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Preparation, dissolution and characterization of albendazole solid dispersions

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Abstract

In this study, solid dispersion systems of the sparingly water soluble drug, albendazole (ABZ), were mixed with varying concentrations of polyvinylpyrrolidone (PVP K 12) in an attempt to improve the solubility and dissolution rate of ABZ. Physical characteristics were investigated by Powder X-ray diffraction. As expected, the albendazole dissolution rate, expressed as the dissolution efficiency, and also the solubility coefficient were increased when albendazole was mixed with PVP. An increase in the concentration of the polymer in the solid dispersion produced an increase in both parameters. The powder X-ray diffraction patterns showed that the solid dispersion presented an amorphous form of albendazole in this coprecipitate system.

Keywords: Albendazole; Polyvinylpyrrolidone; Solid dispersion; Powder X-ray diffraction; Dissolution rate; Drug-carrier

Albendazole (ABZ), methyl [5-(propylthio)-1-H-benzimidazol-2yl] carbamate, is undoubtedly the most effective of the broad-spectrum anthelmintic agents (Cook, 1990). The albendazole therapy is very important in systemic cestode infections specially in inoperable or disseminated cases of hydatidosis (Wen et al., 1993) and neurocysticercosis (Del-Brutto et al., 1993).

The biggest problem of benzimidazoles is its low and erratic availability as a result of its low aqueous solubility. One possible way of overcoming this problem is to alter the physical properties of the drug by forming a solid dispersion.

The dispersion of the drug within an inert water soluble carrier, as PEG or PVP, in the solid state (Sekiguchi and Obi, 1961; Chiou and Riegelman, 1971) known as solid dispersion system has been shown to increase the in vitro dissolution rates of many drugs (Jachowicz et al., 1993; Kearney et al., 1994; and Sheu et al., 1994).

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The present work describes the preparation of PVP-albendazole solid dispersions, their powder X-ray diffraction patterns and the dissolution characteristics of the different albendazole samples.

Albendazole (Chemo Ibérica S.A.). PVP K12 PF (Basf) was used, with an average molecular weight of 3000 Da. All other chemicals were of reagent grade or better (Panreac, Merck).

The solid dispersions were prepared using a solvent evaporation method. The required amounts of albendazole and PVP were codissolved in a minimal volume of 95% ethanol. The solvent was then evaporated in vacuo at 50°C with a rotatory evaporator. The resulting residue was then freeze-dried. A physical mixture of albendazole and PVP K12PF was obtained in a 1:20 ratio.

Formulations

SDA1210: Solid dispersion albendazole – PVP K12PF 1:10 ratio.

SDA1220: Solid dispersion albendazole – PVP K12PF 1:20 ratio.

SDA1240: Solid dispersion albendazole – PVP K12PF 1:40 ratio.

PMA1220: Physical mixture albendazole – PVP K12PF 1:20 ratio.

Fig. 1 shows the dissolution curves of solid dispersions of albendazole and PVP 12 PF at different proportions and the physical mixture plotted against albendazole. For this dissolution studies USP method I was used (1000 ml of pH 1.2 buffer solution (KCl/HCl), 37°C, 100 rev./min).

In order to avoid small particles of albendazole floating on the dissolution medium a particle size fraction (0.84–1 mm) was selected and an amount of the solid dispersion equivalent to 20 mg of albendazole was introduced in the basket. The studies were repeated three times to obtain the mean value.

The dissolution efficiency values at 60, 180 and 480 min are shown in Table 1. The dissolution efficiency is a suitable parameter for the evaluation and comparison of the 'in vitro' dissolution of different formulations. This parameter was defined by Khan and Rhodes (1972) as the area

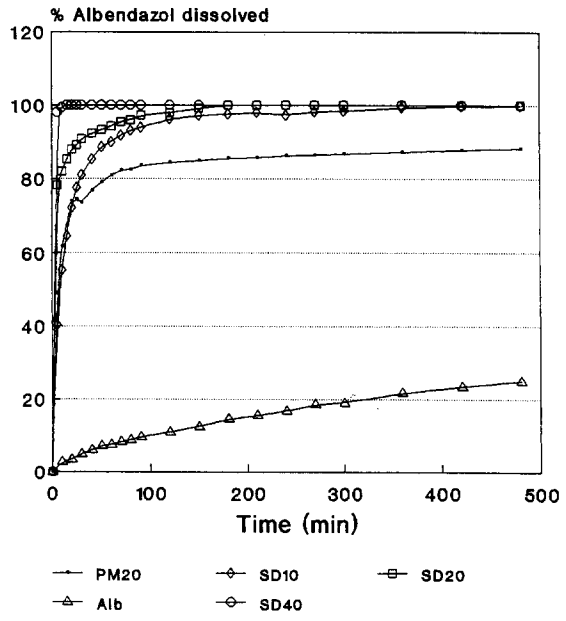

Fig. 1. Dissolution curves of albendazole (△), and the formulations PM20 (●), SD10 (◇), SD20 (□) and SD40 (○) in buffer solution (pH 1.2).

under the dissolution curve up to a certain time, t, expressed as the rectangle described by 100% dissolution in the same time.

A one way variance analysis of the dissolution efficiency data (ANOVA) was done (Table 2).

The albendazole dissolution rate was increased when it was mixed with a easily water-soluble carrier as PVP. The dissolution efficiency (60 min) of the formulation SD10 is 15-fold greater as

Table 1
Dissolution efficiency values

	Time (min)		
	60	180	480
ABZ	4.79 (2.19)	9.02 (3.29)	16.03 (4.52)
PM20	69.40 (3.21)	79.23 (2.98)	84.09 (4.38)
SD10	72.74 (4.95)	87.83 (3.78)	94.71 (2.03)
SD20	85.95 (1.61)	94.0 (0.67)	97.75 (0.25)
SD40	98.61 (2.4)	99.67 (0.58)	99.67 (0.58)

Dissolution efficiency values at 60, 180 and 480 min of the albendazole and the albendazole formulations: PM10, SD10, SD20 and SD40.

Table 2
Dissolution efficiency variance analysis of albendazole and albendazole formulations

	ABZ	SD10	SD20	SD40	PM20
ABZ	—	—	—	—	—
SD10	ED^{c}_{480}	—	—	—	—
	ED^{c}_{180}				
	ED^{c}_{60}				
SD20	ED^{c}_{480}		—	—	—
	ED^{c}_{180}	ED^{c}_{180}			
	ED^{c}_{60}	ED^{c}_{60}			
SD40	ED^{c}_{480}	ED^{a}_{480}		—	—
	ED^{c}_{180}	ED^{c}_{180}	ED^{b}_{180}		
	ED^{c}_{60}	ED^{c}_{60}	ED^{c}_{60}		
PM20	ED^{c}_{480}	ED^{c}_{480}	ED^{c}_{480}	ED^{c}_{480}	—
	ED^{c}_{180}	ED^{c}_{180}	ED^{c}_{180}	ED^{c}_{180}	
	ED^{c}_{60}		ED^{c}_{60}	ED^{c}_{60}	

Dissolution efficiency varianza analysis of albendazole and different albendazole formulations.
DE_{60}, DE_{180}, DE_{480} dissolution efficiency at 60, 180 and 480 min respectively.
[a.b.c]Significant difference ($P < 0.05$), ($P < 0.01$) and ($P < 0.001$) respectively.

compared to the drug alone. All the formulations containing PVP presented a clearly significant difference ($P < 0.001$) of the dissolution efficiency respect to albendazole. This increase in the dissolution efficiency reach to be so important as 20-fold greater at 60 min time for the SD40 than the single albendazole.

An increase on the concentration of the polymer increased the dissolution efficiency, which can be explained on the basis of the wetting and solubilizing effect of the carrier (Jachowicz et al., 1993). The formulation of the drug in a solid dispersion not only increased the dissolution rate but also the dissolution magnitude. The solubility coefficient of the albendazole, physical mixture (PMA1240) and albendazole solid dispersions SDA1210, SDA1220 y SDA1240 were respectively: 0.423; 0.849; 1.228; 1.765; and 5.484 mg/ml in a buffer solution (pH 1.2). Solubility (w/w) at 24°C in pH 1.2 buffer solution (KCl/HCl) was determined using the shaker method (Yu et al., 1994). Albendazole samples were analyzed in a Beckman DU6 spectrophotometer at 291 nm in a pH 1.2 buffer. As for the dissolution rate, the albendazole solubility coefficient (0.423 mg/ml) was increased when it was formulated in a solid dispersion. So the solid dispersion with a albendazole-PVP ratio of 1:10 presented a solubility coefficient near to 3-fold greater as compares to albendazole one. This increase is higher as the albendazole:PVP ratio presented a higher percentage of PVP, becoming 13-fold greater in the case of the albendazole solid dispersion 1:40 comparing to the drug alone, probably due to a lower albendazole-crystals particle size.

When the physical mixture and the solid dispersion with the same concentration of the polymer are compared a significant difference ($P < 0.001$) in the dissolution efficiency at any time (60, 180 and 480 min) can be observed. With respect to the solubility magnitude, the solid dispersion SD20 presented a solubility coefficient double (1.765 mg/ml) than the PM20 solubility coefficient (0.849 mg/ml). These different data of the physical mixture and the solid dispersion with the same concentration of PVP suggest an important physicochemical difference between both formulations.

The physical state of albendazole in various preparations was evaluated by powder X-ray diffraction using a Philips X'PERT-MDP diffractometer, with Ni-filtered Cu-Kα radiation, a voltage of 40 Kv and a current of 40 mA. The samples were analyzed over a 2θ range of 5–40° and with a time per step of 1 s. Fig. 2 shows the diffraction patterns of the pure albendazole, the solid dispersions SD10 and SD20, the physical mixture PM20 and the pure PVP.

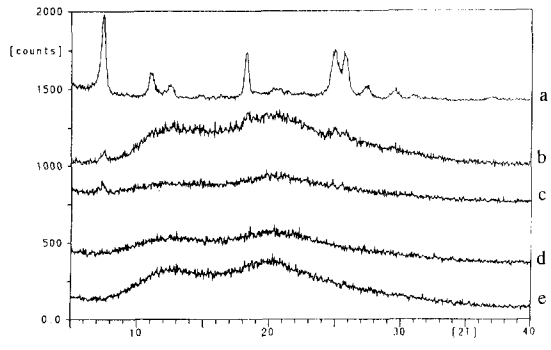

Fig. 2. X-ray diffraction patterns: Pure Albendazole (a), PM20 (b), SD10 (c), SD20 (d) and pure PVP (e).

Albendazole presented a crystalline form as demonstrated by various intense diffraction peaks whereas PVP is amorphous.

The physical mixture having a albendazole-PVP 1:20 ratio presented a more intense crystalline form than the solid dispersion SD10 although this physical mixture contained double amount of PVP.

In this Fig. 2 it is possible to observe that the solid dispersion SD10 presented a slightly crystalline form whereas the SD20 with a albendazole-PVP 1:20 ratio is absolutely amorphous what can explain the high significative difference in the dissolution efficiency values at 60 and 180 min for this two formulations (Table 1 and 2). As for the dissolution rate a clearly increase in the solubility coefficient for this formulation SD20 as compared to the SD10.

The solid dispersion SD20 presents a clearly difference in the X-ray pattern with respect to the physical mixture with the same PVP proportion (PM20) what suggest a different albendazole physical form in both formulations. The presence of an amorphous form of albendazole in the co-precipitate system agrees with the better dissolution properties of this formulation as compared to the drug alone or the physical mixture as observed in other authors studies about solid dispersions systems (Jachowicz et al., 1993) (Kearney et al., 1994).

It can be concluded that for the enhancement of the dissolution rate and the solubility coefficient of albendazole, the co-precipitation method with PVP as carrier is recommended.

Further investigations dealing with the in vivo behaviour including oral bioavailability of these formulations will be done in future studies.

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