AAPS PharmSciTech, Vol. 9, No. 2, June 2008 (© 2008)
DOI: 10.1208/s12249-008-9077-1

Brief/Technical Note

Development and Characterization of Zaleplon Solid Dispersion Systems: A Technical Note

Atish Waghmare,[1,2] Yogesh Pore,[1] and Bhanudas Kuchekar[1]

Received 19 September 2007; accepted 12 February 2008; published online 9 April 2008

KEY WORDS: characterization; crystallinity; dissolution; hydrophilic polymers; solid dispersion; zaleplon.

INTRODUCTION

Zaleplon (Fig. 1) is a pyrrazolopyrimidine hypnotic drug indicated for the short term (2 to 4 weeks) management of insomnia (1). It interacts with $GABA_A$ receptor and also shows some pharmacological properties of benzodiazepines (2). It also possesses potent anticonvulsant activity against pentylenetetrazole- and electroshock-induced convulsions (3) and is rapidly and completely absorbed after oral administration. However, it undergoes extensive first pass hepatic metabolism after absorption, with only 30% of zaleplon being systemically available (4). Zaleplon attains peak concentration (C_{max}) within 1.1 h (t_{max}) approximately after administration, with terminal elimination half life of 1 hour (5). Cmax and area under the plasma concentration–time curve (AUC) both exhibit linear dose proportionality at doses up to 60 mg well above the 10 mg therapeutic dose (6,7).

Although zaleplon is rapidly absorbed after oral administration, its poor aqueous solubility (8) (practically insoluble) can make its absorption dissolution rate limited and thus delay onset of action. The dissolution of drugs is a prime determinant in the absorption of poorly water-soluble drugs and also serves as a rate-limiting step (9). No information is available on the improvement of these drug-like properties of zaleplon. In this article increasing the solubility of zaleplon has been addressed via solid dispersion technique.

The formulation of poorly water-soluble drugs is one of the most challenging tasks to the formulation experts. An enhancement in the solubility and the dissolution rate can improve the oral bioavailability of such drugs, which further improves the therapeutic efficacy and patient compliance. Various techniques have been used to enhance the solubility of poorly water-soluble drugs, including the use of surfactants (10), inclusion complexation (11), use of polymorph (12), and amorphous form of drug micronisation (13) and solid dispersion (14–16). The solubilization of drug from solid dispersion systems is mainly because of the reduction in particle size, increase in the surface area and reduction in the crystallinity that improves dissolution rate. Also, no energy is required to break up the crystal lattice of a drug during dissolution process and drug solubility and wettability may be increased by surrounding hydrophilic carriers (17). The various methods used to prepare solid dispersions are the hot melt method (18,19), solvent evaporation (20), spray drying (21), hot melt extrusion (22), solvent deposition technique (23) and solvent wetting method (24).

The aim of the present study was to enhance the dissolution rate of zaleplon using solid dispersion technique with various hydrophilic polymers. The solvent evaporation method was used to prepare solid dispersion particles of zaleplon. Solid dispersion systems and physical mixtures of zaleplon were prepared with poloxamer F68, polyvinylpyrrolidone K30 (PVP K30), and polyethyleneglycol 6000 (PEG 6000) each in 1:1, 1:3 and 1:5 ratios. The selection of different ratios of polymers was purely on random basis. The solid-state properties of these binary systems were studied by thin layer chromatography, Fourier transformation infrared spectroscopy, X-ray powder diffractometry and differential scanning calorimetry. The dissolution behavior of zaleplon and its binary systems were further evaluated.

MATERIALS AND METHODS

Materials

Zaleplon was obtained from Cipla, Ltd., Mumbai, India. PVP K30 and Lutrol (poloxamer) F68 was gift sample from Signet Chem Lab, Mumbai, India. PEG 6000 was purchased from Loba Chemie, Mumbai, India. All the chemicals used were of analytical grade. Distilled water was used throughout the experiment.

[1] Department of Pharmaceutical Chemistry, Government College of Pharmacy, Karad, Maharashtra 415124, India.
[2] To whom correspondence should be addressed. (e-mail: atish.w31@rediffmail.com)

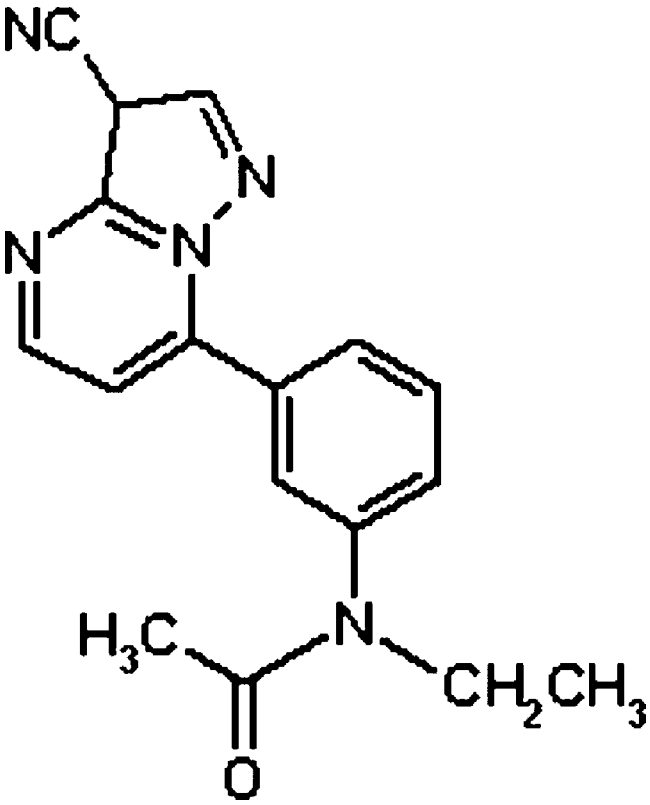

Fig. 1. Chemical structure of zaleplon

Analytical Method

Calibration Curve for Zaleplon

An accurately weighed 5 mg of zaleplon was dissolved in 5 ml of methanol in a 50 ml volumetric flask and the volume was adjusted up to the mark with distilled water to obtain a standard stock solution of 100 μg/ml. Aliquots of 0.1 to 0.8 ml portions of standard solution were transferred to a series of 10 ml volumetric flasks and volume in each flask was adjusted to 10 ml with distilled water to obtain concentration of range of 1.0–8.0 μg/ml. One of the solutions was scanned in UV range using methanol: distilled water (1:9) as a blank and λ_{max} was recorded at 232 nm. The absorbance of solutions was measured at 232 nm against reagent blank and calibration curve was constructed. This calibration curve was used for the quantification of drug in solid dispersions (*Percentage drug content study*) as well as aqueous samples from the dissolution experiments.

Preparation of Physical Mixtures

Physical mixtures were prepared by grinding zaleplon and individual hydrophilic polymer in a mortar in the ratios of 1:1, 1:3, 1:5 (zaleplon: polymer).

Preparation of Solid Dispersions of Zaleplon

Solid dispersions of zaleplon were prepared by solvent evaporation method. Zaleplon and water soluble carriers in different ratios were accurately weighed and transferred to a beaker containing methanol. Then solvent was evaporated in vacuum evaporator and the resulting solid dispersions were stored in desiccators until solid dispersion attains constant weight. The solidified masses were crushed, pulverized and passed through mesh number 40.

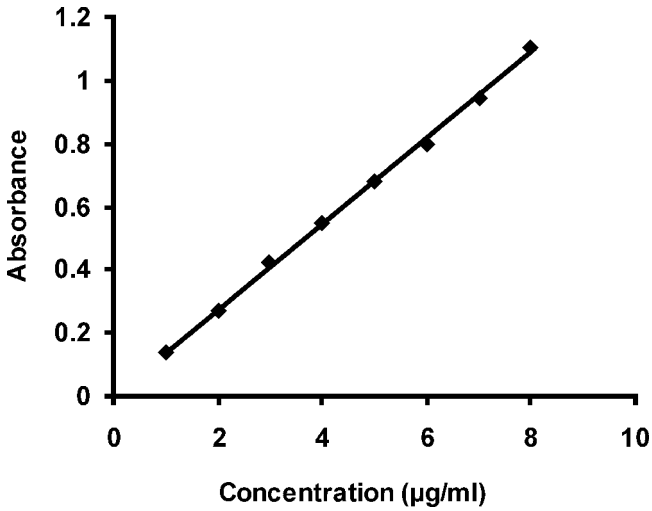

Fig. 2. Calibration curve for zaleplon

Thin Layer Chromatography (TLC)

TLC was carried out using silica gel GF 254 (0.2 mm) glass plates with a solvent system of benzene:methanol (90:10) as mobile phase, to study any drug carrier interaction. The Rf value of pure drug and solid dispersions were calculated.

Fourier Transformation Infrared Spectroscopy (FTIR)

Infrared spectra were obtained on a Perkin-Elmer Spectrum one FTIR spectrometer using KBr pallets. The samples were previously ground and mixed thoroughly with KBr. The KBr disks were prepared by compressing the powder. The scanning range was kept from 4,000 to 450 cm^{-1}.

X-ray Powder Diffractometry (XRD)

The XRD patterns of pure drug, physical mixtures and solid dispersions were recorded by using Philips Analytic X-

Table I. Optical Characteristics and Regression Equation for the Standard Zaleplon

Sr. No.	Parameter	Value
1.	λ_{max} (nm)	232
2.	Beer's range (μg/ml)	1.0–8.0
3.	Correlation coefficient (r^2)	0.9994
6.	Regression equation	$y = 0.135333x + 0.00325$
7.	Intercept (a)[a]	0.00325±0.00043
8.	Slope (b)[a]	0.135333±0.0051
9.	Limit of detection (LOD μg/ml)	0.014
10.	Limit of quantification (LOQ μg/ml)	0.042
11.	Relative S.D.	0.0055

[a] Indicates mean±S.D.

Table II. Rf Values and % Drug Content of Pure Zaleplon and Solid Dispersions

System	Rf Values	Percent drug content[a] ± S.D.
Pure drug Zaleplon	0.70	–
Physical mixtures		
Zaleplon: poloxamer (1:1)	0.70	97.51±0.86
Zaleplon: poloxamer (1:3)	0.70	97.57±0.46
Zaleplon: poloxamer (1:5)	0.71	97.13±1.03
Zaleplon: PVP K30 (1:1)	0.72	98.34±1.09
Zaleplon: PVP K30 (1:3)	0.71	98.41±0.68
Zaleplon: PVP K30 (1:5)	0.70	98.62±0.82
Zaleplon: PEG 6000 (1:1)	0.72	97.55±1.20
Zaleplon: PEG 6000 (1:3)	0.71	98.31±1.11
Zaleplon: PEG 6000 (1:5)	0.71	97.77±0.79
Solid dispersions		
Zaleplon: poloxamer (1:1)	0.73	96.34±0.39
Zaleplon: poloxamer (1:3)	0.74	96.37±0.62
Zaleplon: poloxamer (1:5)	0.73	97.48±1.19
Zaleplon: PVP K30 (1:1)	0.71	98.26±0.93
Zaleplon: PVP K30 (1:3)	0.70	96.44±0.72
Zaleplon: PVP K30 (1:5)	0.69	96.84±0.83
Zaleplon: PEG 6000 (1:1)	0.71	97.15±1.08
Zaleplon: PEG 6000 (1:3)	0.70	98.24±0.47
Zaleplon: PEG 6000 (1:5)	0.71	97.82±1.15

[a] Indicates mean of three readings (n=3)
S.D. Standard deviation

Ray—PW 3710 (Holland) diffractometer with tube anode Cu over the interval 5–70°/2θ. The operation data were as follows: Generator tension (voltage) 40 kV, Generator current 30 mA, and scanning speed 1°/min.

Differential Scanning Calorimetry (DSC)

DSC measurements were performed on a TA SDT 2960 DSC (USA) differential scanning calorimeter. The accurately weighed sample was placed in an aluminum pan. An empty aluminum pan was used as reference. The experiment was carried out in nitrogen atmosphere (flow rate 100 ml/min) at scanning rate of 10 °C/min in the range of 0–350 °C.

Percentage Drug Content Study

Drug content was determined by dissolving solid dispersions equivalent to 10 mg of drug in methanol and kept in ultrasonicator for 20 min. The volume was adjusted to 100 ml with distilled water. The solution was filtered through Whatman filter paper no. 41, suitably diluted and absorbance was measured at 232 nm using double beam UV spectrophotometer. (Shimadzu 1700, Japan).

Dissolution Studies

The dissolution rate studies of zaleplon alone, physical mixtures and solid dispersions were performed in triplicate in

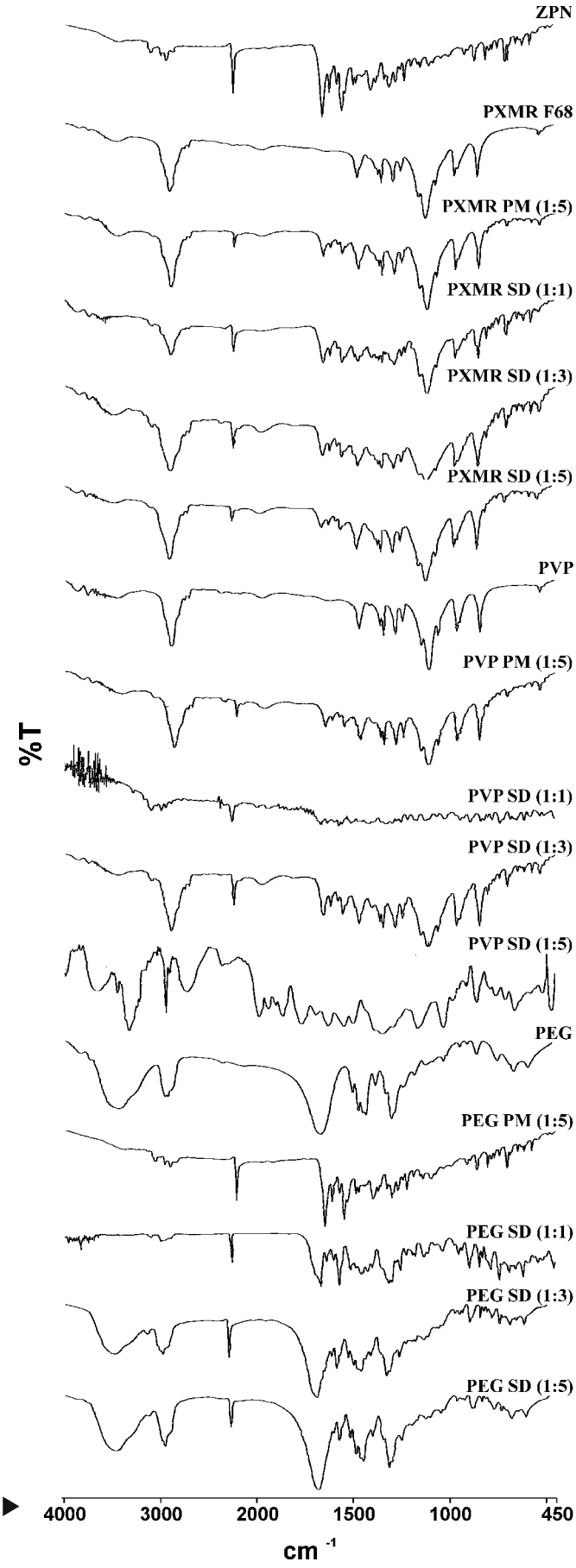

Fig. 3. FTIR spectra of zaleplon and all its binary systems with hydrophilic polymers. *ZPN* zaleplon, *PXMR* poloxamer F68, *PM* physical mixture, *SD* solid dispersion

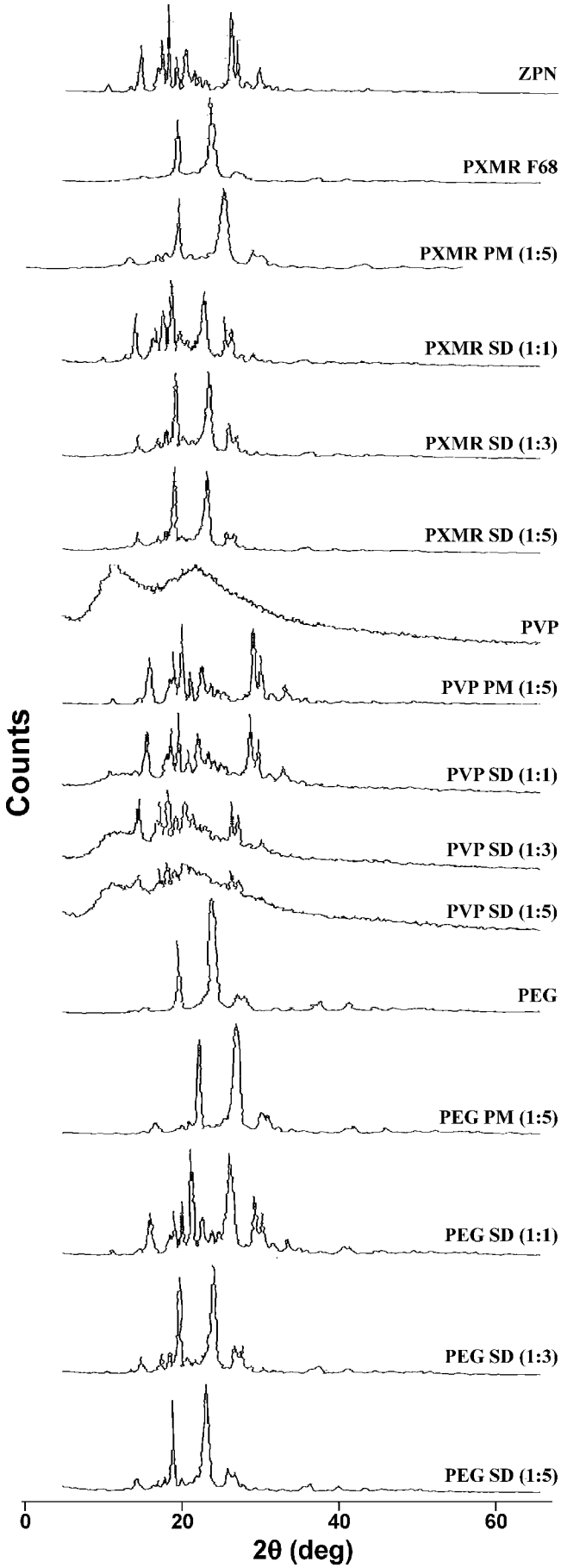

Fig. 4. XRD pattern of zaleplon and all its binary systems with hydrophilic polymers. *ZPN* zaleplon, *PXMR* poloxamer F68, *PM* physical mixture, *SD* solid dispersion

a dissolution apparatus (Lab India, Model Disso 2000 Tablet dissolution test apparatus, Mumbai, India) using the paddle method, according to USP Type II. Dissolution study was carried out in a 900 ml of distilled water at 37±0.5 °C at 75 rpm according to US FDA guidelines (25). 10 mg of pure drug or its equivalent amount of solid dispersion was added to 900 ml of distilled water. 5 ml of samples were withdrawn at time intervals of 5, 10, 15, 20, 25, 30, 45 and 60 min. The volume of dissolution medium was adjusted to 900 ml by replacing each 5 ml aliquot withdrawn with 5 ml of fresh distilled water. The solution was immediately filtered through 0.45 μm membrane filter, suitably diluted and the concentrations of zaleplon in samples were determined spectrophotometrically at 232 nm. The results obtained from the dissolution studies were statistically validated using ANOVA (Tukey–Kramer Multiple Comparisons Test).

RESULTS AND DISCUSSION

Analytical Method

Figure 2 illustrates a calibration curve for zaleplon in methanol: distilled water. The optical characteristics are presented in Table I. Zaleplon exhibits its maximum absorption at 232 nm and obeyed Beer's law in the range of 1.0–8.0 μg/ml. Linear regression of absorbance on concentration gave equation

$$y = 0.135333x + 0.00325 \tag{1}$$

with a correlation coefficient of 0.9994. Relative standard deviation of 0.0055 was observed for analysis of three replicate samples, indicating precision and reproducibility of analytical method. The limit of detection (LOD) and limit of quantification (LOQ) were calculated by Eqs. 2 and 3, respectively, where δ is the SD of blank and s is slope of calibration (26).

$$\mathrm{LOD} = \frac{3.3\delta}{s} \tag{2}$$

$$\mathrm{LOQ} = \frac{10\delta}{s} \tag{3}$$

The limit of detection (LOD) and limit of quantification (LOQ) were found to be 0.014 μg/ml and 0.042 μg/ml respectively.

Percentage Drug Content Study

Percentage drug content was found to be in the range of 96.27±0.15 to 98.62±0.08 (Table II).

Thin Layer Chromatography (TLC)

TLC study showed Rf values from 0.69–0.74 for all solid dispersions, which was almost identical with Rf value of pure

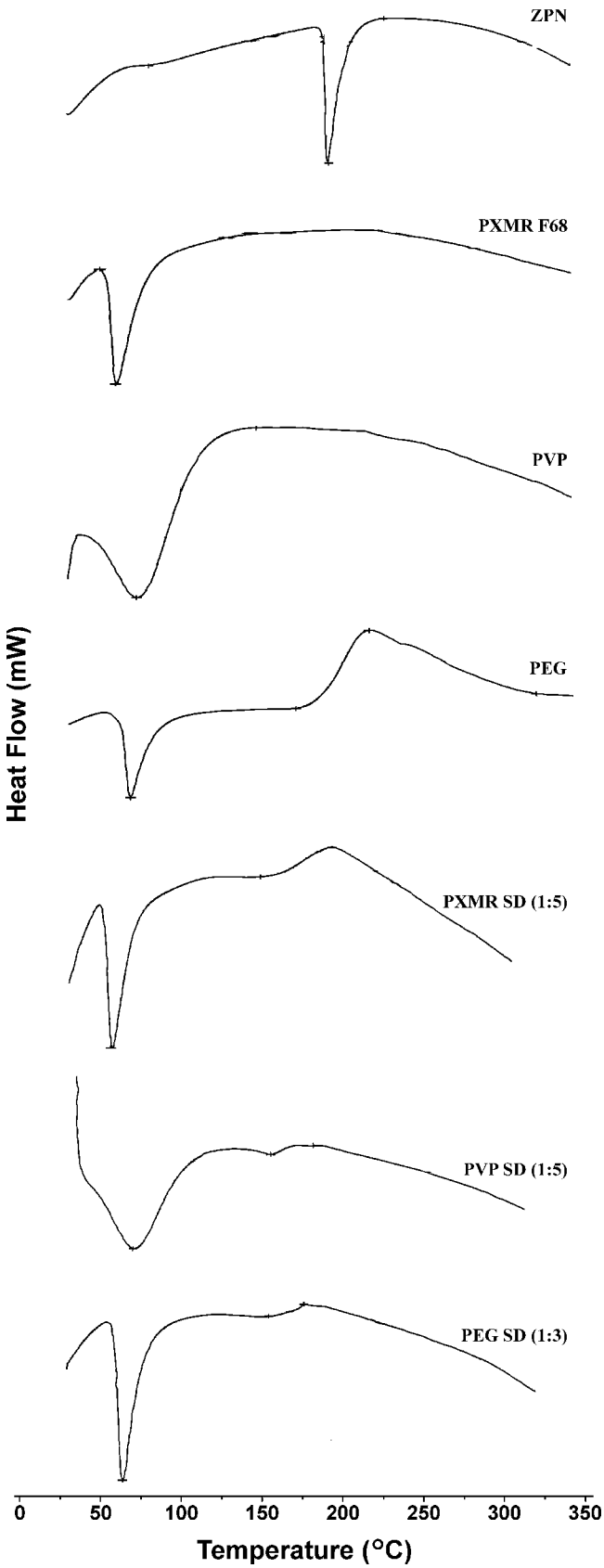

Fig. 5. DSC diagram of zaleplon, poloxamer F68, PVP K30, PEG 6000, and solid dispersions: *ZPN* zaleplon, *PXMR* poloxamer F68, *PM* physical mixture, *SD* solid dispersion

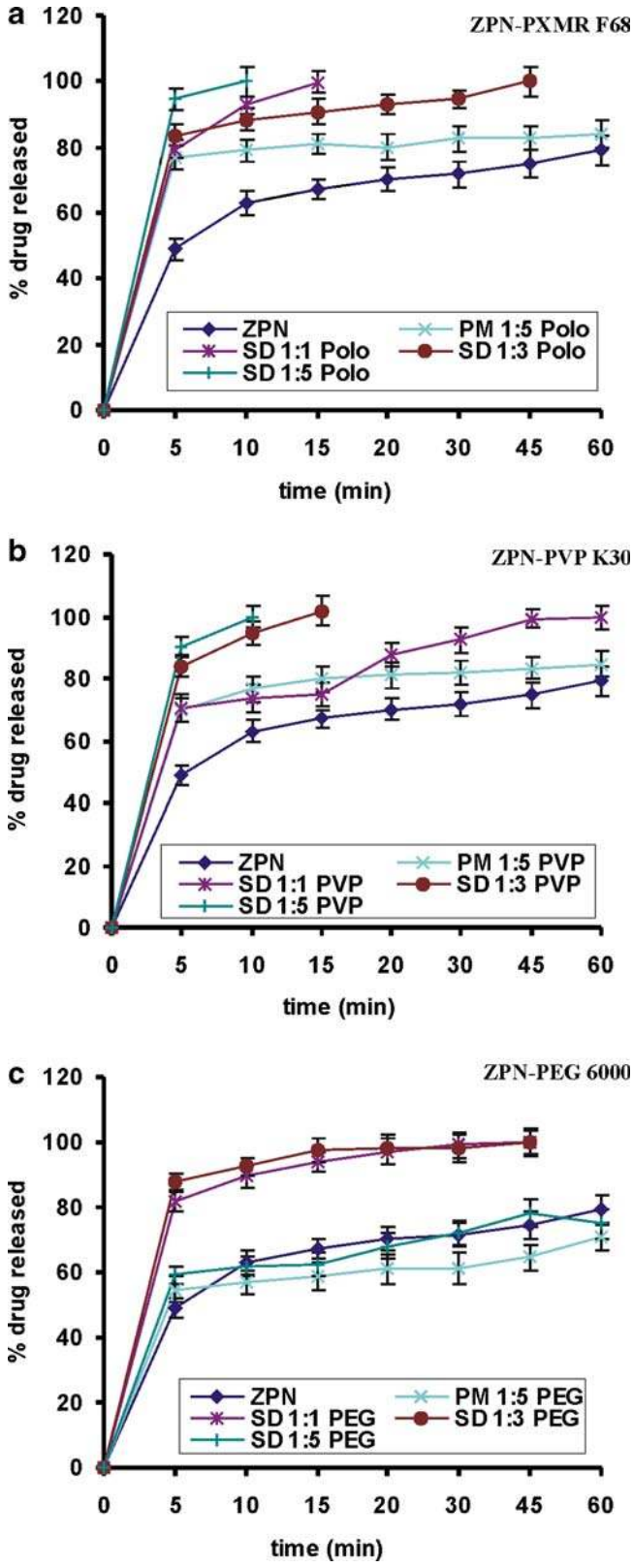

Fig. 6. Dissolution curves of zaleplon alone and from binary systems of zaleplon with hydrophilic polymers. *SD* Solid dispersion, *PM* physical mixture. **a** Dissolution curves of zaleplon with poloxamer F68; **b** Dissolution curves of zaleplon with PVP K30; **c** Dissolution curves of zaleplon with PEG 6000

drug (Table II). It indicates that there was no interaction between drug and carrier.

Fourier Transformation Infrared Spectroscopy (FTIR)

IR spectra of binary systems of zaleplon (Fig. 3) showed IR peaks of zaleplon and carriers and no any additional peak was observed in binary systems. IR spectrum of zaleplon is characterized by principal absorption peaks at 3,088 cm^{-1} (C–H aromatic), 2,928 cm^{-1} (C–H aliphatic), 2,232 cm^{-1} (C≡N), 1,651 cm^{-1} (C=O), 1,614 cm^{-1} (C=N), 1,223 cm^{-1} (C–N), 1,576 cm^{-1} (C=C aromatic) and 684 cm^{-1} and 801 cm^{-1} (*m* substituted benzene). Zaleplon shows strong absorption peaks at 2,232 cm^{-1} and 1,651 cm^{-1} indicating presence of cyanide and amide carbonyl group respectively while, peaks at 684 and 801 cm^{-1} may be assigned to aromatic stretching of the phenyl group in the molecule which is *m*-substituted. The IR spectra of all solid dispersions show disappearance of some peaks of zaleplon. The peaks at 3,088, 2,928, 1,576 and 684 cm^{-1} have been completely disappeared in all zaleplon-poloxamer F68 binary systems including physical mixtures (1:5). All other peaks appeared with decreased intensity. In the binary systems of zaleplon-PVP K30, the peak at 1651 cm^{-1} (C=O) was disappeared in addition to the peaks described in poloxamer solid dispersions. However physical mixture (1:5) has shown all peaks of zaleplon. IR spectra of solid dispersions of zaleplon-PEG 6000 also show disappearance of these peaks while no significant difference was found in physical mixture (1:5). All other peaks of zaleplon were found to be smoothened indicating strong physical interaction of zaleplon with polymers. However, no additional peak was observed in all binary systems indicating absence of any chemical interaction between zaleplon and polymers.

X-ray Powder Diffractometry (XRD)

The XRD patterns of zaleplon and solid dispersions are represented in Fig. 4. The XRD pattern of zaleplon showed intense and sharp peaks indicating its crystalline nature. Crystallinity was determined by comparing some representative peak heights in the diffraction patterns of the binary systems with those of a pure drug zaleplon (27). Zaleplon showed sharp peaks at 18° and 25° (2θ) with peak intensities of 1,560 and 1,204 respectively. The diffraction pattern of physical mixtures (1:5) of poloxamer F68 and PVP K30 showed decrease in the peak intensity of zaleplon at the same angle. However, complete disappearance of peaks of zaleplon was observed with the physical mixture (1:5) prepared with PEG 6000 indicating relative decrease in the crystallinity of zaleplon. Also, complete disappearance of peaks of zaleplon was observed in all solid dispersions prepared by using PVP K30 and poloxamer F68 whereas only 1:3 ratio of zaleplon-PEG 6000 solid dispersion has shown complete disappearance of peaks of zaleplon indicating decrease in the crystallinity of zaleplon in these binary systems.

Table III. Dissolution Efficiency of Zaleplon from Different Binary Systems in Comparison with Pure Drug

System	DP_5[a]±S.D.	DE_5[a]±S.D.	DE_{10}[a]±S.D.
Zaleplon	49.05±3.20	24.36±1.85	40.10±2.69
Zaleplon: poloxamer (1:5) PM	76.72±3.40	38.36±1.70[b]	58.11±2.04[b]
Zaleplon: poloxamer (1:1) SD	79.42±3.10	39.71±1.55[b]	63.89±2.12[b]
Zaleplon: poloxamer (1:3) SD	83.65±2.90	41.83±1.45[b]	63.95±1.75[b]
Zaleplon: poloxamer (1:5) SD	94.55±3.30	47.28±1.34[b]	72.24±2.26[b]
Zaleplon: PVP K30 (1:5) PM	69.98±3.91	34.99±1.95[b]	54.16±2.42[b]
Zaleplon: PVP K30 (1:1) SD	70.32±4.51	35.16±2.25[b]	53.58±2.79[b]
Zaleplon: PVP K30 (1:3) SD	83.82±3.09	41.91±1.26[b]	65.75±2.32[b]
Zaleplon: PVP K30 (1:5) SD	90.33±3.01	45.17±1.22[b]	70.33±2.67[b]
Zaleplon: PEG 6000 (1:5) PM	54.69±3.90	27.34±1.58[c]	41.62±2.44[c]
Zaleplon: PEG 6000 (1:1) SD	81.96±3.41	40.98±1.38[b]	63.39±2.12[b]
Zaleplon: PEG 6000 (1:3) SD	87.65±2.72	43.83±1.10[b]	66.95±1.69[b]
Zaleplon: PEG 6000 (1:5) SD	59.32±2.79	29.66±1.14[d]	45.13±1.77[e]

Dissolution Efficiency (DE) is defined as the area under dissolution curve up to the time t expressed as percentage of the area of rectangle described by 100% dissolution in the same time (32). The dissolution efficiency at 10 min was calculated as follows: $DE_{10} = \frac{\text{AUC of dissolution curve at 10 min}}{\text{AUC of rectangle at time 10 min}}$ Where, AUC is area under the curve Similarly, the dissolution efficiency at 5 min was calculated.

Alternatively, $\text{Dissolution efficiency(D.E.)} = \frac{\int_{t_1}^{t_2} y \cdot dt}{y_{100} \cdot (t_2 - t_1)} \times 100\%$ where y is the percentage of dissolved product. D.E. is then the area under the dissolution curve between time points t_1 and t_2 expressed as a percentage of the curve at maximum dissolution, y_{100}, over the same time period. The integral of the numerator, is the area under the curve which is calculated by trapezoidal rule. The area under the curve is the sum of all the trapeziums defined by: $AUC = \sum_{i=1}^{i=n} \frac{(t_1 - t_{i-1})(y_{i-1} + y_i)}{2}$ where t_i is the ith time point, y_i is the percentage of dissolved product at time t_i (33) The dissolution efficiency values were calculated using these methods described as above.

S.D. Standard deviation, *PM* physical mixture, *SD* solid dispersion, DP_5 percent dissolved at 5 min, DE_5 dissolution efficiency at 5 min, DE_{10} dissolution efficiency at 10 min

[a] Indicates mean of three experiments

[b] Indicates P value compared to pure zaleplon ($P<0.001$) i.e. significant

[c] Indicates P value compared to pure zaleplon but not significant ($P>0.05$)

[d] Indicates P value compared to pure zaleplon ($P<0.05$) i.e. significant

[e] Indicates P value compared to pure zaleplon but not significant ($P>0.05$)

Differential Scanning Calorimetry (DSC)

The DSC thermograms of zaleplon and solid dispersions with poloxamer F68, PVP K30 and PEG 6000 are represented in Fig. 5. The DSC thermograms of zaleplon alone showed endothermic *T*max of 190.05 °C, corresponding to the melting point of crystalline form of the drug zaleplon. The DSC thermogram of poloxamer F68, PVP K30 and PEG 6000 showed a sharp endothermic peak at 62.81 °C, 71.90 °C and 68.49 °C, respectively, indicating melting points of the polymers. The sharp melting point peak of pure zaleplon appeared at 190.05 °C, whereas no such peak was observed in solid dispersions prepared with poloxamer F68, PVP K30 or PEG 6000, indicating that zaleplon was molecularly dispersed (24). However, the peaks of all polymers in solid dispersions were found to be shifted to lower values; 59.40 °C, 70.19 °C and 66.22 °C for poloxamer F68, PVP K30 and PEG 6000 respectively, indicating solid–solid phase transition.

Dissolution Studies

The dissolution curves of zaleplon, physical mixtures and solid dispersions in distilled water at 37 °C±0.5 °C are shown in Fig. 6. The release rate profiles were expressed as the percentage of drug released (*vs*.) time.

It is evident that the solid dispersion (SD) technique has improved the dissolution rate of zaleplon to a greater extent. Table III shows % drug dissolved in 5 min (DP_5), dissolution efficiency at 5 min (DE_5), and dissolution efficiency at 10 min (DE_{10}) for zaleplon and its binary systems with hydrophilic polymers. All binary systems of zaleplon, except physical mixture with PEG (1:5), have shown significant improvement in dissolution rate compared to pure drug alone ($P<0.001$). Within the binary systems of different polymers with zaleplon, the 1:5 ratios of poloxamer F68 and PVP K30 and 1:3 ratios of PEG 6000 were found to be superior to their corresponding other ratios. It showed that increase in weight fraction of polymer gave more rapid dissolution (28). However, in solid dispersions of PEG 6000; it was found that, higher proportion of polymer retards the release rate of zaleplon. From the DP_5, DE_5 and DE_{10} values, it is evident that the 1:5 ratios of poloxamer F68 has shown faster dissolution rate than any other binary systems of zaleplon. However, no significant difference was found in dissolution rate among the polymers used when compared statistically. The order of efficiencies of polymers based on DE values is, poloxamer F68 (1:5) SD>PVP K30 (1:5) SD>PEG 6000 (1:3) SD.

The rapid dissolution of zaleplon from solid dispersion may be attributed to decrease in the crystallinity of drug and its molecular and colloidal dispersion in hydrophilic carrier matrix. As soluble carrier dissolves, the insoluble drug gets exposed to dissolution medium in the form of very fine particles for quick dissolution (29,30). The other factors that might be contributing in enhancing the dissolution rate are greater hydrophilicity and surfactant property of polymers, increased wettability and dispersibility and particle size reduction of drug (31). The greater hydrophilicity and surfactant property of polymers results in greater wetting and increases surface available for dissolution by reducing interfacial tension between hydrophobic drug and dissolution media. During dissolution experiments, it was noticed that drug carrier systems sank immediately, whereas pure drug floated on the surface of dissolution medium for a longer period of time. Further, solvent evaporation technique results in uniform distribution of drug in the polymer.

SUMMARY AND CONCLUSION

The dissolution profile of a poorly water-soluble drug, zaleplon, from its solid dispersion systems with various hydrophilic polymers has been investigated. The solid-state properties of binary systems were characterized by powder XRD and DSC, showed gradual decrease in the crystallinity of drug in the binary systems of zaleplon with increase in the proportion of carrier. The study shows that the dissolution rate of zaleplon can be enhanced to a great extent by solid dispersion technique using solvent method. Based on the results, Solid dosage forms containing zaleplon for oral administration could be manufactured with poloxamer F68, PVP K30 or PEG 6000 with high dissolution rate to improve its bioavailability to some extent.

ACKNOWLEDGEMENT

The authors are thankful to Cipla Ltd, Mumbai, India for providing drug samples. Authors are also thankful to Shivaji University, Kolhapur, India for providing all analytical facilities.

REFERENCES

1. M. Dooley, and G. Plosker. Zaleplon a review of its use in the treatment of insomnia. *Drugs* **60**:413–445 (2000).
2. M. Hurst, and S. Noble. Zaleplon. *CNS Drugs* **11**:387–392 (1999).
3. K. Damgen, and H. Luddens. Zaleplon displays a selectivity to recombinant $GABA_A$ receptors different from zolpidem, zopiclone and benzodiazepines. *Neurosci. Res. Commun.* **25**:139–148 (1999).
4. D. R. Drover. Comparative pharmacokinetics and pharmacodynamics of short-acting hypnosedatives zaleplon, zolpidem and zopiclone. *Clin. Pharmacokinet.* **43**:227–238 (2004).
5. D. Drover, H. Lemmens, S. Naidu, W. Cevallos, M. Darwish, and D. Stanski. Pharmacokinetics, pharmacodynamics, and relative pharmacokinetic/pharmacodynamic profiles of zaleplon and zolpidem. *Clin. Ther.* **22**:1443–1461 (2000).
6. A. S. Rosen, P. Fournie, M. Darwish, P. Danjou, and S. M. Troy. Zaleplon pharmacokinetics and absolute bioavailability. *Biopharm. Drug Dispos.* **20**:171–175 (1999).
7. D. J. Greenblatt, J. S. Harmatz, L. L. von Moltke, *et al.* Comparative kinetics and dynamics of zaleplon, zolpidem, and placebo. *Clin. Pharmacol. Ther.* **64**:553–561 (1998).
8. RxList.com [homepage on the internet]. New York: The Internet Drug Index, Sonata Discription, WebMD, Inc.; c1996–2005, Available at http://www.rxlist.com/cgi/generic/zaleplon.htm. Accessed January 11, 2007.
9. D. Horter, and J. B. Dressman. Influence of physicochemical properties on dissolution of drugs in the gastrointestinal tract. *Adv. Drug Deliv. Rev.* **25**:3–14 (1997).
10. H. Schott, L. C. Kwan, and S. Feldman. The role of surfactant in the release of very slightly soluble drugs from tablets. *J. Pharm. Sci.* **71**:1038–1045 (1982).
11. F. Veiga, J. J. C. Teixeria-Dias, F. Kedzeierewicz, A. Sousa, and P. Maincent. Inclusion complexation of tolbutamide with β-cyclodextrin and hydroxypropyl-β-cyclodextrin. *Int. J. Pharm.* **129**:63–71 (1996).

12. J. O. Henck, U. J. Griesser, and A. Burger. Polymorphie von Arzneistoffen. Eine wirtschaftliche Herausforderung? *Pharm. Ind.* **59**:165–169 (1997).
13. B. C. Hancock, and G. Zografi. Characteristics and significance of the amorphous state in pharmaceutical systems. *J. Pharm. Sci.* **86**:1–12 (1997).
14. W. L. Chiou, and S. Riegelman. Pharmaceutical applications of solid dispersion systems. *J. Pharm. Sci.* **60**:1281–1302 (1971).
15. L. Christian, and J. Dressman. Improving drug solubility for oral delivery using solid dispersions. *Eur. J. Pharm. Biopharm.* **50**:47–60 (2000).
16. A. T. M. Serajuddin. Solid dispersion of poorly water-soluble drugs: Early promises, subsequent problems, and recent breakthroughs. *J. Pharm. Sci.* **88**:1058–1066 (1999).
17. D. Q. M. Craig. The mechanisms of drug release from solid dispersions in water-soluble polymers. *Int. J. Pharm.* **231**:131–144 (2002).
18. N. Zajc, A. Obreza, M. Bele, and S. Srcic. Physical properties and dissolution behavior of nifedipine/mannitol solid dispersions prepared by hot melt method. *Int. J. Pharm.* **291**:51–58 (2005).
19. L. Wang, F. D. Cui, and H. Sunada. Preparation and evaluation of solid dispersions of nitrendipine prepared with fine silica particles using the melt-mixing method. *Chem. Pharm. Bull.* **54**:37–43 (2006).
20. V. Tantishaiyakul, N. Kaewnopparat, and S. Ingkatawornwong. Properties of solid dispersions of piroxicam in polyvinylpyrrolidone. *Int. J. Pharm.* **181**:143–151 (1999).
21. I. Weuts, D. Kempen, G. Verreck, A. Decorte, K. Heymans, J. Peeters, M. Brewster, and G. V. Mooter. Study of the physicochemical properties and stability of solid dispersions of loperamide and PEG 6000 prepared by spray drying. *Eur. J. Pharm. Biopharm.* **59**:119–126 (2005).
22. M. Adel El-Egakey, M. Soliva, and P. Speiser. Hot extruded dosage forms. *Pharm. Acta Helv.* **46**:31–52 (1971).
23. S. Dastmalchi, A. Garjani, N. Maleki, G. Sheikhee, V. Baghchevan, P. Jafari-Azad, H. Valizadeh, and M. Barzegar-Jalali. Enhancing dissolution, serum concentrations and hypoglycemic effect of glibenclamide using solvent deposition technique. *J. Pharm. Pharm. Sci.* **8**:175–181 (2005).
24. E. J. Kim, M. K. Chun, and J. S. Jang. Preparation of a solid dispersion of felodipine using a solvent wetting method. *Eur. J. Pharm. Biopharm.* **64**:200–205 (2006).
25. U.S. Food and drug administration. Dissolution methods for drug products Website. Available at: http://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults_Dissolutions.cfm?PrintAll=1. Accessed January 24, 2007.
26. K. Busaranon, W. Suntornsuk, and L. Suntornsuk. Comparison of UV spectrophotometric method and high performance liquid chromatography for the analysis of flunarizine and its application for the dissolution test. *J. Pharm. Biomed. Anal.* **41**:158–164 (2006).
27. J. A. Ryan. Compressed pellet X-ray diffraction monitoring for optimisation of crystallinity in lyophilised solids: imipenem: cilastatin sodium case. *J. Pharm. Sci.* **75**:805–807 (1986).
28. O. I. Corrigan, E. M. Holohan, and M. R. Reilly. Physicochemical properties of indomethacin and related compound co-spray dried with polyvinyl pyrrolidone. *Drug Dev. Ind. Pharm.* **11**:677–695 (1985).
29. A. S. Geneidi, A. A. Ali, and R. B. Salama. Solid dispersions of nitrofurantoin, ethotoin and coumarin with polyethylene glycol 6000 and other coprecipitates with povidone 25000. *J. Pharm. Sci.* **67**:114–116 (1978).
30. T. Save, and P. Venkitachalam. Studies on solid dispersions of nifedipine. *Drug Dev. Ind. Pharm.* **18**:1663–1679 (1992).
31. J. L. Ford. The current status of solid dispersions. *Pharm. Acta Helv.* **61**:69–88 (1986).
32. K. A. Khan. The concept of dissolution efficiency. *J. Pharm. Pharmacol.* **27**:48–49 (1975).
33. N. H. Anderson, M. Bauer, N. Boussac, R. Khan-Malek, P. Munden, and M. Sardaro. An evaluation of fit factors and dissolution efficiency for the comparison of *in vitro* dissolution profiles. *J. Pharm. Biomed. Anal.* **17**:811–822 (1998).