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Influence of temperature on the solubilization of thiabendazole by combined action of solid dispersions and co-solvents

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ABSTRACT

Co-solvents and solid dispersions with polyvinyl pyrrolidone were tested to increase solubility of thiabendazole. Solid dispersions were prepared by the solvent method and analyzed by differential scanning calorimetry. The solubility was measured at 15–35 °C in aqueous (ethanol–water) and non-aqueous (ethanol–ethyl acetate) mixtures. Combination of solid dispersions with cosolvents increased the water solubility of thiabendazole in a larger extent that each method separately. The effect of the solid dispersions is greatest in water and it decreases nonlinearly as the volume fraction of ethanol-in water increases. The solubility enhancement is smaller in ethanol–ethyl acetate and is uncorrelated with co-solvent concentration.

Solubility parameters δ were used to predict drug/carrier compatibility and related to solubility profiles. Thiabendazole shows an intermediate behaviour between solubility curves with two peaks (more polar drugs with larger δ values) and a single peak (less polar drugs with lower δ values). The solid dispersions increase the solubility parameter of thiabendazole from $\delta = 24$ to $\delta = 25.7$ MPa$^{1/2}$.

The model of Bustamante et al. allowed solubility prediction including jointly both mixtures whereas the equation of Jouyban et al. was able to predict the solubility at several temperatures in each binary mixture separately, using a few experiments.

1. Introduction

The poor water solubility of many drugs used in therapeutics makes difficult preparation of injectables and other liquid dosage forms. Co-solvents, pH changes, solid dispersions and complexation are some of the methods useful to increase the aqueous solubility and/or the dissolution rate (Jung et al., 1999). Solid dispersions enhance the aqueous solubility due to several factors such as improved wettability and drug particle size reduction (Mura et al., 1996, 1999). Some limitations of these systems include physical instabilities on storage (Ford and Rubinstein, 1981; Sugimoto et al., 1981) and problems of immiscibility (El-Banna et al., 1975). Combination of co-solvency with other methods such as complexation with ciclodextrins, pH control and surfactants have been also investigated to solubilise non-polar solutes (Li et al., 1998, 1999).

The purpose of this work is to investigate the possibility of a synergic effect of co-solvents and solid dispersions with polyvinyl pyrrolidone K-30 (PVP K30) to improve the aqueous solubility of thiabendazole. The results are compared with those obtained from each method separately. To our knowledge the combination of both methods has not been reported earlier. Thiabendazole is an anthelmintic and antifungal agent employed to treat roundworm infections such as threadworm, hookworm/creeping eruption, and visceral larva migrans (toxocariasis). This drug is also used for other types of roundworm infections such as pinworm, whipworm and large roundworm (ascariasis). Polyvinyl pyrrolidone K-30 is a hydrophilic polymer widely used as a carrier for preparing solid dispersions (Sethia and Squillante, 2004), hydrogels and as plasma substitute due to its high aqueous solubility, excellent biocompatibility with living tissues and low toxicity (Caykara, 2004). Lewis base (ethyl acetate) and amphiprotic co-solvents (ethanol and water) are chosen to obtain binary model co-solvent systems covering a wide polarity range that allow to detect different types of solubility curves, showing one or two peaks (Peña et al., 2006).

Models for predicting the solubility profile of the drug and that of the solid dispersions are also tested. Bustamante and coworkers proposed an equation to model the chameleonic effect characterized by solubility curves with two maxima (Bustamante et al., 1994; Escalera et al., 1994):

$$\ln X_2 = C_0 + C_1\delta_1 + C_2\delta_1^2 + C_3\delta_{1a} + C_4\delta_{1b} + C_5\delta_{1a}\delta_{1b} \quad (1)$$

This model combines the Hildebrand solubility parameter δ_1 (Hildebrand et al., 1970) and the acidic and basic partial solubility parameters δ_{1a} and δ_{1b} of Karger et al. (1976).

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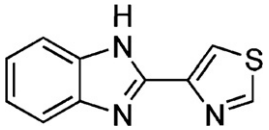


Fig. 1. Chemical structure of thiabendazole.

Eq. (1) is able to include two or three binary mixtures jointly at a given temperature. Although the model is empirical, the variables used may be related to several types of interactions. The properties of the drug solid phase are included as a constant into the intercept C_0. The squared term δ_1^2 and the product $\delta_{1a}\delta_{1b}$ account for self-association of the solvent through non-specific and specific interactions that decrease solubility. The linear terms are related to van der Waals (δ_1) and Lewis acidic and basic (δ_{1a} and δ_{1b}) solute–solvent interactions that increase solubility.

Solubility parameters have been applied to polymer science for predicting interactions between materials (Barton, 1991; Rowe, 1989) and to estimate the solubility profile of drugs (Peña et al., 2006, 2009). The Hildebrand solubility parameter is a measure of the overall polarity, ranging from 18.49 to 47.86 $MPa^{1/2}$ from the least to the most polar compounds. This parameter can be measured experimentally from the solubility maximum in solvent mixtures (Escalera et al., 1999) or using the solubility mole fraction of the drug X_{2i} in three or five pure solvents of known solubility parameter values δ_{1i} (Lin and Nash, 1993):

$$\delta_2 = \frac{\sum(X_{2i}\,\delta_{1i})}{\sum X_{2i}} \tag{2}$$

The Hildebrand solubility parameter can also be calculated from the additive contribution of atoms and groups to the energy of vaporization ΔEv and the molar volume Vm of the compound (Fedors, 1974).

The Hildebrand and partial solubility parameters of the solvent blends (Eq. (1)) are obtained from the solubility parameter values of the pure solvents and their volume fraction in the mixture (Bustamante et al., 1993).

Jouyban et al. (2002) proposed the following model to predict the solubility of a drug at several temperatures in a binary mixture:

$$\ln X_{m,T} = \phi_1 \ln X_{1,T} + \phi_2 \ln X_{2,T} + J_1\left(\frac{\phi_1\phi_2}{T}\right) + J_2\left(\frac{\phi_1^2\phi_2}{T}\right) \tag{3}$$

$X_{m,T}$, $X_{1,T}$ and $X_{2,T}$ are the solute solubility in the binary mixture, the pure solvents 1 and 2 at temperature T, respectively and J_1 and J_2 are the constants of the model. This model was also tested using a limited number of experiments at two temperatures to predict the solubility at a different temperature.

The models above are tested to predict the solubility profiles of the drug and that of the solid dispersions. With Eq. (1) the solubility data of thiabendazole in both binary mixtures (ethanol–water and ethanol–ethyl acetate) are jointly fitted to the model at each temperature. Eq. (3) includes solubility data at several temperatures but it must be applied to each binary mixture separately. The coefficients of the models are obtained from multiple linear regressions with the statistical package NCSS (2001) (Hintze, 2001).

2. Materials and methods

Thiabendazole (2-(1,3-thiazol-4-yl)-1H-benzoimidazole) (Sigma–Aldrich, Steinheim, Germany) (Fig. 1) and polyvinyl pyrrolidone K-30 (PVP K30) (1-vinyl-2-pyrrolidone polymers) (Basf, Ludwigshafen, Germany) were used as received. All these products were anhydrous, as tested with the Karl–Fisher method. Binary mixtures were prepared by volume with ethanol, ethyl acetate (UV grade, Panreac, Monplet & Esteban, Spain) and double distilled water.

2.1. Solubility measurements

The equilibrium solubility of thiabendazole and thiabendazole:PVP K30 solid dispersions was measured at 15–35 °C in ethanol–water and ethanol–ethyl acetate mixtures. The equilibrium solubility measured is the drug concentration in a saturated solution which is at equilibrium with the solid phase (Martin et al., 1993). To obtain the saturated solutions, 50-mL samples containing a slight powder excess were introduced in an ultrasound bath (Branson 3200, Connecticut, USA) for 3 h and then they were equilibrated in a temperature-controlled shaking bath (Heto SH 02/100, Denmark; ±0.1 °C) at the highest temperature (48 h at 35 °C). Equilibrium solubility was reached at the asymptotic region of the dissolution curve, i.e. when the drug concentration does not vary with time. The saturated solutions were then cooled and equilibrated for 24 h at the lower temperatures (25 and 15 °C). A solid phase excess was always present to ensure that the equilibrium condition was reached at each temperature and to prevent the formation of oversaturated solutions. Three or four samples of the saturated solutions were filtered through Durapore membranes compatible with the solvents (0.2 μm pore size, Millipore Ibérica S.A., Spain) to eliminate the solid non-dissolved phase. The drug did not significantly adsorb onto the membranes. The clear solutions were diluted with ethanol 96% (v/v) and assayed in a double-beam spectrophotometer (Shimadzu UV-2001PC, USA) at the maximum absorption wavelength of the solute (300 nm). Pipettes and filter devices were maintained at the appropriate temperature in a thermostated incubator (Raypa FKS 1800, USA). The concentration (molarity units) of the solute was determined from Beer's law plots. The densities of the solutions were measured at each temperature in 10-mL pycnometers, to convert the molar solubility into mole fraction units at each temperature.

2.2. Preparation of the solid dispersions

The solvent method was used (Habib, 2001) employing ethanol as the common solvent for the drug and the carrier. The solid dispersions were prepared at a ratio of 1:2 thiabendazole–PVP K30. Two grams of thiabendazole and 4 g of PVP K30 were separately dissolved in 400 mL of ethanol. Both dissolutions were mixed and the organic solvent was then dried under reduced pressure using a vacuum dryer at 70 °C until complete evaporation.

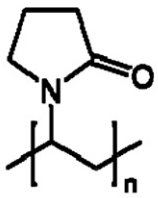
2.3. Differential scanning calorimetry (DSC)

The thermograms of the original powder of the drug and that of the polymer were obtained in a Mettler TA 4000, Switzerland DSC at a heating rate of 5 °C/min using aluminium sealed pans, under nitrogen flow (20 mL/min). The same analysis was performed on the solid non-dissolved phases of the physical drug–polymer mixture and of the solid dispersion after equilibration in water at 37 °C. The solvent excess was evaporated at room temperature.

3. Results and discussion

3.1. Solubility parameters of the drug and the carrier to predict compatibility

These parameters were used to predict interactions or incompatibilities between thiabendazole (hydrophobic) and the hydrophilic carrier (PVP K30). The solubility parameter of thiabendazole obtained with the Lin and Nash method (Eq. (2)) using the experimental values in the three pure co-solvents (ethanol,



GROUP	ΔEv (cal/mol)	ΔVm(cm^3/mol)	Nº
>CH-	820	-1.0	1
-CH_2-	1180	16.1	4
Ring closure 5 or more atoms	250	16	1
-N<	1000	-9	1
C=O	4150	10.8	1
	Σ ΔEv=10940	Σ ΔVm=81.2	
$\delta_2 = \left(\Delta Ev / \Delta Vm\right)^{1/2}$ (eq. 2)	→	**Vm=81.2 cm^3/mol** **δ_2=11.60 (cal/cm^3)$^{1/2}$** **δ_2= 23.72 MPa$^{1/2}$**	

ΔEv, is the energy of vaporization and Vm, is the molar volum at 25ºC (Fedors 1974)

Fig. 2. Calculation of the Hildebrand solubility parameter of PVP K30.

water, and ethyl acetate) is δ = 24 MPa$^{1/2}$. The value determined from the solubility maximum (60% ethanol in ethyl acetate) is δ = 21.7 MPa$^{1/2}$. The solubility parameter of PVP K30 calculated from the Fedors theoretical method is δ = 23.7 MPa$^{1/2}$ (Fig. 2) whereas the experimental value from swelling measurements is δ = 32.3 MPa$^{1/2}$ (Caykara, 2004). Greenhalgh et al. (1999) observed a trend between differences in drug/carrier solubility parameters and compatibility to form solid dispersions. Systems with $\Delta\delta$ = 1.6–7.5 MPa$^{1/2}$ show complete miscibility when molten, between $\Delta\delta$ = 7.5–15 MPa$^{1/2}$ the drug and the carrier are partially miscible in the liquid state, and when (δ is above 15.9 MPa$^{1/2}$) the system displayed total inmiscibility. The difference between the experimental parameters of thiabendazole and PVP K30 is $\Delta\delta$ = 8.3. Therefore it can be expected that the drug will be at least partially miscible with the carrier to form a solid dispersion.

3.2. Solid dispersions

Fig. 3 shows the thermograms of thiabendazole (original powder), PVP K30, a physical drug–polymer mixture and the solid dispersion. Thiabendazole exhibits a sharp endothermic peak at 300.7 °C corresponding to melting (the heat of fusion is 35.19 kJ/mol). The endothermic peak found for PVP K30 between 150 and 190 °C due to water loss was also reported by other workers (Tantishaiyakul et al., 1996; Sethia and Squillante, 2004; Liu and Wang, 2007). The polymer does not change the peak of fusion of thiabendazole in the physical mixture suggesting no drug–polymer interaction in the solid phase. However the peak of fusion of thiabendazole disappeared in the solid dispersion, indicating that the drug might be in an amorphous state possibly because the carrier acts inhibiting crystallization in the solid dispersion (Liu and Wang, 2007).

3.3. Solubility profiles of the drug and the solid dispersions

For comparison, the solubility of a 1:2 drug–polymer physical mixture was measured in water at 35 °C. There is a solubility increase from 0.00002 to 0.00005 mg/mL that may be explained as follows. The physical mixture does not change the peak of fusion of thiabendazole but the endothermic peak of PVP is absent (Fig. 3).

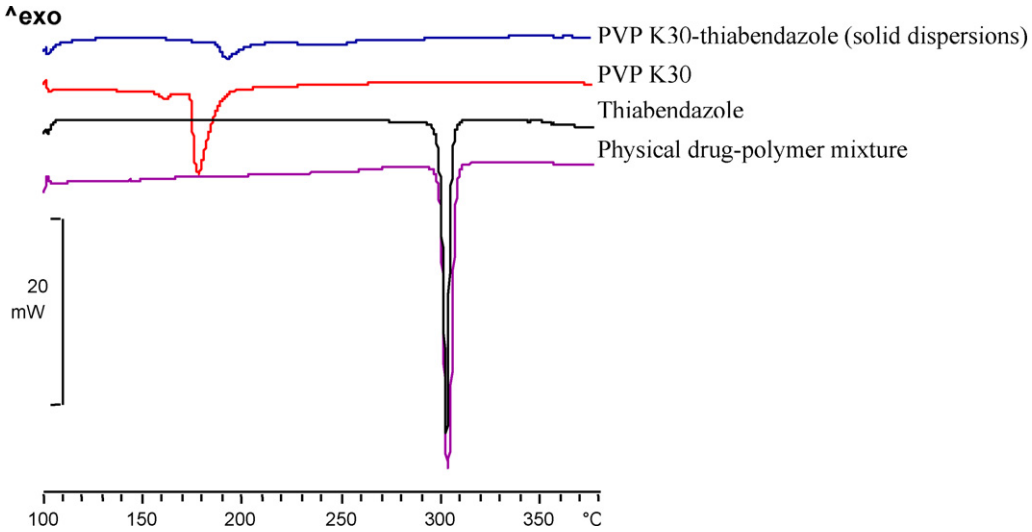


Fig. 3. Thermograms of thiabendazole, PVP K30, physical drug–polymer mixture and thiabendazole:PVP K30 solid dispersions.

Table 1
Solubility parameters of ethanol–water and ethanol–ethyl acetate mixtures.

%	δ_1[a]	δ_{1a}[a]	δ_{1b}[a]
Ethanol			
0	47.86	13.7	65.46
10	45.73	14.03	60.04
20	43.59	14.36	54.62
30	41.46	14.69	49.2
40	39.32	15.01	43.77
50	37.19	15.34	38.36
60	35.05	15.67	32.93
70	32.92	16	27.51
80	30.78	16.32	22.09
90	28.64	16.65	16.67
100	26.51	16.98	11.25
Ethyl acetate			
10	25.71	16.37	10.51
20	24.91	15.75	9.78
30	24.10	15.14	9.04
40	23.30	14.52	8.31
50	22.50	13.91	7.57
60	21.70	13.30	6.83
70	20.91	12.68	6.1
80	20.09	12.07	5.36
90	19.29	11.45	4.63
100	18.49	10.84	3.89

[a] Bustamante et al. (1993).

Table 3
Experimental solubility mole fraction (X_2) of solid dispersions at several temperatures.

%	X_2 (35 °C)	X_2 (25 °C)	X_2 (15 °C)
Ethanol			
0	2.80×10^{-6}	2.37×10^{-6}	1.77×10^{-6}
10	3.75×10-6	2.99×10^{-6}	2.48×10^{-6}
20	7.31×10^{-6}	5.90×10^{-6}	4.74×10^{-6}
30	1.69×10^{-5}	1.27×10^{-5}	9.83×10^{-6}
40	4.82×10^{-5}	3.77×10^{-5}	2.73×10^{-5}
50	7.73×10^{-5}	6.15×10^{-5}	4.94×10^{-5}
60	0.00012	0.00010	8.77×10^{-5}
70	0.00021	0.00018	0.00015
80	0.00037	0.00031	0.00025
90	0.00044	0.00037	0.00030
100	0.00042	0.00036	0.00030
Ethyl acetate			
10	0.00070	0.00054	0.00039
20	0.00079	0.00066	0.00054
30	0.00087	0.00073	0.00059
40	0.00094	0.00080	0.00067
50	0.00100	0.00090	0.00076
60	0.00103	0.00088	0.00074
70	0.00090	0.00078	0.00067
80	0.00082	0.00072	0.00062
90	0.00049	0.00044	0.00039
100	0.00021	0.00019	0.00015

This suggests that PVP, a freely water-soluble polymer, dissolves in water acting as a co-solvent to enhance the solubility of the drug. Total dissolution of the polymer was corroborated in a separate experiment using PVP alone. The solid dispersion enhances solubility in a larger extent (from 0.00002 to 0.0002 mg/mL) due to drug–polymer interactions in the solid phase (Fig. 3).

Table 1 lists the co-solvent ratio, the Hildebrand solubility parameter (δ_1) and the acidic and basic partial solubility parameters δ_{1a} and δ_{1b} of the ethanol–water and ethanol–ethyl acetate mixtures. The solubility mole fraction X_2 of thiabendazole and that of the solid dispersions increases with temperature in both mixtures (Tables 2 and 3), indicating that the dissolution process is endothermic. The solubility of thiabendazole (Fig. 4) shows a maximum ($\delta_1 = 21.70\ \mathrm{MPa}^{1/2}$) within the polarity range corresponding to the less polar mixture (ethanol–ethyl acetate, between 18.49 and 47.86 $\mathrm{MPa}^{1/2}$). In the most polar mixture a small shoulder was obtained instead of a peak at 90–100% ethanol in water that becomes more apparent as the temperature is raised (15–35 °C). In the case of the solid dispersions (Fig. 5) the solubility curve shows a maximum at the same co-solvent ratio found for the original powder (60% ethyl acetate) at 35 °C. This maximum shifts to a higher polarity value, from $\delta_1 = 21.70$ to 22.50 $\mathrm{MPa}^{1/2}$, at lower temperatures (15–25 °C).

Table 2
Experimental solubility mole fraction (X_2) of thiabendazole at several temperatures.

%	X_2 (35 °C)	X_2 (25 °C)	X_2 (15 °C)
Ethanol			
0	4.79×10^{-7}	3.54×10^{-7}	2.30×10^{-7}
10	1.79×10^{-6}	1.31×10^{-7}	7.65×10^{-7}
20	4.74×10^{-6}	3.35×10^{-6}	1.99×10^{-6}
30	1.30×10^{-5}	8.46×10^{-6}	5.39×10^{-6}
40	3.01×10^{-5}	2.21×10^{-5}	1.55×10^{-5}
50	7.85×10^{-5}	5.06×10^{-5}	3.4×10^{-5}
60	0.00012	9.11×10^{-5}	6.73×10^{-5}
70	0.00022	0.00016	0.00013
80	0.00036	0.00028	0.00020
90	0.00044	0.00035	0.00024
100	0.00045	0.00040	0.00034
Ethyl acetate			
10	0.00051	0.00045	0.00036
20	0.00064	0.00054	0.00039
30	0.00069	0.00059	0.00053
40	0.00077	0.00065	0.00055
50	0.00089	0.00073	0.00062
60	0.00091	0.00078	0.00067
70	0.00075	0.00063	0.00048
80	0.00068	0.00052	0.00040
90	0.00066	0.00048	0.00034
100	0.00027	0.00022	0.00018

The solid dispersions show a small maximum in the ethanol–water mixture (90% ethanol) that becomes higher as the temperature is raised (Fig. 5). The transition from the more polar to the less polar mixture produces a minimum at 100% ethanol ($\delta_1 = 26.51\ \mathrm{MPa}^{1/2}$).

The nature of the solvents, the formation of solid dispersions and temperature influence the shape of the solubility profile of thiabendazole. Caffeine, a relatively polar drug (higher solubility parameter, $\delta_2 = 26.8\ \mathrm{MPa}^{1/2}$) showed a chameleonic behaviour characterized by two well defined peaks, in the most polar and in the least polar mixture (Bustamante et al., 2002). Benzocaine, a less polar drug with a lower solubility parameter, $\delta_2 = 21.5\ \mathrm{MPa}^{1/2}$

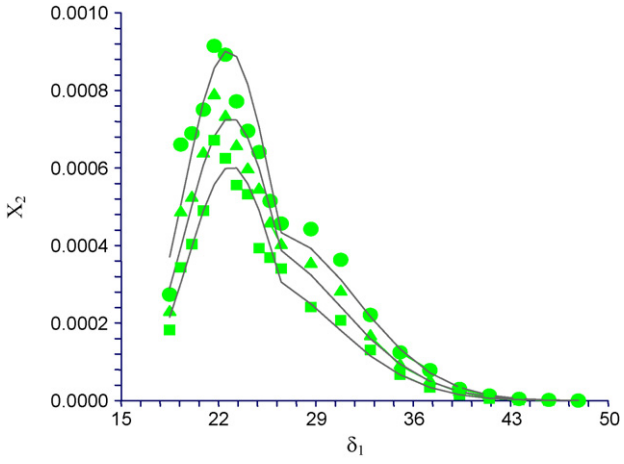


Fig. 4. Solubility of thiabendazole against the solubility parameter (δ_1) of ethanol–water and ethanol ethyl acetate mixtures. Key: ■ (15 °C); ▲ (25 °C); ● (35 °C). Solid lines: predicted curves from Eq. (5).

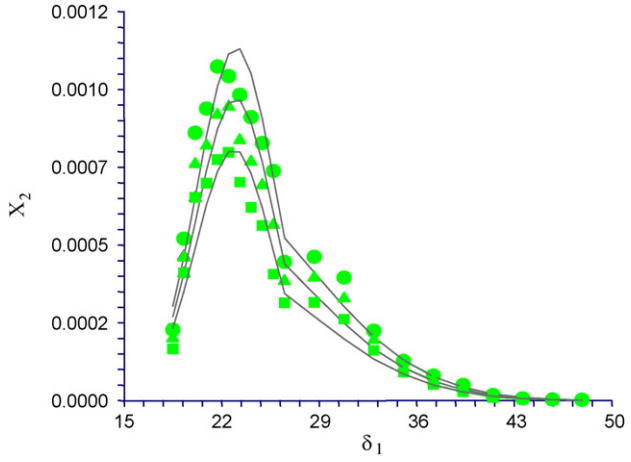


Fig. 5. Solubility of thiabendazole:PVP solid dispersions against the solubility parameter (δ_1) of ethanol–water and ethanol–ethyl acetate mixtures. Key: ■ (15 °C); ▲ (25 °C); ● (35 °C). Solid lines: predicted curves from Eq. (6).

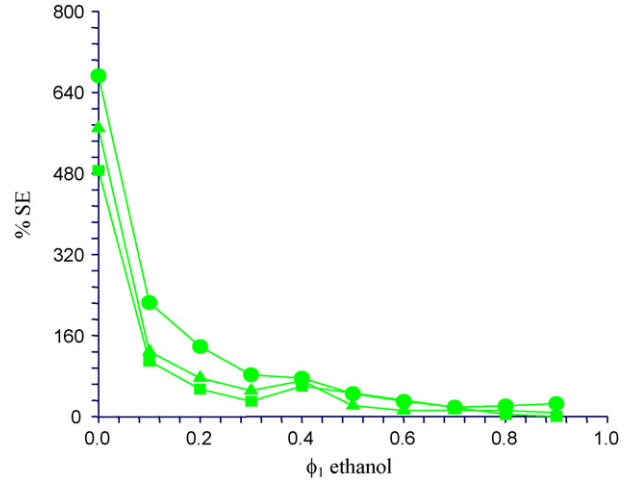


Fig. 6. Percent solubility enhancement (%SE) of thiabendazole solid dispersions against the ethanol–in water volume fraction (ϕ_1). Key: ■ (15 °C); ▲ (25 °C); ● (35 °C).

(Escalera et al., 1999), displayed a single peak in the less polar mixture (Peña et al., 2006). Thiabendazole shows an intermediate behaviour showing a high peak in the less polar mixture (ethanol–ethyl acetate) and a shoulder or a small peak in the most polar mixture (ethanol–water). The solubility parameter of this drug ($\delta_2 = 24\,\mathrm{MPa}^{1/2}$) is an intermediate value between those of caffeine and benzocaine. The formation of the solid dispersions seems to increase the apparent polarity of the drug increasing the magnitude of the peak in ethanol–water. The solubility parameter obtained from the Lin and Nash method for the solid dispersion is 1.7 units larger ($\delta_2 = 25.7\,\mathrm{MPa}^{1/2}$).

The per cent solubility enhancement (%SE) produced by the solid dispersion was calculated with Eq. (4) at 15, 25 and 35 °C:

$$\%\mathrm{SE} = \frac{(X_{T,1} - X_{T,2})}{X_{T,2}} \times 100 \qquad (4)$$

where $X_{T,2}$ and $X_{T,1}$, are the thiabendazole:PVP K30 and thiabendazole mole fractions, respectively, at a given temperature T. The greatest solubility enhancement was found in water (750%). As shown in Fig. 6, %SE decreases nonlinearly as the volume fraction of ethanol-in water increases and it is negligible in pure ethanol. The solubilising effect of the solid dispersions is higher at the lower temperatures (15 °C > 25 °C > 35 °C, Fig. 6). The solubility enhancement

Table 4
Regression coefficients of the quadratic–linear relationships for the percent solubility enhancement (%SE) at 15 and 35 °C in the ethanol–water mixtures.

T (°C)	C_0	C_1	C_2	δ_1 range
35	215.87	−15.35	0.26	$\delta_1 \geq 45.6\,\mathrm{MPa}^{1/2}$
	−7908.81	175		$\delta_1 < 45.6\,\mathrm{MPa}^{1/2}$
25	316.14	−23.09	0.42	$\delta_1 \geq 45.6\,\mathrm{MPa}^{1/2}$
	−9313.03	208.11		$\delta_1 < 45.6\,\mathrm{MPa}^{1/2}$

in ethanol–water can be fitted to a quadratic-linear relationship against the solubility parameter of the ethanol–water mixture ($r^2 = 0.99$). The following relationships were obtained at 25 °C:

$$\%\mathrm{SE} = 101.2 - 9.10\,\delta_1 + 0.20\,\delta_1^2 \quad \text{if } \delta_1 = 45.6\,\mathrm{MPa}^{1/2}$$
$$\%\mathrm{SE} = -9267 + 201\,\delta_1 \quad \text{if } \delta_1 > 45.6\,\mathrm{MPa}^{1/2}$$

The %SE at other temperatures is summarized in Table 4 for the ethanol–water mixture.

The solubility increase of the solid dispersion is small (10–20%) in the case of the non-aqueous mixture (ethanol–ethyl acetate), and this effect is uncorrelated with the volume fraction of the co-solvent or with the solubility parameter of the mixture.

3.4. Solubility prediction

The experimental solubility data obtained in the two solvent mixtures are fitted jointly to Eq. (1) at each temperature. An excellent correlation was obtained in all cases ($r^2 \geq 0.98$). The equations obtained at 25 °C are:

Thiabendazole:

$$\ln X_2 = -24.0871\,(\pm 1.7) + 1.2938\,(\pm 0.12)\,\delta_1 - 0.0253\,(\pm 0.002)\,\delta_1^2 + 0.5215\,(\pm 0.08)\,\delta_{1b} - 0.0321\,(\pm 0.005)\,\delta_{1a}\,\delta_{1b} \qquad (5)$$

$r^2 = 0.9977$, $n = 21$, RMSE = 0.1203

Thiabendazole:PVP K30 dispersions:

$$\ln X_2 = -28.4245\,(\pm 3.1) + 1.5572\,(\pm 0.23)\,\delta_1 - 0.02757\,(\pm 0.004)\,\delta_1^2 + 0.7583\,(\pm 0.16)\,\delta_{1b} - 0.05134\,(\pm 0.009)\,\delta_{1a}\,\delta_{1b} \qquad (6)$$

$r^2 = 0.9893$, $n = 21$, RMSE = 0.2248

RMSE is the root mean square error (RMSE) and n the number of cases.

Table 5 summarizes the coefficients obtained for Eq. (1) at 15 and 35 °C. The signs on the regression coefficients do not vary with temperature and agree with those expected from the model allowing a physical interpretation of the factors that influence solubility. The signs on the terms associated with solute–solvent interactions are positive, increasing solubility. The signs on the terms associated with solvent self-association are negative, decreasing solubility. Since the solubility profile in ethanol does not show a peak for thiabendazole or the peak is small in the case of the solid dispersions, the variable δ_{1a} is not needed in the equations. The calculated

Table 5
Regression coefficients of the solubility model (Eq. (1)) at 15 and 35 °C for the drug (TBZ) and the solid dispersions (SDTBZ) in ethanol–water and ethanol–water mixtures.

T (°C)		C_0	C_1	C_2	C_4	C_5	R^2
35	TBZ	−23.9686	1.3246	−0.0271	0.5780	−0.0331	0.99
	SDTBZ	−28.5953	1.5778	−0.0278	0.7622	−0.0515	0.99
15	TZ	−25.9188	1.4057	−0.0269	0.5781	−0.0365	0.99
	SDTBZ	−28.5277	1.5623	−0.0281	0.7820	−0.0520	0.99

Eq. (1) includes both solvent mixtures. The coefficient C_3 is not included (see the text).

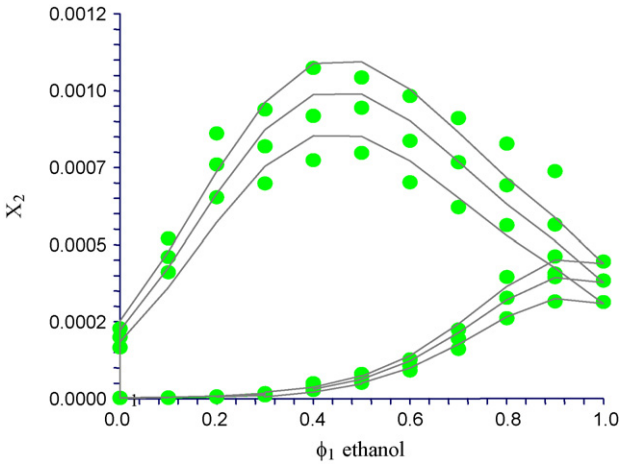


Fig. 7. Experimental (●) and calculated (solid lines, Eqs. (8)–(10)) solubility of thiabendazole:PVP K30 solid dispersions in ethanol–water (upper curves) and ethanol–ethyl acetate (lower curves) at several temperatures.

curves correlate well with the experimental values and reproduce the shape of the solubility profile (Figs. 4 and 5).

The experimental solubility values were fitted to Eq. (3) using only 8 values taken at co-solvent volume fractions (ethanol in water and ethanol in ethyl acetate) of $\phi_1 = 0$, 0.3, 0.5 and 1, at two temperatures, $T = 15\,^{\circ}C$ and $T = 35\,^{\circ}C$. The solubility at the remaining volume fractions and at a different temperature (25 °C) was predicted from the model. The model was applied separately to each binary mixture. According to Eq. (3), the coefficients associated to $\phi_1 \ln X_1$ and $\phi_2 \ln X_2$ are equal to unity. In the regression analysis the computer is let to freely assign regression coefficients to both variables. The intercept is set equal to zero.

Thiabendazole in ethanol–water:

$$\ln X_2 = 0.9998\,\phi_1 \ln X_1 + 0.9997\,\phi_2 \ln X_2 + 2362.895\left(\frac{\phi_1\phi_2}{T}\right) - 1155.925\left(\frac{\phi_1^2\phi_2}{T}\right) \quad (7)$$

Solid dispersions in ethanol–water:

$$\ln X_2 = 0.9999\,\phi_1 \ln X_1 + 0.9998\,\phi_2 \ln X_2 + 2442.148\left(\frac{\phi_1\phi_2}{T}\right) - 3028.442\left(\frac{\phi_1^2\phi_2}{T}\right) \quad (8)$$

Thiabendazole in ethanol–ethyl acetate:

$$\ln X_2 = 0.9999\,\phi_1 \ln X_1 + 0.9999\,\phi_2 \ln X_2 + 1697.939\left(\frac{\phi_1\phi_2}{T}\right) - 1201.5\left(\frac{\phi_1^2\phi_2}{T}\right) \quad (9)$$

Solid dispersions in ethanol–ethyl acetate:

$$\ln X_2 = 1.0365\,\phi_1 \ln X_1 + 0.9994\,\phi_2 \ln X_2 + 1564.208\left(\frac{\phi_1\phi_2}{T}\right) - 526.908\left(\frac{\phi_1^2\phi_2}{T}\right) \quad (10)$$

Fig. 7 shows as a sample the experimental and calculated solubility curves for the solid dispersion in ethanol–water and ethanol ethyl acetate at 15 and 35 °C (Eqs. (8) and (10)) and the experimental and predicted values at 25 °C, that were not used to obtained the equations. With this model it is possible to predict the drug solubility at different ϕ_1 and T employing 8 only experimental values from each solvent mixture. Predictions using a few experimental are very useful when a limited amount of drug is available and to avoid experiments that are time consuming.

4. Conclusions

Combination of co-solvents and solid dispersions with PVP K30 increases the solubility of thiabendazole. The solid dispersions produce the highest solubility increase in pure water (750%). The solubilising powder of the solid dispersions is higher at lower temperatures and it decreases nonlinearly as the concentration of ethanol-in water increases. In the case of the non-aqueous mixture, the solubility increase by solid dispersions is smaller (20–30%), and it is uncorrelated with solvent composition.

The solubility parameter was related with the shape of the solubility profile of the drug and that of the solid dispersions. Thiabendazole shows an intermediate behaviour between solubility profiles with two peaks (more polar drugs with larger δ_2 values) and a single peak (less polar drugs with lower δ_2 values). The solid dispersions increase the apparent polarity of thiabendazole from $\delta_2 = 24$ to $\delta_2 = 25.7\ \mathrm{MPa}^{1/2}$.

The model of Bustamante et al. provided good results to predict the solubility profiles of the drug and the solid dispersions, including both mixtures in a single equation. The model of Jouyban et al. was able to predict the solubility of each binary mixture separately using a few experimental results.

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