from this system was directed towards a Sciex API III tandem mass spectrometer, where multiple reaction monitoring was performed at *m*/*z* 755–249 for Compound 1. A gradient mobile phase system was used consisting of water, acetonitrile and ammonium acetate at pH 3.0. The standard curve range was 0.05–20 ng/ml.

3. Results and discussion

A partial pH–solubility profile of Compound 1 is given in Fig. 2. The drug is practically insoluble in water (solubility <1 μg/ml, pH 3.5–5.5) at 24 ± 3 °C. With available instrumentation, the solubility could not be determined above pH 5.5 because the value was less than the detection limit (0.02 μg/ml). The solubility increases with a decrease in pH, reaching a maximum value of ∼100 μg/ml in the region of pH 1.3–1.6

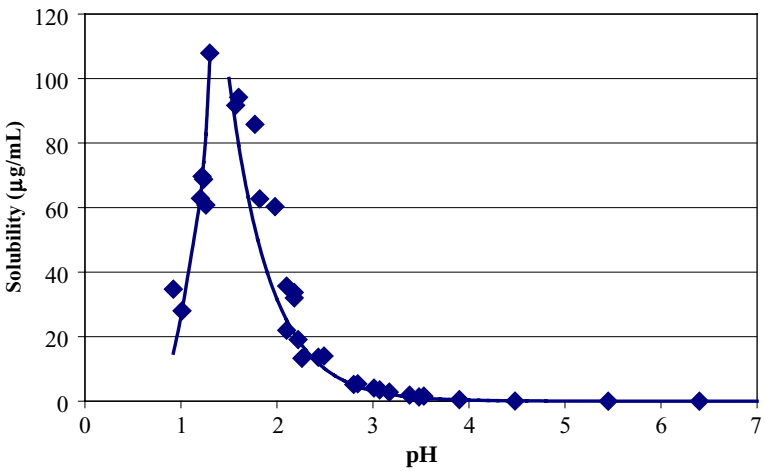

Fig. 2. pH–solubility profile of Compound 1 at 25 ± 1 °C.

(pH_{max}). However, below pH 1.3 the solubility decreases due to the in situ formation of a hydrochloride salt and the resultant common ion effect with HCl. Because of such a low pH_{max}, only strong acids can be used for preparing a salt. Among the attempted salts, only mono-hydrochloride was isolated as a crystalline material, however, it could not be prepared reproducibly. Additionally, this salt instantly disproportionates above the microenvironmental pH of 1.6. Therefore, the free base form was selected for further development as a formulation.

Unlike in water, the drug is highly soluble in many pharamaceutically acceptable organic solvents. The solubility in PEG 400 is ~110 mg/g at 25 °C, and the solubility in Gelucire 44/14®, PEG 1450 and PEG 3350 at 60–65 °C is >200 mg/g. Although the solubility of the drug in polysorbate 80 at 25 °C is lower (~20 mg/g), the solubility in the 3:1 mixture of PEG and polysorbate 80 at 60–65 °C is still greater than 200 mg/g. In addition, the drug is compatible with these vehicles since no significant degradation of drug was observed when various drug solutions were stored at 60 °C over a period of 2 weeks. Based on these results, prototype solid dispersions in Gelucire 44/14® or PEG 3350–polysorbate 80 mixture were selected for further evaluation.

Dissolution profile of the prototype solid dispersion capsules (50 mg) containing either Gelucire 44/14® or a 3:1 mixture of PEG 3350–polysorbate 80 in 0.05N HCl at 37 °C is shown in Fig. 3. The dissolution profile of the capsule containing micronized drug (50 mg) is also given in this figure. Complete release of drug from the solid dispersion formulations was observed in less than 30 min. The dissolution profiles of 25 mg solid dispersion capsules were essentially similar. The dissolution profiles remained unchanged if two or even four 50 mg solid dispersion capsules were tested with the same volume of dissolution medium. On the other hand, only about 60% of drug dissolved in 2 h from a capsule containing 50 mg micronized drug.

In addition to dissolution, the rate of dispersion of drug in distilled water at 37 °C from 50 mg solid dispersion capsule was also studied. The visual observation of unfiltered dissolution media showed a complete dispersion of drug in water (pH ~6) from the solid dispersion formulations containing Gelucire 44/14® as the vehicle. A complete dispersion was obtained from PEG 3350–polysorbate 80 based capsule

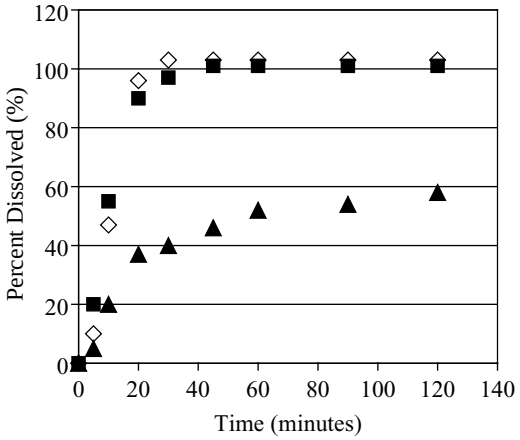

Fig. 3. Dissolution profiles of Compound 1 capsules (50 mg) in 0.05 M HCl at 37 °C. Key: (◇) capsule containing 3:1 PEG 3350–polysorbate 80 solid dispersion, (■) capsule containing Gelucire 44/14® and (▲) capsule containing micronized drug.

when the concentration of polysorbate 80 in the capsule was in excess of 20% (w/w). This dispersion of the formulations in water appeared like a milky emulsion. Although it is known that PEG and polysorbate 80 may not be miscible in all proportions, the great excess of water in the dissolution medium was sufficient to dissolve all the PEG and polysorbate 80 from the formulation (Tejwani et al., 2000). Hence the milky appearance could be due to the finely dispersed Compound 1 only. The rate of dispersion of Compound 1 in water from the solid dispersion formulation, where the unfiltered aliquots were used, was similar to the dissolution rate in an acidic medium shown in Fig. 3. When the aliquots were filtered through 0.45-μm pore size filters, approximately 25% of the amount passed through the filter, which indicates that approximately 25% of the drug was either dissolved or had particle size below 0.45 μm. Over 75% of drug from the dissolution medium (water) passed through 1.2-μm pore size filters. This experiment somewhat emulates what would happen in GI fluid where the pH conditions might not necessarily be acidic enough for all the drug to dissolve. The finely dispersed drug with very high surface area would dissolve much faster than the micronized drug and thus be available for absorption.

Although both solid dispersion formulations were similar in their dissolution behavior, the formulation

Table 1
Stability of the solid dispersion capsules of Compound 1 in a 3:1 mixture of PEG 3350 and polysorbate 80 stored in HDPE bottles under accelerated storage conditions

Time point	Storage condition	Potency[a] (mg per capsule)	Total impurity index[b]	Microscopic analysis[c]	Percent dissolved				
					10 min	15 min	30 min	45 min	60 min
Initial	–	24.6	0.42	No crystals	63	87	97	97	97
2 weeks	25 °C/60% RH	24.4	0.47	No crystals	50	82	101	100	100
	40 °C/75% RH	24.3	0.40	No crystals	42	73	100	100	100
4 weeks	5 °C	ND[d]	ND[d]	No crystals	–	–	–	–	–
	25 °C/60% RH	24.6	0.53	No crystals	55	84	100	100	100
	40 °C/75% RH	24.5	0.53	No crystals	41	73	100	101	101
13 weeks	5 °C	ND[d]	ND[d]	No crystals	41	78	103	103	104
	25 °C/60% RH	24.7	0.41	No crystals	57	87	99	99	99
	40 °C/75% RH	24.8	0.48	No crystals	60	91	101	100	100
26 weeks	5 °C	24.8	ND[d]	No crystals	44	74	100	100	100
	25 °C/60% RH	24.8	ND[d]	No crystals	48	75	100	101	101
	40 °C/75% RH	24.7	ND[d]	No crystals	18	48	94	101	102

[a] Determined using the HPLC assay described in the experimental section.
[b] Total impurity index is the sum of chromatographic area percent of all the peaks other than that of the Compound 1.
[c] Determined using a light microscope equipped with cross polarizers (magnification 100×).
[d] ND = not determined.

containing Gelucire 44/14® showed some leakage from the capsules during preliminary stability testing at 40 °C. This was not unexpected since the peak melting temperature of the vehicle is about 44 °C. Because of this reason, only the PEG 3350–polysorbate 80 solid dispersion capsule was used for further development. This formulation showed excellent stability of Compound 1 with respect to any physical, chemical and dissolution changes (Table 1). Prior to the commencement of the stability study, it was decided that only 25 mg capsules would be developed clinically. Therefore, this table contains data on 25 mg capsules only. In the formulation used for Table 1 the drug could be in a dissolved or an amorphous state. If it is in an amorphous state, there was a potential for crystallization. The solid dispersion capsule formulation was monitored closely for any occurrence of crystallization during the accelerated stability testing period. Contents of the capsules did not produce drug crystals in the matrix upon storage at room temperature. Although formal stability data is shown for 26 weeks, subsequent examination did not show any crystallization of drug even after 3 years. This indicated that there was a large margin of safety with respect to potential crystallization of Compound 1 in the solid dispersion formulation. It may be mentioned here that the microscopic examination was found to be the most appropriate method of examining the potential for drug crystallization. Other methods, such as differential scanning calorimetry (DSC) and powder X-ray diffraction (XRD), were not suitable; during the DSC analysis, the amount of drug present in the formulation dissolves in the matrix below its own melting temperature and, in the XRD study, the drug concentration is below the sensitivity of detection.

A slowdown in the dissolution rate was observed after 6 months in capsules stored at 40 °C/75% RH only (Table 1). This slowdown in dissolution has been attributed to possible cross-linking of the gelatin shell after storage at stress conditions. The phenomenon of gelatin cross-linking and corresponding slowdown in dissolution especially after storage at elevated temperature and humidity conditions has been extensively studied and reviewed (Murthy and Ghebre-Sellassie, 1993; Digenis et al., 1994).

The pharmacokinetic parameters of the formulations tested in bioavailability study are given in Table 2. After adjusting for the dose, C_{max} value for the solid dispersion capsule was at least 15 times that of the capsule containing micronized drug while C_{max} of the oral solution was only twice that of the solid dispersion capsule. The area under the curve (AUC) values show that by formulation as a solid dispersion the bioavailability of Compound 1 in dogs

Table 2
Bioavailability of Compound 1 in dogs from different formulations

Formulation	Dose (mg)	C_{max}[a] (ng/ml)	AUC[a] (ng h/ml)	Absolute[a] bioavailability
IV solution	25	10681 (1252)	9782 (1071)	–
Oral capsule (powder)	50	39.2 (6.9)	326 (153)	1.7 (1.0)
Oral solution	100	2558 (1386)	23769 (10023)	59.6 (21.4)
Oral capsule (solid dispersion)	100[b]	1206 (319)	14004 (2611)	35.8 (5.2)

[a] Mean (standard deviation) for $n = 3$.
[b] Two 50 mg capsules formulated in 3:1 PEG 3350–polysorbate 80 mixture.

was increased by a factor of 21 as compared to a capsule containing micronized drug. Although the bioavailability of the oral solution was approximately 1.5 times that of the solid dispersion, the difference may not be statistically significant when the standard deviations are considered.

The in vivo performance of the conventional capsule formulation could be correlated to its poor in vitro dissolution profile as compared to the solid dispersion formulations (Fig. 3). In the solid dispersion formulation the drug may be in a dissolved or amorphous state as observed by the microscopic examination of the solid matrix. Upon exposure to aqueous media, the drug disperses in a very finely subdivided form. The presence of polysorbate 80 in the formulation prevents agglomeration of drug into large globules or particles in the aqueous environment. Since concentration of polysorbate 80 from the solid dispersion in the dissolution medium may not be sufficient to cause solubilization of drug, it may be fair to conclude that polysorbate 80 only assists in the dispersion of drug into mostly sub-micron size particles (Serajuddin et al., 1988a). The release of drug in such a metastable emulsified state resulted in a significant increase in surface area which could facilitate the dissolution of a practically water insoluble drug in presence of biological surfactants in the intestinal fluid (Serajuddin et al., 1988b).

Table 3
Solubility of Compound 1 in 0.01 M phosphate buffer (pH 6.8) containing 40 mM sodium taurocholate at 37 °C as a function of lecithin concentration in the solution

Lecithin (mM)	Solubility (μg/ml)
0	1.4
3.6	5.1
6.9	7.0
9.6	11.0
13.8	18.8

While the solubility of Compound 1 at pH above 6 was below the HPLC detection limit of 0.02 μg/ml, the solubility in a 40 mM sodium taurocholate solution was 1.4 μg/ml. As shown in the Table 3, the solubility increased further when lecithin was added to the bile salt solution. Thus, it may be concluded that the release of Compound 1 as submicron globules, coupled with the high solubility in presence of surfactants and solubilizing agents present in the GI fluid, was responsible for the bioavailability enhancement by the PEG 3350–polysorbate 80 solid dispersion system.

References

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

Digenis, G.A., Gold, T.B., Shah, V.P., 1994. Cross-linking of gelatin capsules and its relevance to their in vitro-in vivo performance. J. Pharm. Sci. 83, 915–921.

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

Horter, D., Dressman, J.B., 1997. Influence of physicochemical properties on dissolution of drugs in the gastrointestinal tract. Adv. Drug Deliv. Rev. 25, 3–14.

Morris, K.R., Knipp, G.T., Serajuddin, A.T.M., 1992. Structural properties of polyethylene glycol–polysorbate 80 mixture, a solid dispersion vehicle. J. Pharm. Sci. 81, 1185–1188.

Murthy, K.S., Ghebre-Sellassie, I., 1993. Current perspectives on the dissolution stability of solid oral dosage forms. J. Pharm. Sci. 82, 113–126.

Serajuddin, A.T.M., 1999. Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems and recent breakthroughs. J. Pharm. Sci. 88, 1058–1066.

Serajuddin, A.T.M., Sheen, P.C., Mufson, D., Bernstein, D.F., Augustine, M.A., 1988a. Effect of vehicle amphiphilicity on the dissolution and bioavailability of a poorly water-soluble drug from solid dispersions. J. Pharm. Sci. 77, 414–417.

Serajuddin, A.T.M., Sheen, P.C., Mufson, D., Bernstein, D.F., Augustine, M.A., 1988b. Physicochemical basis of increased bioavailability of a poorly water-soluble drug following oral administration as organic solutions. J. Pharm. Sci. 77, 325–329.

Serajuddin, A.T.M., Sheen, P.C., Augustine, M.A., 1990. Improved dissolution of a poorly water-soluble drug from solid dispersions in polyethylene glycol:polysorbate 80 mixtures. J. Pharm. Sci. 79, 463–464.

Sheen, P.C., Khetarpal, V.K., Cariola, C.M., Rowlings, C.E., 1995. Formulation studies of a poorly water soluble drug in solid dispersions to improve bioavailability. Int. J. Pharm. 118, 221–227.

Tejwani, R.W., Joshi, H.N., Varia, S.A., Serajuddin, A.T.M., 2000. Study of phase behavior of poly(ethylene glycol)–polysorbate 80 and poly(ethylene glycol)–polysorbate 80–water mixtures. J. Pharm. Sci. 89, 946–950.

Wadke, D.A., Serajuddin, A.T.M., Jacobson, H., 1989. Preformulation testing. In: Lieberman, H.A., Lachman, L., Schwartz, J.B. (Eds.), Pharmaceutical Dosage Forms: Tablets, vol. 1. Dekker, New York, pp. 1–73.

Wiley, G.J., Ullah, I., Agharkar, S.N., 1995. Development of a semiautomatic system for R&D and clinical use for liquid-filled hard gelatin encapsulation. Pharm Tech. 19, 72, 74, 76.