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Physicochemical characterization and in vivo properties of Zolpidem in solid dispersions with polyethylene glycol 4000 and 6000

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Abstract

Solid dispersions and physical mixtures of Zolpidem in polyethylene glycol 4000 (PEG 4000) and 6000 (PEG 6000) were prepared with the aim to increase its aqueous solubility. These PEG based formulations of the drug were characterized in solid state by FT-IR spectroscopy, X-ray powder diffraction, and differential scanning calorimetry. By these physical determinations no drug-polymer interactions were evidenced. Both solubility and dissolution rate of the drug in these formulations were increased. Each individual dissolution profile of PEG based formulation fitted Baker–Lonsdale and first order kinetic models. Finally, significant differences in ataxic induction time were observed between Zolpidem orally administered as suspension of drug alone and as solid dispersion or physical mixture. These formulations, indeed, showed almost two- to three-fold longer ataxic induction times suggesting that, in the presence of PEG, the intestinal membrane permeability is probably the rate-limiting factor of the absorption process.

Keywords: Zolpidem; Solid dispersions; Physical mixtures; PEG 4000; PEG 6000; Water-solubility; Dissolution rate; Ataxic induction

1. Introduction

Zolpidem (ZP), *N*,*N*-Dimethyl-[2-(4-tolyl)-6-methylimidazo[2,1-*a*]pyridin-3-yl]acetamide, is a hypnotic agent used for the treatment of the insomnia and sleep disorders characterized by a rapid onset and short duration of action (Martindale, The Extra Pharmacopoeia, 1996). It is a ligand for the central benzodiazepine receptors (BZ) endowed of high affinity and selectivity for the BZ1 subtypes. At present, the available dosage form of ZP is the tablet of the correspond-

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ing emitartrate salt marketed as Stilnox®. Following administration of these tablets, the bioavailability is somewhat limited, probably due to poor aqueous solubility of the drug and/or to its unsatisfactory dissolution rate.

Given the increasing popularity of ZP for the treatment of the above mentioned disorders, the development of an alternative dosage form of this drug should be considered of interest. An attractive possibility could be represented by the use of water-soluble polymers employing the solid dispersion technology (Chiou and Riegelman, 1971). 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. In particular, polymers such as polyethylene glycols and polyvinylpyrrolidone have been extensively used as carriers for dispersions due to their low melting point and their hydrophilic environment.

The aim of this study was to investigate the solubility and dissolution rate of ZP containing solid dispersions in PEG 4000 and PEG 6000. To this purpose, physical characterizations based on IR spectroscopy, X-ray diffractometry and differential scanning calorimetry (DSC) were performed. Solubility diagrams and dissolution studies were also carried out. In addition, the ataxic induction in rats of ZP-solid dispersions or physical mixtures was also investigated.

2. Materials and methods

2.1. Chemicals

ZP was extracted from tablets of Stilnox® purchased from a local drugstore as follows. Thirty Stilnox® tablets were powdered in a mortar and the powder dissolved in 10% aqueous $NaHCO_3$ (50 ml, pH = 8). The solution was transferred to a shake flask and extracted with ethyl ether (3 × 30 ml), dried(Na_2SO_4) and evaporated. Identity and purity of ZP was checked by means of spectroscopic methods (IR, ^{1}H-NMR, and mass spectroscopy). Polyethylene glycol 4000 (PEG 4000), and polyethylene glycol 6000 (PEG 6000) were purchased from Sigma and Fluka, respectively. Reagents used for preparations of buffers were of analytical grade. Fresh deionized water from all glass apparatus was used. HPLC mobile phase was prepared employing HPLC-grade methanol.

2.2. Apparatus

High-performance liquid chromatography (HPLC) analyses were performed using a Water Associates Model 600 pump equipped with a Water 990 variable wavelength UV detector and a 20-μl loop injection valve (U6K). For analysis, a reversed phase μ Bondapack C_{18} (30 cm × 3.9 mm; 10 μm particles) column or a reversed phase Simmetry (25 cm × 3.9 mm; 5 μm particles) column in conjunction with a precolumn module was eluted by using mixtures of methanol and deionized water. A flow rate of 1 ml/min was maintained. The column effluent was monitored continuously at 245 nm. Quantification of the compounds was carried out by measuring the peak areas in relation to those of standards chromatographed under the same conditions.

2.3. Preparation of solid dispersions and physical mixtures of ZP/PEG 4000 and ZP/PEG 6000

Solid dispersions of ZP in PEG 4000 or 6000 containing three different weight ratios (1:10, 1:20, 1:30) and denoted as SD4 or SD6 1/10, 1/20, 1/30, respectively, were prepared by the solvent method as follows. To a solution of ZP (60 mg) in ethanol 80° (25 ml) the appropriate amount of PEG 4000 or PEG 6000 was added. Next, the solvent was evaporated under reduced pressure at 40°C and the resulting residue, dried under vacuum for 3 h, was stored overnight in a desiccator. The samples prior to be used for the analysis were pulverized using a mortar and pestle and the powders were passed through a 280-μm sieve.

Physical mixtures having the same weight ratios were prepared by thoroughly mixing in a mortar the appropriate amounts of ZP and PEG 4000 or PEG 6000. The resulting mixtures were sieved through a 280-μm sieve and denoted as PM4 or PM6 1/10, 1/20, 1/30, respectively.

2.4. Fourier transform infrared spectroscopy

Fourier transform IR spectra were obtained on a Perkin–Elmer 1600 FT-IR spectrometer equipped with a DTSG detector. Samples were prepared in KBr disks (2 mg sample in 200 mg KBr). The scanning range was 450–4000 cm^{-1} and the resolution was 1 cm^{-1}.

2.5. X-ray analysis

Powder X-ray diffraction patterns were recorded on a Philips PW 1800 powder X-ray diffractometer using Ni-filtered, CuKα radiation, a voltage of 45 kV and a current of 25 mA.

2.6. DSC

DSC curves were obtained by a Perkin–Elmer DSC 7, equipped with a thermal analysis (TA) automatic program.

Aliquots of about 5 mg of each sample were placed in an aluminium pan of 50 μl capacity and 0.1 mm thickness, press-sealed with a not perforated aluminium cover of 0.1 mm thickness. An empty pan sealed in the same way was used as reference. Thermograms were measured by heating the sample from 30 and 300°C at a rate of 10°C/min, under a nitrogen flow of 20 cm^3/min. Indium was used as standard for calibrating the temperature. Reproducibility was checked running the sample in triplicate.

2.7. Determination of solubility

Solubility studies were carried out by adding an excess of ZP to 2 ml of solutions of PEG 4000 or 6000 (0–30% w/v) in deionized water in screw-capped test tubes. The mixtures were vortexed for 10 min and kept in a bath at appropriate temperature under magnetic stirring for 36 h. Then, an aliquot of each mixture was transferred to a 10-ml glass syringe preheated at the appropriate temperature and filtered through a 0.22-μm membrane filter (Millipore®, cellulose acetate) in thermostated test tubes. About 0.5 ml of the clear filtrate after appropriate dilution, were allowed to stand in bath at appropriate temperature until analyzed by HPLC. The injection volume was 20 μl. All of the manipulations were made without the removal of the test tubes from the water bath, using thermostated pipettes, syringes.

2.8. Dissolution studies

Dissolution experiments were carried out in triplicate with an Erweka DT dissolution test in deionized water at 37°C using the paddle method at a rotation speed of 60 rpm. Samples of each preparation equivalent to 50 mg of ZP were added to the dissolution medium (400 ml of demineralized water at 37°C). At appropriate time intervals, 2 ml of the mixture were withdrawn, filtered through a 0.22-μm membrane filter (Millipore®, cellulose acetate) in thermostated test tubes. The initial volume of dissolution medium was maintained by adding 2 ml of deionized water. About 1 ml of the clear filtrate after appropriate dilution, were allowed to stand in bath at 37°C until analyzed by HPLC. The injection volume was 20 μl. The results were computed with a standard calibration curve of the drug.

To compare dissolution profiles, several approaches can be followed such as analysis of variance (ANOVA)-based, model-independent and model-dependent approaches (Polli et al., 1997). ANOVA methods are commonly used to detect significant differences between groups and, thereby can be used to detect statistically significant differences between dissolution profiles. Model-independent approaches are based on the ratio of area under the dissolution curve (dissolution efficiency) or on mean dissolution time (Khan and Rhodes, 1975; Arias et al., 1996). In the model-dependent approaches, some mathematical models are employed to successfully fit the individual dissolution data. Although each of these methods presents complications and limitations (Polli et al., 1997), they yield numerical

results that can serve as quantitative metrics for comparing entire dissolution profiles and for in vitro–in vivo correlations.

2.9. Pharmacological studies

Male Sprague–Dawley rats (Charles River, Como, Italy) weighing 120–150 g were kept under a 12-h light–dark cycle at a temperature of 23 ± 2°C and 65% humidity. Upon arrival at the animal facilities there was a minimum of 7 days of acclimatization during which the animals had free access to food and water. Rats (five for each experimental group) received by an appropriate needle an intragastric administration of the ZP as solid dispersions or physical mixtures (SD4 1/30, SD6 1/30, PM4 1/30 and PM6 1/30, respectively) given in equimolar doses (10 mg/kg of animal) as solutions in 5 ml of water. As controls were administered ZP suspended in water, ZP suspended in water containing one drop of Tween 80 per 5 ml, and an extemporary mixture (1:30, w:w) of ZP and PEG 6000 vortexed and immediately administered. This last was an opalescent mixture. Rats were observed for the following 90 min and the time of ataxic induction, which was defined as the time from drug administration to the status of profound sedation characterized by motor incoordination of all four legs, was recorded. The statistical significance of differences in behavioral data were analyzed utilizing ANOVA test followed by Newman–Keuls post hoc test.

3. Results and discussion

3.1. Solid state studies

3.1.1. Infrared spectroscopy

The FT-IR spectra of ZP, SD6 1/30, and the corresponding physical mixture PM4 PM6 1/30 are shown in Fig. 1. Similar spectra were recorded for all the ZP/PEG systems prepared. As can be seen, a strong absorption band of amide carbonyl stretching at 1633 cm^{-1} occurs in the IR spectrum of ZP. Whereas, a reduced absorption band at 1633 cm^{-1} is present in the spectra of physical mixtures and solid dispersions of ZP/PEGs, becoming more intense as the percentage of drug in the mixture increased. The absence of any shift of the carbonyl stretching band suggested that no chemical interaction occurs between ZP and PEG 4000 or PEG 6000.

3.1.2. X-ray diffraction

Fig. 2 shows the X-ray diffraction patterns recorded for pure ZP, PEG 6000, PM6 1/30, and SD6 1/30. Characteristic peaks appeared in the powder X-ray diffractogram of ZP at a diffraction angle of 2ϑ 9.54, 19.18, 23.28, 26.37, 26.96, and 33.51° suggesting that the drug is present as a crystalline material. PEG 6000 produced peaks at 2ϑ 19.08, 23.26, 25.98, and 26.85°. The ZP crystalline peaks were observed in all formulations (SD and PM), similar being the intensity of the peaks produced by SDs and PMs of the same

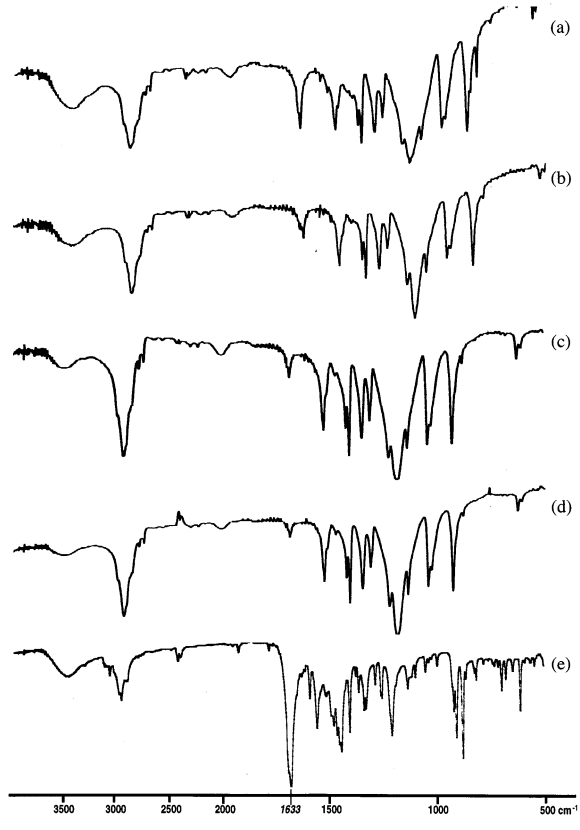


Fig. 1. FT-IR spectra of: (a) PM4 1/10; (b) SD4 1/10; (c) PM6 1/30; (d) SD6 1/30; and (e) Zolpidem alone.

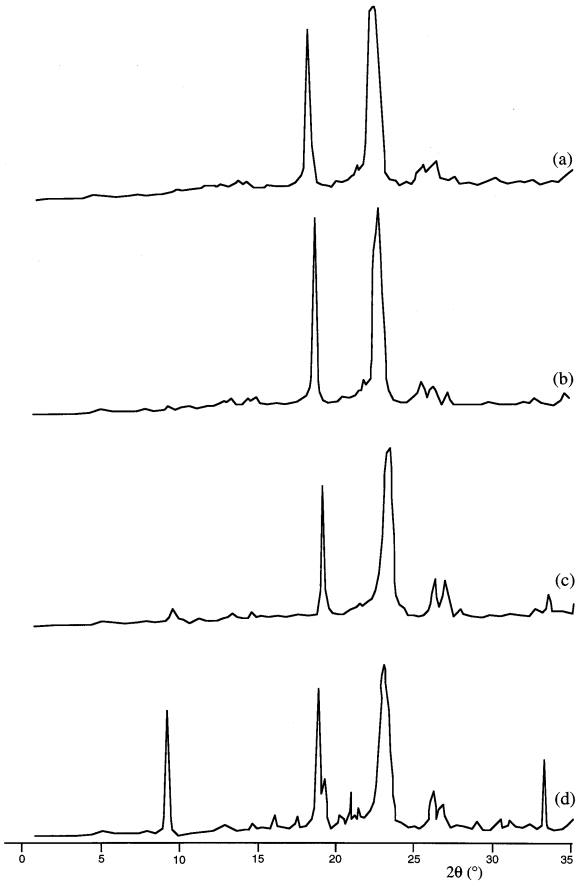


Fig. 2. X-ray powder diffraction spectra of: (a) PEG 6000; (b)PM6 1/30; (c) SD6 1/30; and (d) Zolpidem alone.

composition. These results indicate that the crystallinity of ZP-PEG 6000 solid dispersions is roughly comparable to that of the corresponding physical mixtures.

3.1.3. DSC

In Fig. 3 the melting endothermic peak of pure ZP, PEG 6000, and the endothermic peaks of PM6 1/30 and SD6 1/30 are shown. In the spectra of PEG based formulations the endothermic peak attributable to the melting of ZP was not observed and it should probably be due to the low amount of the drug in the dispersions and mixtures examined. A slight change occurs in the shape of PEGs endothermic peaks which appeared broadened in some solid dispersions or physical mixtures. A remarkable difference was observed between the thermograms of PM4 1/10 and the corresponding solid dispersion SD4 1/10 which are also shown in Fig. 3. Two endothermic peaks are clearly seen in the spectrum of PM4 1/10 at 45 and 52°C, whereas, in the thermogram of SD4 1/10 a single endothermic peak at 52°C was observed. It may likely due to the melting of the polymeric carrier, PEG 4000, in two different conformations (folded and extended; Lloyd et al., 1997).

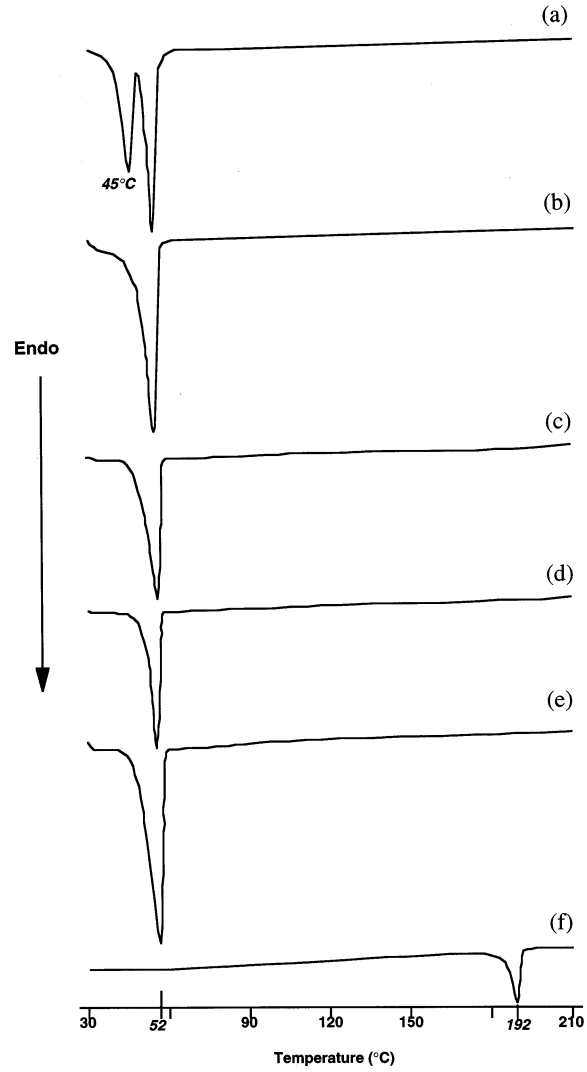


Fig. 3. DSC thermogram of: (a) PM4 1/10; (b) SD4 1/10; (c) PEG 6000; (d) PM6 1/30; (e) SD6 1/30; and (f) Zolpidem alone.

Table 1
Effect of various concentrations of PEG 4000 or PEG 6000 on Zolpidem solubility[a]

PEG 4000 (% w/v)	S (mg/ml) at 37°C	S (mg/ml) at 25°C
0.0	0.25 ± 0.04	0.19 ± 0.02
9	0.51 ± 0.02	0.43 ± 0.07
15	0.79 ± 0.01	0.58 ± 0.04
21	1.10 ± 0.05	0.84 ± 0.03
24	1.25 ± 0.07	1.00 ± 0.02
30	1.65 ± 0.03	1.32 ± 0.04
PEG 6000 (% w/v)	S (mg/ml) at 37°C	
0.0	0.25 ± 0.04	
6	0.68 ± 0.02	
10.8	0.63 ± 0.02	
14.4	0.79 ± 0.04	
22.5	1.14 ± 0.11	
30	1.53 ± 0.20	

[a] Data are the mean ± S.D. of three determinations.

3.2. Solubility studies

Solubility experiments showed that the concentration of ZP in deionized water is notably affected by the presence of PEG 4000 or PEG 6000 (Table 1). The phase-solubility diagrams investigated in deionized water (pH 6.5) were linear in a wide range of PEG 4000 or PEG 6000 concentrations and correspond to A_L-type (Higuchi and Connors, 1965) profiles (plots not shown). The apparent stability constants ($K_{1:1}$; Table 2) were estimated from the slope of the straight line of the phase-solubility diagrams according to the following equation: $K_c = \text{slope}/S_0(1 - \text{slope})$ (Higuchi and Connors, 1965) where S_0 is the solubility value of ZP in deionized water. The stability constant values vary slightly with the polymer molecular weight (102 and 92 M^{-1} for PEG 6000 and PEG 4000, respectively). Thus, a 30% w/v PEG 4000 solution provided for a 1.65 ± 0.03 mg/ml content of ZP corresponding to a 6.6-fold increase in concentration of ZP compared to S_0 value. On the other hand, a 30% w/v PEG 6000 solution provided for a 1.53 ± 0.20 mg/ml content of ZP corresponding to a 6.1-fold increase in ZP concentration.

Table 2
Stability constants for the systems Zolpidem-PEG 4000 or -PEG 6000 in deionized water

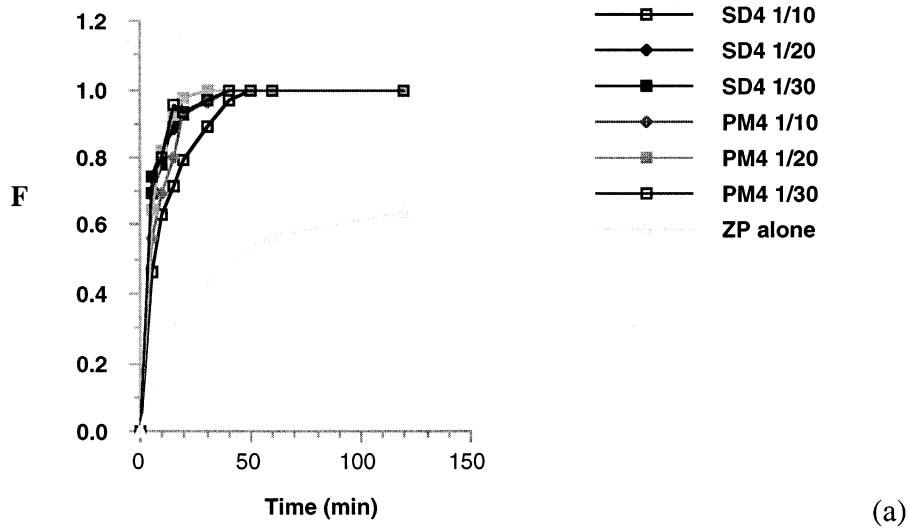
Temp. (°C)	Apparent stability constant $K_{1:1}$ (M^{-1})[a]
37	92 ± 4.3[b]
25	80 ± 9.4[b]
37	102 ± 9[c]

[a] Data are the mean ± S.D. of three determinations.
[b] In PEG 4000.
[c] In PEG 6000.

3.3. Dissolution studies

Zolpidem is characterized by poor aqueous solubility (0.25 g/l at 37°C). The investigated amounts (50 mg in 400 ml of dissolution medium) were below the saturation concentration, so that sink conditions could be assumed. The results of the dissolution studies for individual samples (ZP alone, SDs and physical mixtures) are shown in Fig. 4 and the reported values are the mean of three determinations (CV < 10%). In few cases, at times soon after dissolution begins, the dissolution data showed greater variability (CV 15–20%; Elkoshi, 1997).

To compare dissolution profiles in this work we employed a model-dependent approach and release data were fitted to non-linear models using MSFIT (Lu et al., 1996) computer program. Five popular release models are implemented in the program: Baker–Lonsdale, Peppas, Hixon–Crowell, Higuchi, and first order release kinetic models (Table 3). However, the Hixon–Crowell, Higuchi, and Peppas equations failed to fit each individual dissolution profile, whereas Baker–Lonsdale and first order models were found to successfully fit each individual dissolution profile but not that of the drug alone. The values of the kinetic constants arising from Baker–Lonsdale and first order models indeed show small standard deviations and small confidence intervals (Table 4). Confidence intervals are also included in Table 4 to allow a comparison. Fig. 4 illustrates that the dissolution rates of ZP both from solid dispersions and physical mixtures are remarkably enhanced compared to that of the drug alone. Furthermore, data in Table 4 show that, in general, PEG based formulations (SD and PM) at



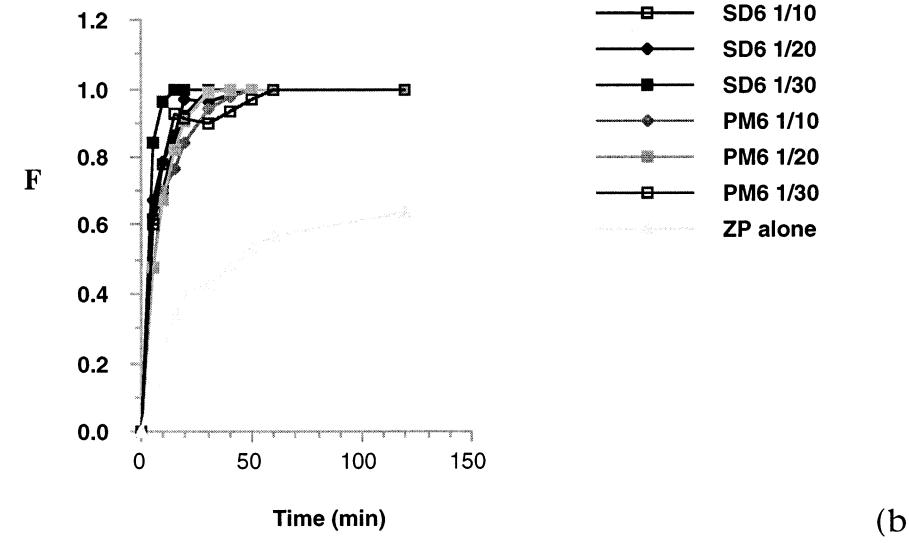


Fig. 4. Dissolution profiles of Zolpidem, physical mixtures, and solid dispersions of Zolpidem/PEG 4000 (a) or PEG 6000 (b) at 37°C.

high carrier levels showed dissolution rates higher than those at low polymer levels (compare PM4 1/30, PM6 1/30, and SD6 1/30, with PM4 1/10, PM6 1/10 and SD6 1/10, respectively). Even though the kinetic differences among these PEG based formulations are not very great, it must be pointed out the advantage offered by the SD6 1/30, over the remaining systems, in providing a remarkable increase in dissolution rate.

Finally, to include also the dissolution data of drug alone, the release profiles were linearized by the Weibull distribution (Langenbucher, 1976; Table 5). The Weibull β, shape parameters, which characterizes the curve as either exponential ($\beta = 1$, first order kinetic), sigmoid ($\beta > 1$) or parabolic ($\beta < 1$) were in most cases close to 1 (Table 5) indicating the first order exponential curve. On

Table 3
Kinetic models used for fitting dissolution data

Model	Equation[a]
Zero order	$F = kt$
Baker–Lonsdale	$3/2[1-(1-F)^{2/3}]-F = kt$
Peppas	$F = kt^n$
Hixon–Crowell	$1-(1-F)^{1/3} = kt$
Higuchi	$F = kt^{1/2}$
First order	$F = 1-e^{-kt}$
Weibull[b]	$F = 1-e^{-(t-t_0/\tau)\beta}$

[a] F = Cumulative fraction dissolved of drug.
[b] In the corresponding equation the t_0 is the time-lag (neglected in our calculations), τ is the scale parameter, and β is the shape parameter.

the other hand, the Weibull τ, that is the scale parameters or the time intervals necessary to dissolve 63.2% of the material, were less than or equal to 10 min for both SD and PM formulations and it indicates high release rates. For the drug alone the corresponding values were $\beta = 0.63$ and $\tau = 115$ min.

Several mechanisms have been proposed to account for the increase in the dissolution kinetics of drugs from polyethylene glycol solid dispersions. These mechanisms include the carrier controlled dissolution (Corrigan et al., 1979; Dubois and Ford, 1985; Craig and Newton, 1992), the continuous drug layer formation (Dubois and Ford, 1985) and that involving the release of intact particles with dissolution occurring over a large surface area (Saers Sjökvist and Craig, 1992). The latter mechanism has been suggested to be important at low drug levels. It is also clear that a modification of the surface properties and hence a reduction of the value of the contact angle which improves the wettability of the powder should lead to an increase of dissolution kinetics. An improvement of wettability of the powder could result from the formation of a film of polyethylene glycol around the drug substance particles which modifies the hydrofobicity of their surfaces (Van den Mooter et al., 1998). Which mechanism is involved in the increase in the dissolution kinetics of ZP from PEG 6000 or PEG 4000 dispersions could not be at present established.

3.4. Pharmacological studies

To detect possible correlations between dissolution rates observed with PEG based (SD or PM) formulations and pharmacological effects, we investigated on ataxic action in rat by administration of the following formulations: ZP drug alone and ZP as solid dispersions or physical mixtures ((SD4 1/30, SD6 1/30, PM4 1/30 and PM6 1/30, respectively) given in equimolar doses (10 mg/kg). Times of ataxic induction following the intragastric administration of each formulation were

Table 4
Dissolution rate constants (min^{-1}) of Zolpidem solid dispersions and physical mixtures[a]

Sample	k_{bl}	Standard deviation[b]	95% Confidence interval[b]	k	Standard deviation[b]	95% Confidence interval[b]
PM_4 1/10	0.0135	0.0005	0.0124–0.0147	0.1310	0.0081	0.1122–0.1497
PM_4 1/20	0.0205	0.0000	0.0203–0.0207	0.1915	0.0060	0.1775–0.2055
PM_4 1/30	0.0227	0.0021	0.0179–0.0275	0.2215	0.0225	0.1696–0.2734
PM_6 1/10	0.0111	0.0003	0.0103–0.0119	0.1105	0.0056	0.0975–0.1236
PM_6 1/20	0.0125	0.0005	0.0112–0.0138	0.1188	0.0028	0.1123–0.1254
PM_6 1/30	0.0176	0.0017	0.0135–0.0217	0.1648	0.0149	0.1303–0.1993
SD_4 1/10	0.0092	0.0001	0.0090–0.0094	0.0931	0.0058	0.0796–0.1066
$SD_4$1/20	0.0220	0.0018	0.0178–0.0262	0.2202	0.0222	0.1690–0.2715
SD_4 1/30	0.0193	0.0013	0.0163–0.0223	0.1887	0.0167	0.1501–0.2272
SD_6 1/10	0.0149	0.0006	0.0133–0.0165	0.1448	0.0120	0.1170–0.1725
SD_6 1/20	0.0186	0.0011	0.0159–0.0212	0.1798	0.0154	0.1443–0.2154
SD_6 1/30	0.0422	0.0013	0.0391–0.0454	0.3677	0.0062	0.3532–0.3822

[a] k_{bl} is the Baker and Lonsdale kinetic constant; k is the first order kinetic constant.
[b] Standard deviations and confidence intervals are calculated for estimated parameters (k_{bl} or k).

Table 5
β and τ parameters of Weibull

Sample	Weibull β	Weibull τ (min)	Sample	Weibull β	Weibull τ (min)
PM_4 1/10	0.83	<10	SD_4 1/10	0.96	10
PM_4 1/20	0.90	<10	$SD_4$1/20	0.60	<10
PM_4 1/30	0.60	<10	SD_4 1/30	0.50	<10
PM_6 1/10	1.03	10	SD_6 1/10	0.89	<10
PM_6 1/20	0.91	10	SD_6 1/20	1.30	<10
PM_6 1/30	0.60	<10	SD_6 1/30	0.75	<10
Zolpidem	0.63	115			

recorded and the results are summarized in Table 6. In these experiments, rats displayed a marked sedation and ataxia, characterized by motor incoordination involving all four legs; however, no loss of the righting reflex was observed if the animals were laid on their back. As illustrated in Table 6, ataxic induction times subsequent to intragastric administration of ZP as solid dispersions or physical mixtures were longer than that observed when administrating the corresponding reference formulations. The differences observed in ataxic action are therefore very significant. Data from this pharmacological paradigm, in fact, suggested that ZP as solid dispersions or physical mixtures, in spite of their fast dissolution rates, show almost two- to three-fold longer ataxic induction times than controls. Since the intensity of the pharmacological effect of any drug orally administered essentially depends on its concentration in the plasma which, in turn, results from both the dissolution in GI fluids and intestinal membrane permeability (Hoener and Benet, 1990), it follows that in the presence of PEG the intestinal membrane permeability may be the rate-limiting factor in the gastrointestinal absorption process. It taking into account that, with the exception of the extemporary mixture, the ataxic induction times of all PEG based formulations are very similar. Of course, further experiments (i.e. Caco-2 cells monolayer permeation studies) are necessary to draw definitive conclusions in this regard.

Table 6
Effect of intragastric administration of different Zolpidem formulations on ataxic induction time in rat[a]

Zolpidem formulations	Ataxic induction time (min)
SD4 1/30	15.3 ± 1.7*
SD6 1/30	12.3 ± 2.7*
PM4 1/30	16.3 ± 1.4*
PM6 1/30	15.0 ± 1.5*
ZP suspended in water	5.2 ± 0.4
ZP suspended in water containing Tween 80[b]	5.4 ± 1.2
ZP/PEG 6000	8.6 ± 0.2*

[a] Rats were injected intragastrically with different Zolpidem formulations (Zolpidem in equimolar doses of 10 mg/kg) and observed for the following. Zolpidem/water was a suspension of the drug in water. Zolpidem/PEG 6000 was a mixture (1:30, w:w) of Zolpidem with PEG 6000. Rats were then observed for the following 90 min. Values are the means $\pm$ S.E.M. of five animals per experimental group.

[b] One drop of Tween 80 per 5 ml of suspension.

* $P < 0.01$ versus Zolpidem/water formulation.

4. Conclusions

In this paper we demonstrated that ZP as solid dispersion or physical mixture in PEG 4000 or 6000 shows a considerable increase in solubility and dissolution rate. Since no drug-carrier interaction in the solid state has been evidenced, the increased dissolution rate in systems containing PEG 4000 or PEG 6000 probably can be accounted for by increased wettability and dispersibility of ZP. However, pharmacological evaluations in rats indicated that there are significant differences in the ataxic induction time between the orally administered ZP-PEG systems

and ZP alone as suspension, which may indicate that in the presence of PEG the intestinal membrane permeability is the rate-limiting factor in the absorption process.

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