Pharmaceutical Development and Technology, 2013; 18(2): 434–442

ISSN 1083-7450 print/ISSN 1097-9867 online
DOI: 10.3109/10837450.2012.693509

informa
healthcare

RESEARCH ARTICLE

Enhanced dissolution and systemic availability of albendazole formulated as solid dispersions

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Abstract

Solid dispersions (SDs) containing the anthelmintic compound albendazole (ABZ) and either Pluronic 188 (P 188) or polyethylene glycol 6000 (PEG 6000) as hydrophilic carriers were formulated. Drug–polymers interactions in solid state were investigated using different techniques.

Only a 4% of total ABZ was dissolved at 5 min post-incubation, reaching dissolution rates of 32.8% (PEG 6000) and 69.4% (P 188) in SDs. In this way, P 188 was substantially more efficient as ABZ dissolution promoter in comparison to PEG 6000, especially at the initial stages of the dissolution processes (<30 min).

An increased systemic availability ($p < 0.001$) was obtained when ABZ was administered as ABZ-P 188 SDs, with a 50% enhancement in systemic exposure (AUC values) compared to treatment with an ABZ suspension. Consistently, the Cmax increased 130% ($p < 0.001$) following treatment with P 188 based SD ABZ formulation. For the ABZ-PEG 6000 SD formulation, the favorable effect on ABZ systemic availability did not reached statistical significance compared to the control group.

The study reported here showed the utility of pharmacokinetic assays performed on mice as a model for preliminary drug formulation screening studies.

Keywords: Solid dispersions, albendazole, poloxamer, pharmacokinetic, mice

Introduction

The permeability and solubility of some drugs can be limiting conditions for oral absorption with the consequent decrease of bioavailability. Although permeability is an intrinsic drug property, different strategies have been developed aiming to improve the dissolution rate for the design of a suitable formulation for oral administration.[1] This increase on dissolution rate would be especially useful for Class II compounds (Biopharmaceutical Classification System, BCS), which have low gastrointestinal solubility and high permeability.[2] Several techniques have been used to improve the solubility/dissolution rate of poorly water-soluble drugs. Among them, the solid dispersion technique is the most frequently used.[3–5]

Solid dispersions (SDs), which are defined as molecular mixtures of poor water-soluble drugs and hydrophilic carriers, have been proposed as alternative for improvement of dissolution rate of this kind of drugs.

Different materials have been evaluated as carriers. The first SD generation involved the use of crystalline carriers[6,7] and sugars,[8] while for the second generation several types of hydrophilic polymers such as polyethylene glycol,[9,10] polyvinylpyrrolidone[11,12] among others, have been assayed.

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(Received 03 April 2012; revised 24 April 2012; accepted 26 April 2012)

For this kind of drugs, it is especially important the *in vitro-in vivo* correlation of the dissolution data regarding to its expected biopharmaceutical behavior, which is often not conveniently addressed.

In previous works, we have studied the *in vitro* behavior of SDs using poloxamer 188 (P 188)[13] and PEG 6000[14] as carriers.

Poloxamers are polyoxyethylene–polyoxypropylene block copolymer nonionic surfactants that have been widely used as wetting and solubilizing agents. The polyoxyethylene segment is hydrophilic whereas the polyoxypropylene segment is hydrophobic. All poloxamers are chemically similar in composition, differing only in the relative percentage of propylene and ethylene blocks.

Poloxamers are used in a variety of oral, parenteral, and topical pharmaceutical formulations and it is generally regarded as nontoxic and nonirritant material. Poloxamers are not metabolized in the body.[15] Particularly, P 188 was also used as meltable solid binder in the formulation of particulate pharmaceutical dosage forms involving new techniques such as fluidized hot melt granulation)[16] and melt agglomeration process],[17] since this material presents low melting point (about 52–57°C).

On the other hand, Polyethylene glycols (PEGs) – $HOCH_2(CH_2OCH_2)_mCH_2OH$ where *m* represents the average number of oxyethylene groups – are widely used in a variety of pharmaceutical formulations, including parenteral, topical, ophthalmic, oral, and rectal preparations.[18]

The number that follows PEG indicates the average molecular weight of the polymer. In particular, PEG 6000 has been widely used as a solid dispersion carrier.[19–21]

Helminthes parasites that have an intra and extra intestinal phase are able to infect humans as well as animals. The treatment of intestinal helmintiosis is usually carried out with benzimidazole 2-carbamate drugs (BDZ), which have a wide spectrum of activity such as albendazole (ABZ) and mebendazole. However, the treatment of systemic parasitosis with this type of drugs requires high doses and long treatments because of their poor solubility in body fluids which usually produces the decrease of their absorption and bioavailability.[22]

BZD compounds are all relatively insoluble in water, benzene and ether, but highly soluble in alcohol and nonpolar solvents.[23] The latter limits the practical use of the most potent BZD compounds, including fenbendazole (FBZ), oxfendazole (OFZ) and albendazole (ABZ), to suspensions, which are most commonly administered by the oral route in domestic animals.

ABZ, contain a sulphur atom as a sulphide at position 5 of the BZD molecule. These sulphides are subjected, mainly in the liver, to phase I reactions (oxidation), catalysed by the flavine monooxygenase and the cytochrome P-450 (Cyt P- 450) enzyme systems to form albendazole sulphoxide (ABZSO) being the primary pharmacologically active metabolites generated. In a second metabolic reaction (sulphonation), catalysed by the Cyt P-450 system ABZSO is transformed into inactive sulphone $ABZSO_2$.[24]

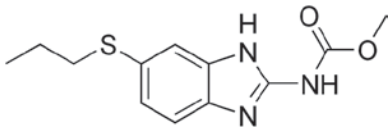

Figure 1. Chemical structure of albendazole.

ABZ (Figure 1) possesses low aqueous solubility (0.01 mg/mL in water at 25°C) and high permeability[25] belonging to type II biopharmaceutical classification system. The melting point of ABZ is 209°C and its solubility constant (n-octanol) at neutral pH is 0.75 ± 0.2 (g/mL).[26]

It is well known that the slow dissolution rate of albendazole is able to limit its absorption leading generally to a poor and erratic absorbtion from the gastrointestinal tract. Furthermore, it is also well known that low solubility drugs offer only few formulation possibilities, limiting the administration routes.[27]

In earlier investigations[13,14] we observed that the inclusion in SD of both P 188 and PEG 6000 increased the dissolution rate of ABZ. The former was particularly effective since at lower concentrations of the carrier the increment in dissolution rate was quantitative more evident. This behavior was attributed to the formation of the gel layer that occurs above the critical temperature of gelation of poloxamers. In the case of PEG 6000, the dissolution rate were dependent on the proportion of the carrier in the SD, being more efficient at lower PEG 6000:ABZ ratios.

At this stage of our investigation and according to previous results, elucidation of the pharmacokinetic behavior of ABZ-based SDs is needed. The work reported here describes the comparative pharmacokinetic behavior of ABZ metabolites after oral administration of both ABZ:P 188 and ABZ:PEG 6000 solids dispersion formulations to mice.

Materials and methods

In vitro study

Materials

For the preparation of SDs the following materials were used: Albendazole (Pharmaceutical grade-USP, Parafarm, Buenos Aires, Argentina), POLOXAMER 188 (BASF, Germany) and POLYETHYLENE GLYCOL 6000 (FLUKA, Germany). All other reagents were of analytical grade.

Methods

Samples preparation

SDs were prepared by melting of ABZ and carrier at 50% w/w in a water bath at 63°C for P 188 and 68°C for PEG 6000. The mixtures were homogenized by stirring. The resulting homogenous preparations were rapidly cooled, pulverized and sieved (212-micron).

The particle size fraction was obtained by sieving and kept in a screw-capped glass vial until use. The powders were stored in a screw-cap vial at low temperature until use.

XRP Diffraction and IR spectroscopy

The powder X-ray diffraction was performed using a Rigaku Miniflex 2000 diffractomer (Λ: 1.5418 Å with a Bragg-Brentano geometry).

The radiation was generated by a Cu Kα lamp. The instruments was operated in the continuous scan mode with the scanning speed at 2°/min. Scan range was 3–70° 2 θ/θ with a scan speed 0.066° 2 θ/s.

The SDs were also characterized using infrared spectroscopy (FTIR; Nicolet 5SXC FT-IR Spectrometer) using KBr disks.

Differential scanning calorimetry

DSC measurements for all powder sample was performed on a differential scanning calorimeter (Modulated-DSC 2920, TA-instruments, USA) using 1 mg of sample in a closed aluminium pan at a heating rate of 20°C/ min from 25 to 250°C under nitrogen purge of 60 mL/ min.

Hot stage microscopy

In order to characterize the systems under study, samples were subjected to a HSM study. The procedure carried out in different samples was as follows: approximately 1 mg of sample were placed over glass slides with coverglass and heated up to 25°C and 220°C using the furnace provided by the HSM equipment (Microscopio Óptico Zeiss Phomi III POL) at the rate of 10°C/min.

Scanning electron microscopy

The morphology of the samples was examined by scanning electron microscopy (LEO, EVO 40-XVP). The samples were placed in the holder and then metallized with gold by Ar plasma.

Solubility studies

An excess of drug was suspended in a 3 mL 0.1 N HCl solution aliquot containing increasing concentrations of carrier (1, 3, 5, 10, 15 and 20% w/v) and stored into sealed glass containers. The samples were shaken for 1 min every 60 min.

The test tubes were stored 4 days at room temperature aiming to reach the solubility equilibrium. Before measuring, the suspensions were filtered, the filtrate was suitably diluted and analyzed spectrophotometrically at 297 nm.

Dissolution tests

Dissolution tests of powdered SDs were performed using an USPXXIV dissolution apparatus 2 (SOTAX AT 7 smart). The rotational paddle speed was set at 50 rpm and the temperature remained constant at 37 ± 0.5°C. The assayed amount of ABZ was 50 mg in all experiments. As dissolution medium 900 mL 0.1 N HCl solution was used. Five-milliliter aliquots were withdrawn at predetermined time intervals during 1 h, and the same amount of fresh medium was added in order to keep the volume constant throughout the test. The samples were filtered and the concentration of dissolved drug was measured at 297 nm using a UV–vis spectrophotometer (Thermo Electron Corporation, Evolution 300 BB, England).

The measurements were performed by triplicate. In previous test, we verified that the presence of carriers dissolved in the dissolution medium did not affect the λ_{max} of ABZ.

The percentages of dissolved drug were statistically analyzed by one-way analysis of variance. The differences were considered statistically significant at $p < 0.05$.

In vivo study

Pharmacokinetic study

Experimental animals

Male Balb/c mice were used in the PK study. The animals were housed in temperature controlled (21 ± 2°C), light-cycled (12 h light/dark cycle) room. Food and water were provided ad libitum. Animal procedures and management protocols were approved by the Ethics Committee according to the AnimalWelfare Policy (act 087/02) of the Faculty of Veterinary Medicine, Universidad Nacional del Centro de la Provincia de Buenos Aires (UNCPBA), Tandil, Argentina (http:// www.vet.unicen.edu.ar).

One hundred forty-four (144) healthy mice were allocated into three groups of 48 animals each to which either ABZ, ABZ: P 188 or ABZ:PEG 6000 powdered SDs suspended in water were inmediatly orally administered (25 mg/kg) using an intragastric tube. Blood samples were collected in heparinized plastic tubes at the following times post-treatment: 0 (control), 0.08, 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 10 and 12 h. Blood samples were centrifuged at 2000*g*. for 15 min. and the recovered plasma was stored at –20°C until analysis by HPLC.

Analysis of ABZ and its metabolites

Sample clean up

ABZ, ABZSO and $ABZSO_2$ were extracted by a double extraction method liquid-liquid. Five microlitres of OBZ (5 μg/mL) was added to 100 μL of plasma in a glass test tube. First the extraction was realized in acetonitrile and then in hexane. Finally, all samples were concentrated to dryness in a vacuum concentrator and then reconstituted with 200 μL of mobile phase.

HPLC analysis

Experimental and spiked plasma sample (used for validation) were analysed by HPLC with a UV detector. Chromatography was performed on a Shimadzu HPLC equipment (Shimadzu Corporation, Kyoto, Japan), with two LC-10AS solvent pumps, an automatic sample injector (SIL-10A) with a 50 μL loop, an ultraviolet visible spectophotometric detector (UV) (SPD-10A) reading at 292 nm, a column oven (Eppendorf TC-45, Eppendorf, Madison, WI, USA) set at 30°C, and a CBM-10A integrator. Data and chromatograms were collected and analyzed using the Class LC10 software (SPD-10A, Shimadzu

Corporation, Kyoto, Japan). A C18 reversed-phase column (5 µm, 250 mm × 4.6 mm) was used (Kromasil®, Sweden). Elution from the stationary phase was carried out at a flow rate of 1.2 mL/min using acetonitrile (40%) and potassium phosphate buffer (25 mM, pH 5.3, 40%) as mobile phase.

Fifty (50) microlitres of sample processed as described above was injected and eluted (flow 1.2 mL/min) using a linear gradient method as reported by Sanchez et al (1996). The compounds were identified by comparison of the corresponding retention time with those of reference compounds. Plasma calibration curves for each analyte were constructed by least squares linear regression analysis giving a correlation coefficient (r) between 0.9987 and 0.9995. Quantification limits were 0.01 ug/mL (ABZ and ABZSO) and 0.03 µg/mL ($ABZSO_2$).

Pharmacokinetic analysis of the data

The concentration vs. time curves for the metabolites ABZSO and $ABZSO_2$ in plasma for each individual animal after the different treatments were fitted with PK Solution 2.0 (Summit research services, Ashland, OH, USA). The following Eq. 1[28] was used to describe the biexponential concentration–time curves for ABZSO and $ABZSO_2$ after the oral treatment:

$$C_p = Be^{-\lambda_2.t} - Be^{-\lambda_1.t} \quad (1)$$

where: Cp = concentration in plasma at time t after administration (µg/mL); B = concentration at time zero extrapolated from the elimination phase (µg/mL); e = base of the natural logarithm; λ_2 = terminal slope (h^{-1}); and λ_1 is the slope obtained by feathering, which represents either the first-order absorption rate constant (λ_1) or first-order metabolite formation rate constant (λ_{for}) (h^{-1}). The peak concentration (C_{max}) and time to peak concentration (Tmax) were displayed from the plotted concentration–time curve of each analyte. The area under the concentration–time curve (AUC) were calculated by the linear trapezoidal rule.[29]

$$AUMC_{(0-t)} = \sum_{i=0}^{n-1} \frac{t_{i+1} - t_i}{2}\left(C_i t_i + C_{i+1} t_{i+1}\right) + \frac{C_{last} \times t_{last}}{\lambda_2} + \frac{C_{last}}{\lambda_2^2} \quad (2)$$

Statistical analysis of the data

The ANOVA test was used for the multiple statistical comparisons of the PK data obtained from the different groups. A value of $p < 0.001$ was considered statistically significant.

Results

In vitro study

It is well known that the observed increase in drug dissolution can be attributed to changes of crystal properties of the resulting SD as consequence of carrier-drug interactions. In order to get information about this XRD diffractograms for the systems ABZ/P188 were obtained and the results are shown in Figure 1. Different signals for ABZ (θ/2θ= 6.96, 11.37, 17.91, 22.12, 24.58) and P 188 (θ/2θ=19.32, 23.46) allowed the identification of each component.

No interactions between the components of SDs were observed since the signals assigned to each component were practically not changed.

A lack of molecular interactions was also verified through the comparative analysis of FTIR spectrum of SDs and its components alone. Signals corresponding to N-H stretching vibration at 3,324.94 cm^{-1} and bending vibration at 1,653.07 cm^{-1} of ABZ remain unaltered when it is incorporated in SDs (Figure 2).

Table 1 shows the fusion temperature and the ΔH corresponding to ABZ, PEG 6000, P 188 and SDs.

In the microphotographs presented in Figure 3 and 4, the morphology of a ABZ/PEG 6000 and ABZ:P 188 SDs is shown before and after heating from 25°C until 220°C, at a rate of 10°C/min. By increasing the temperature the carriers melts and different sized drops containing solid drug particles are observed (Figures 3 and 4 b-2).

On the other hand, scanning electron micrographs showed ABZ particles as irregular shaped crystalline

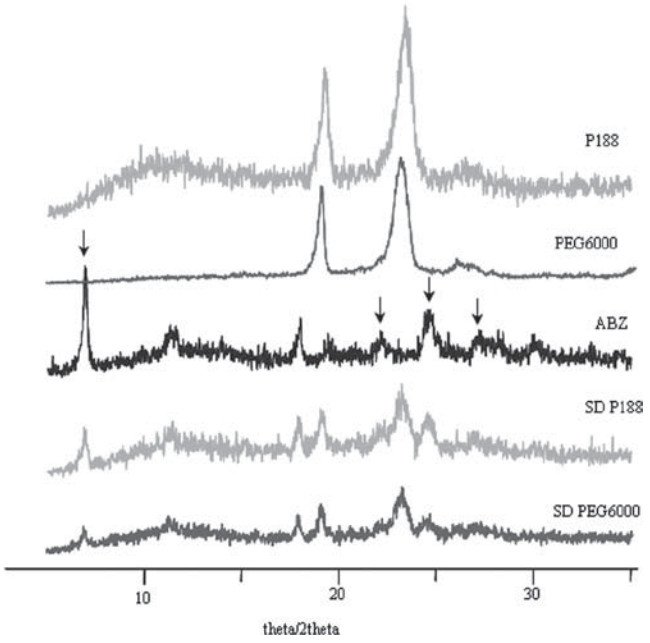

Figure 2. Diffraction patterns Albendazole (ABZ), PEG6000, P 188 and its corresponding solid dispersion.

Table 1. Melting temperatures of albendazole (ABZ), polyethylene glycol 6000 (PEG6000), Poloxamer (P 188) and its corresponding solid dispersions (SD).

Sample	Melting point (°C)	ΔH (J/g)	Melting Point (°C)	ΔH (J/g)
ABZ	–	–	219.58	134.2
PEG6000	62.93	199.1	–	–
P 188	57	137.4	–	–
SD PEG6000	62.01	91.08	201.92	7.04
SD P 188	54.94	60.00	204.28	39.75

solid with relative small size (2–10 μm) and rough surface (Figure 5a-b). In Figure 5 c, smooth surfaced spherical P 188 particles, with an average size of about 200 μm, can be observed. PEG 6000 appears as particles of about 25 μm with a regular and compact appearance (Figure 5d). Regarding SDs, they present homogeneous irregular particles which seem to be a conglomerate of smaller particles (Figure 5d–f).

As shown in Figure 6, drug solubility increased linearly as the concentration of carriers in the solution were increased from 0% to 20% (w/v), being more noticeable in the case of P 188, probably as consequence of its surfactant properties. The solubility increased 2.3 and 1.3 folds for P 188 and PEG 6000, respectively.

The dissolution profiles of pure ABZ and SDs of ABZ: PEG 6000 and ABZ: P 188 are shown in Figure 7.

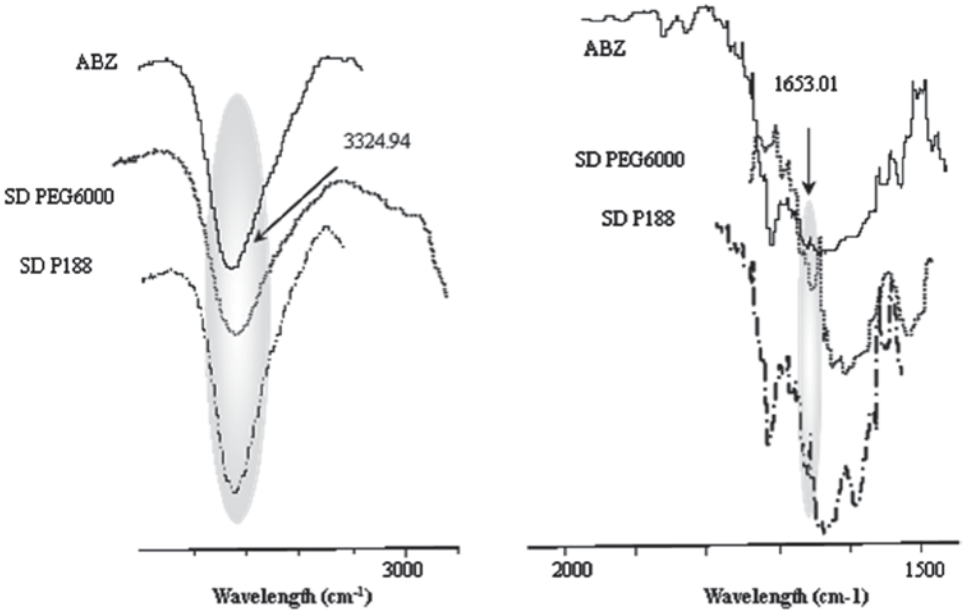

Figure 3. FT-IR Infrared spectra of Albendazole (ABZ) and their corresponding solid dispersions (SD) using Peg6000 and P 188 as a carrier. (a) Stretching vibration at 3324.94 cm^{-1}; (b) bending vibration at 1653.07 cm^{-1}.

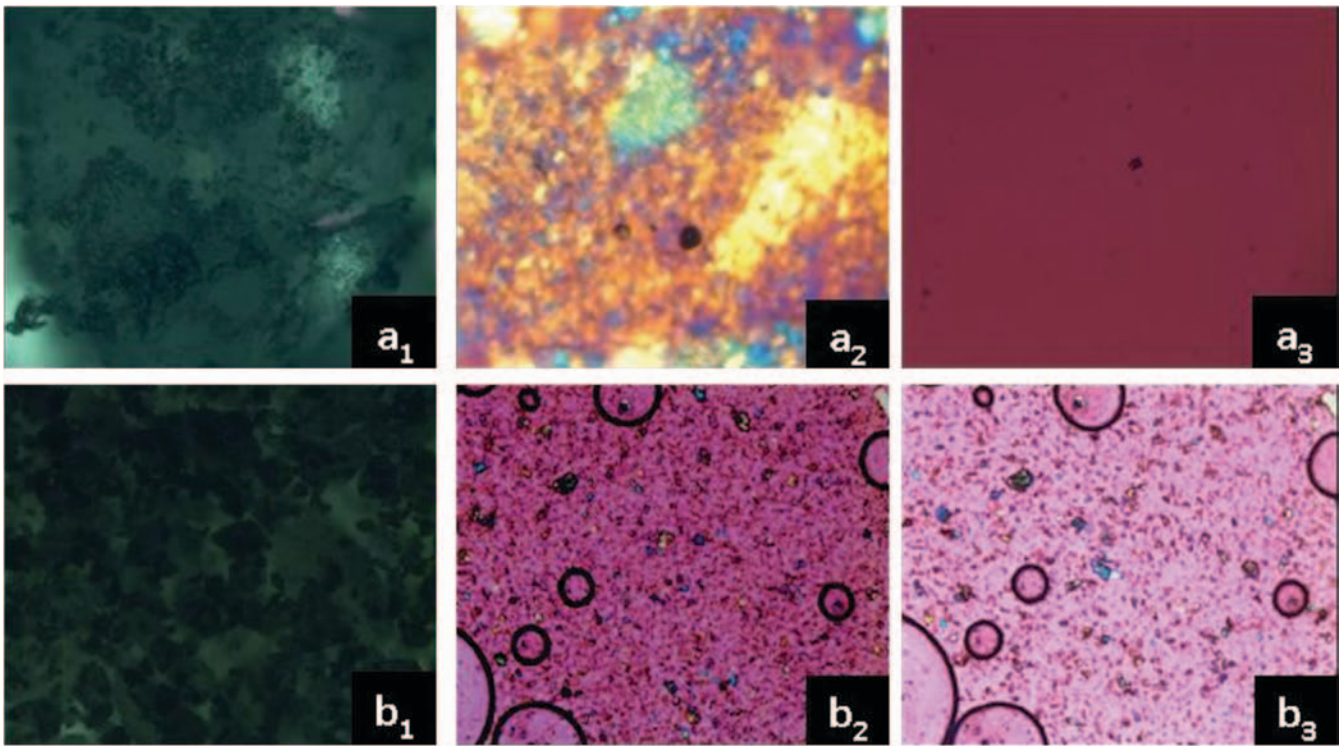

Figure 4. Photographs obtained by microscopy with heated platinum (HSM): (a) PEG 6000 and (b) SD a different temperatures: 1–25, 2–64 and 3–100°C.

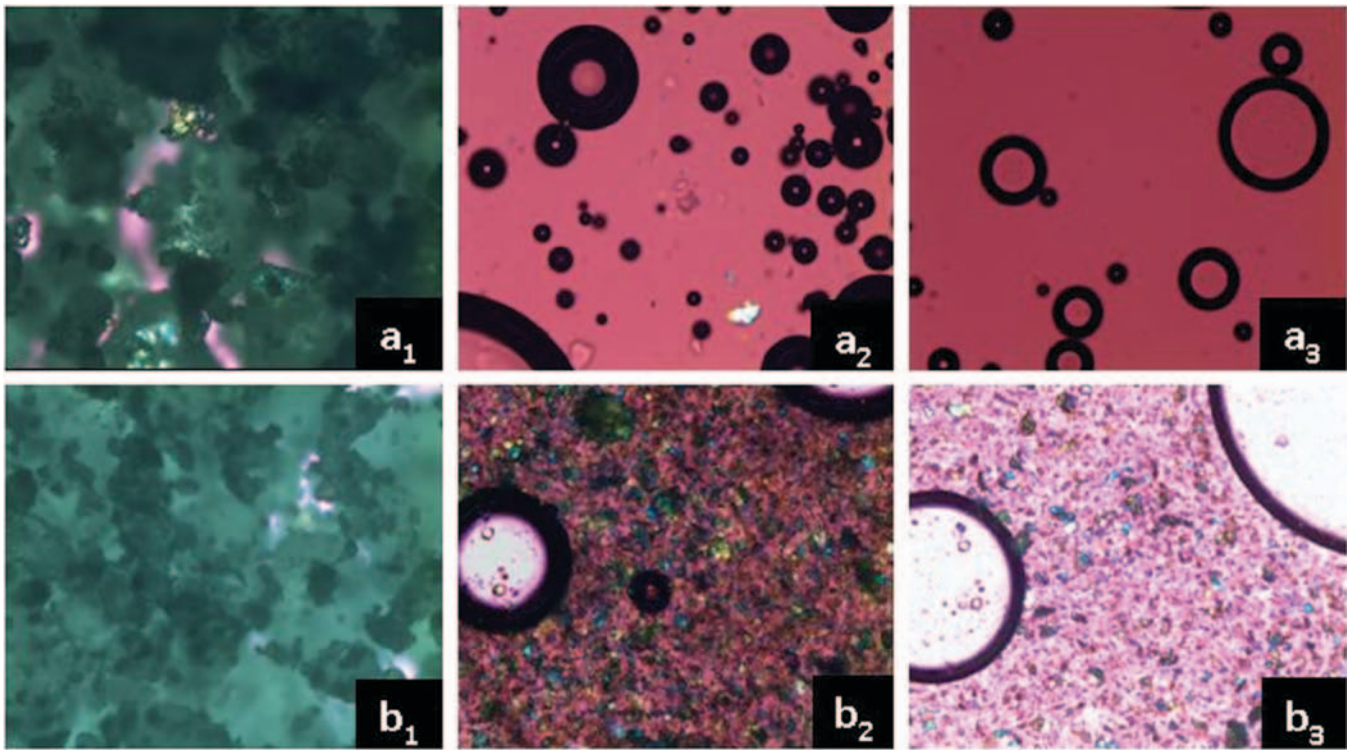

Figure 5. Photographs obtained by microscopy with heated platinum (HSM): (a) P 188 and (b) SD a different temperatures: 1–25, 2–64 and 3–00°C.

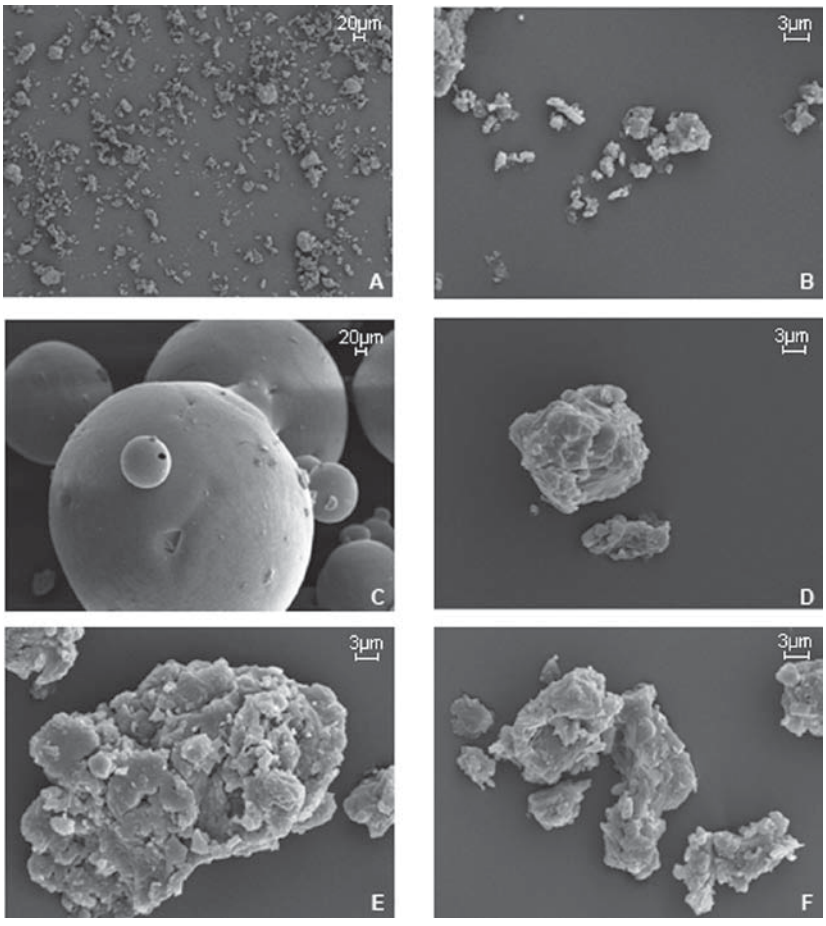

Figure 6. SEM microphotographs. (a) ABZ 400×, (b) ABZ 6000×, 9c) P188 400×, (d) PEG6000, 6000× (e) DS4 P188 6000× f) DS4 PEG6000 6000×.

In vivo study

Pharmacokinetic parameters such as $AUC_{0\text{-}inf}$ (μg.h/mL), C_{max} (μg/mL) and T_{max} were measured and they are shown in Table 2.

Mean concentration–time profiles of ABZSO and $ABZSO_2$ (inactive metabolite) obtained after a single dose of ABZ solution and ABZ suspension are reported in Figure 8A and B, respectively.

Discussion

SDs evidenced a slightly reduction in cristallinity. In addition, it has been suggested that the amorphous form plays an important part in solubility and the dissolution rate which, in general, results in higher solubility and a faster dissolution rate. In this research was observed that the peak corresponding to the melting temperature of the carrier did not suffer a major change.

On the other hand, the infrared spectra confirmed that there were not chemical interactions among ABZ and P 188 or PEG6000 as consequence of their close contact in SDs.

To visualize the changes in the samples of SDs during heating, hot stage optical microscopy (HSM) was used. This technique is complementary to DSC and may help in the interpretation of DSC results. Results attained by HSM and DSC might corroborate that ABZ solubilizaton in both carriers is partial and therefore we are in the presence of a traditional SDs without any signs of a homogeneous solid solution.

The solubility studies were carried out in order to obtain comparative information about the solubility of ABZ in solutions of increasing concentration of carriers.

At the first 5 min ABZ was able to dissolve only 4% whereas the dissolution rate was 32.8% and 69.4% for ABZ:PEG 6000 and ABZ:P 188 SDs, respectively. In this way, P 188 was substantially more efficient as ABZ dissolution promoter in comparison to PEG 6000, especially at the initial stages of dissolution processes (<30 min).

Since low aqueous solubility of ABZ may limit absorption during GI transit, the dissolution rate of BZD anthelmintics in the stomach of different animal species is thought to be pivotal.

Aiming to evaluate whether the increasing in observed *in vitro* dissolution rate would have some favorable effect on ABZ bioavailability (Bd), an *in vivo* study was performed.

After oral administration, unmodified ABZ was not detected in plasma samples. This is a consequence of a hepatic first-pass metabolism which is according to the results reported by other authors in dogs and human.[30,31] The main two metabolites are the S-oxidation compounds (ABZSO and $ABZSO_2$). The kinetics of ABZ absorption in the GIT is the consequence of a passive diffusion process and is independent of the administered dose.[32] Since ABZSO has also anthelminthic properties, the ABZ bioavailability can be quantitatively correlated to ABZSO plasmatic concentrations.

The increase in Bd was significant ($p < 0.001$) when ABZ was administered as ABZ-P 188 SDs comparatively

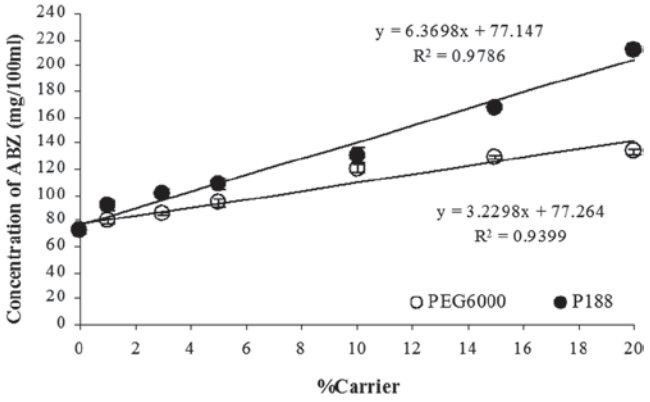

Figure 7. ABZ solubility of increasing concentrations of P188 and PEG6000 in 0.1N HCl.

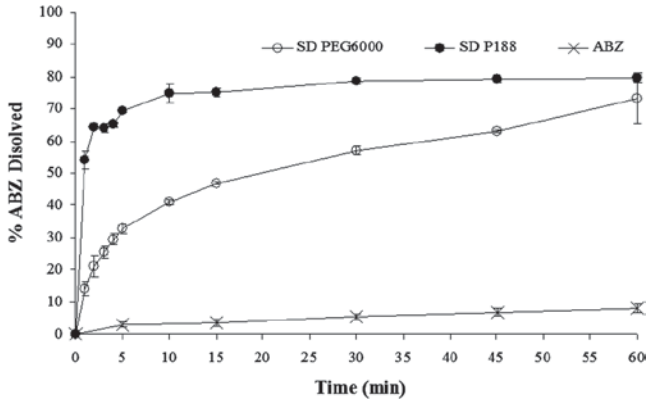

Figure 8. Dissolution profiles.

Table 2. Comparative plasma disposition kinetic variables for albendazole sulphoxide (ABZSO) and albendazole sulphone ($ABZSO_2$) after the oral administration of three different formulations.

	ABZ (Control)		ABZ/PEG6000		ABZ/P188	
Pharmacokinetic parameters	ABZ SO	ABZ SO_2	ABZ SO	ABZ SO_2	ABZ SO	ABZ SO_2
C_{max} (μg/mL)	3.50 ± 0.50[b]	0.20 ± 0.03	4.60 ± 0.70[b]	0.29 ± 0.05	8.00 ± 1.00[a]	0.50 ± 0.10
T_{max} (h)	0.75	2.00	1.00	1.00	0.75	0.75
$AUC_{0\text{-}inf}$(μg.h/mL)	13.0 ± 3.00[b]	1.00 ± 0.200	15.0 ± 2.00[b]	2.00 ± 0.46	19.0 ± 4.00[a]	1.00 ± 0.10
PDP (h)	0.083–12	0.083–12	0.083–8	0.083–12	0.083–10	0.083–12

Different Superscript letters indicate statistical differences among groups at $p < 0.05$. $T_{½}\,\lambda_1$, metabolite formation half-life; C_{max}, peak concentration; T_{max}, time at C_{max}; $AUC_{0-\infty}$, area under the concentration vs. time curve extrapolated to infinity; PDP, plasma detection period.

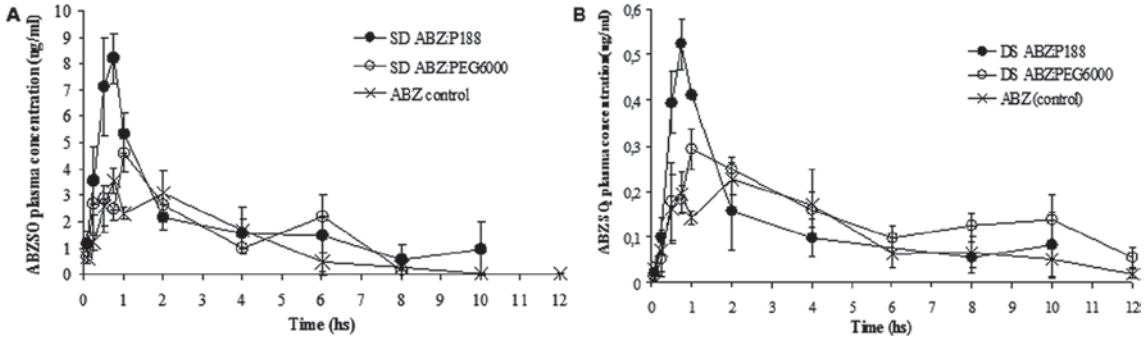

Figure 9. Comparative (mean ± SD) plasma profiles for: a) albendazole sulphoxide (ABZSO) and b) albendazole sulfone (ABZSO2) after the administration of three different oral-based albendazole (ABZ) formulations.

to drug suspensions, with increasing of about 50% in AUC values. Consistently, C_{max} increased 130% ($p < 0.001$). For ABZ-PEG 6000 SDs, the favorable effect on ABZ Bd was not statistically significant compared to the control group. Also, the time at which the maximal ABZSO concentration was reached (T_{max}) remained practically unchanged independent of the carrier used in SDs and in comparison to ABZ control group (suspension).

These observations clearly show an acceptable correlation between *in vitro* dissolution rate of the compounds and the *in vivo* pharmacokinetic studies. For this reason, these results could be very useful for the subsequent design of oral modified release formulations using P 188 as carrier.

The enhanced bioavailability of ABZ in SDs containing P 188 as carrier could be attributed to the improved dissolution rate and the surfactant of this carrier.

On the contrary, PEG 6000 seems not to be as efficient as the former in increasing ABZ Bd, by which no correlation was observed between *in vitro* dissolution tests and *in vivo* pharmacokinetics studies.

It is relevant to note that the enhancing of dissolution rate owed to PEG 6000 was not enough in the first stage of the dissolution process and this would be the explanation for the practically negligible effect of this carrier on ABZ Bd. Besides, this rapid onset of drug dissolution is a key factor in the drug bioavailability in animals with short TGI.

Conclusion

The present study reveals that addition of P 188 as carrier in SDs containing ABZ markedly improves its dissolution properties. This can be mainly attributed to the surfactant properties of this polymer, which is able to increase wetability and solubilization of ABZ. Apparently, this improvement in the dissolution rate was the cause of the increased ABZ Bd observed in *in vivo* pharmacokinetics studies. In addition, the promising results concerning the potential effectiveness of SDs based on P 188 for improvement of ABZ Bd and the utility of pharmacokinetic studies based on mice model for preliminary screen studies, are worthy instead of using superior species (dogs).

Declaration of interest

The authors report no declarations of interest.

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