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Research Article

Improved Albendazole Dissolution Rate in Pluronic 188 Solid Dispersions

Silvina G. Castro,[1] Sergio Sanchez Bruni,[2] Carlos E. Lanusse,[2] Daniel A. Allemandi,[1] and Santiago D. Palma[1,3]

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Abstract. Solids dispersions (SDs) have been proposed as an alternative to improve the dissolution rate of low solubility drugs. SDs containing albendazole (ABZ; 5, 10, 25, and 50% *w*/*w*) and Pluronic 188 (P 188) as hydrophilic carrier were formulated. The obtained SDs were assessed in comparison to physical mixtures (PMs). Drug–polymer interactions in solid state were investigated using Fourier-transform infrared spectroscopy, scanning electron microscopy, and X-ray diffraction analysis. No chemical interaction was found between ABZ and poloxamer. The dissolution profiles indicated that ABZ incorporated in SDs and PMs was rapidly released, reaching rapidly the steady state. Increased dissolution rates are usually observed at the highest polymer proportions. However, an opposite effect for SDs as well as for PMs was observed in the assays described here. The systems with the lowest P 188 percentages (SD4, SD3; PM4, PM3) tended to be more effective in increasing the ABZ dissolution rate. Such a result can be attributed to the fact that concentrated aqueous solutions of Poloxamer may form thermo-reversible gels. The physical–mechanical properties indicated that SDs possess improved flow and compacting properties compared to PMs. Thus, ABZ SDs would be more convenient for solid dosage form design and manufacture.

KEY WORDS: albendazole; dissolution rate; poloxamer; solid dispersions; surfactant.

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; 2), which have low gastrointestinal solubility and high permeability.

Solids dispersions (SD), 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.

Although a large number of studies have been published on the subject, the mechanisms of enhancement of the rate of drug release are not very well understood yet. The reason for this lies in the complexity of the release process and the variety of factors that can affect it, including drug properties (solubility, physical state, particle size) and the properties of the matrix forming polymers (solubility, hydrophilicity, molecular weight, and possible drug–polymer interactions) (3).

Different materials have been evaluated as carriers. The first SD generation involved the use of crystalline carries (4,5) and sugars (6), while for the second generation several types of hydrophilic polymers such as polyethylene glycols (7,8), polyvinylpyrrolidone (9,10) among others, have been assayed.

Recently, some studies evidenced that the dissolution rate may be improved using carriers, which posses surface activity or self-emulsifying properties. This third SD generation showed to be more efficient for bioavailability enhancement of poorly soluble drugs and SD thus obtained were more stable owed mainly to a reduction of drug recrystallization (11).

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 (12). Particularly, Poloxamer 188 (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 (13) and melt agglomeration process (14), since this material presents low melting point (about 52–57°C).

Regarding nominee drugs to be vehiculized in SDs, albendazole (ABZ), methyl [5-(propylthio)-1-H-benzimidazol-2yl] carbamate, is a benzimidazole (BZD) derivative with a broad

[1] Departamento de Farmacia, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Argentina CONICET.
[2] Laboratorio de Farmacología, Facultad de Ciencias Veterinarias, UNCPBA-Tandil (7000), Argentina CONICET.
[3] To whom correspondence should be addressed. (e-mail: sdpalma@fcq.unc.edu.ar)

spectrum of activity against human and animal helmint parasites (15,16,17).

Helmint infections are the most important cause of productivity loss in livestock and a major cause of human morbidity (18,19). BZD, imidazothiazoles (*i.e.* levamisole) and macrocyclic lactones (*i.e.* avermectins and milbemycins) are the main chemical groups used to control helmint infections (20).

The BZD comprise a family of related anthelmintic compounds and their metabolites/derivatives which are widely used in antiparasite therapy in both veterinary and human medicine. Febantel (FBT), a pro-benzimidazole (pro-BZD), fenbendazole, and mebendazole (MBZ) are the only methyl-carbamate BZDs approved for use in anthelmintic therapy in companion animals in Europe and the USA, although ABZ has also been approved for use in dogs and cats in other countries worldwide (21). Also, ABZ and MBZ are the conventional anthelmitics used in human medicine for treatment of several parasitic diseases. Several studies suggest that only limited absorption of BZD anthelmintics are achieved in cats, dogs and humans, owed mainly to their low dissolution rate on the gastric fluid. Consequently, these compounds have to be administrated at higher doses or as multiple doses in order to provide therapeutic concentrations and acceptable anthelmintic efficacy (22,23,24). Because of this particular behavior of BZD, the development of optimized pharmaceutical formulations remained as a challenging task.

ABZ belongs to type II biopharmaceutical classification system, with low aqueous solubility (0.01 mg/ml in water at 25°C) and high permeability (25).

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)

The unsatisfactory dissolution rate of albendazole is known to limit its absorption; therefore, it is poorly and erratically absorbed from the gastro-intestinal tract. Furthermore, it is well known that low solubility drugs offer only few formulation possibilities, limiting the administration routes (27).

Consequently, to overcome these drawbacks, the increasing of aqueous solubility and dissolution rate of ABZ is a relevant goal. In the same address, different strategies have been designed, such as vehiculization of ABZ in solid dispersions (28), cogrinding (27), cyclodextrins (30), and the synthesis of new analogs with higher solubility (30,31).

The aim of this work was to develop a novel based-ABZ formulation vehiculized in SD. P 188 was selected as hydrophilic carrier and a process for particulate SDs manufacture is proposed. The systems were characterized (X-ray powder (XRP) diffraction, scanning electron microscopy (SEM), and infrared spectroscopy (IR) spectroscopy) and some properties were evaluated (physical–chemical and mechanical properties, solubility, dissolution rate).

MATERIALS AND METHODS

Materials

For the preparation of solid dispersions the following materials were used: ABZ (Pharmaceutical grade, Parafarm, Buenos Aires, Argentina), and POLOXAMER 188 (BASF, Germany). All other reagents were of analytical grade.

Methods

Preparation of Solid Dispersions and Physical Mixtures

SDs were prepared by melting of ABZ and poloxamer (at different proportions, see Table I) in a water bath at 63°C. The mixtures were homogenized by stirring. The resulting homogenous preparations were rapidly cooled and pulverized. The 212-micron particle size fraction was obtained by sieving and kept in a screw-capped glass vial until use.

Physical mixtures were obtained by blending the components (212-micron particle size fraction) whose composition is detailed in Table I. 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 solid dispersions and their respective physical mixtures were also characterized using IR (FT; Nicolet 5SXC FT-IR Spectrometer) using KBr disks.

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.

Phase Solubility Studies

An excess of drug was suspended in a 3 ml 0.1 N HCl solution aliquot containing increasing concentrations of P 188 (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.

Table I. Solid Dispersions and Physical Mixtures Composition

Solid dispersion or physical mixture		Binary system	
		Albendazole	P 188
DS	PM	(% *w*/*w*)	
SD1	PM1	5	95
SD2	PM2	10	90
SD3	PM3	25	75
SD4	PM4	50	50

Dissolution Tests

Dissolution tests of powdered SDs and PMs 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 2 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 (Termo Evolution 300). 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 $p<0.05$.

Physical Mechanical Properties

Density and compressibility. To determine the density of the samples, the powder was gently poured into 10 cm^3 graduate cylinder. The bulk density (BD) was calculated as the ratio between weight (g) and volume (cm^3). To determine the ultimate tap density (TD), the cylinder was tapped over 1.0 in vertical drop, at 1-s interval, until no measurable change in volume was noticed. The compressibility of the powder was evaluated using the Hausner Ratio (HR) (32) and the Carr's Index according to the following equations: HR=TD/BD; $CI = (TD - BD)/TD \times 100$.

Angle of repose (α). The dynamic α for each mixture of powders was determined by the funnel method as described in literature (31).

Tablet compaction. The blend of powders (400 mg) was compressed for 5 s at 3,000, 3,500, 4,000, and 4,500 mPa in a hydraulic press (Delfabro, Argentina); 13.0 mm flat punches were used. Tablet hardness was measured on recently prepared tablets using an electronic hardness tester (AVIC, Argentina).

The physical mechanical properties were measured only for SD4 and PM4 taking into account the high doses used in human and veterinary medicine.

RESULTS AND DISCUSSION

XRD diffractograms for the systems ABZ/P188 are shown in Fig. 1. There are some signals (theta/2theta=ABZ: 6.96, 11.37, 17.91, 22.12, 24.58; P 188: 19.32, 23.46) that allowed us to identify each component.

Diffractograms from both physical mixtures and solid dispersions clearly showed that the signals assigned to each component were practically not changed. So, no interactions between them have been detected, although SD evidenced a slightly reduction in cristallinity when compared to PM, especially at high drug/carrier ratio (SD1).

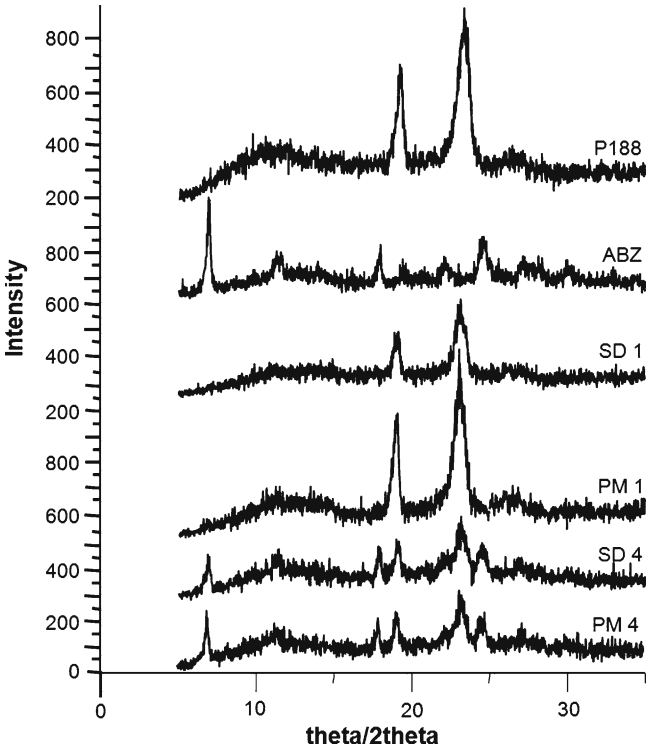

Fig. 1. XRD diffractograms

In Fig. (2a–b) is illustrated the spectrum for ABZ showing N-H stretching vibration at 3,324.94 cm^{-1} and bending vibration at 1,653.07 cm^{-1}. Such signals remain unaltered for SDs and PMs at the same wave numbers. In this way, the infrared spectra confirmed that there were not chemical interactions among ABZ and P 188 as consequence of their close contact in solid dispersions as well as in physical mixtures.

Scanning electron micrographs showed ABZ particles as irregular shaped crystalline solid with relative small size (2–10 μm) and rough surface (Fig. 3a). In Fig. 3b, smooth surfaced spherical P 188 particles, with an average size of about 200 μm, is observed. The variation in drug/surfactant polymer ratio seems not to affect the morphology and size distribution of the particles for SDs neither for PMs. A greater quantity of fines can be observed when compared with the formers.

As previously mentioned, P 188 possesses surfactant properties $\left(CMC = 1.25 \times 10^{-4}M\right)$ (34). Thus, some influence of this compound on ABZ dissolution rate should be expected. In this particular circumstance, the solubility of the drug increased linearly (from 0.72 to 2.12 mg/ml; Fig. 4) as the concentration of the surfactant polymer in the solution was increased from 0% to 20% (*w*/*v*). This means that ABZ aqueous solubility augmented almost threefold.

Although it is unlikely that the increase of ABZ solubility may be only attributed to a solubilization phenomenon, it was described that the wetting effect of the surfactant would be able to create a favorable micro-environment around the particles facilitating the dissolution process (35). The dissolution profiles of pure ABZ, SDs, and PMs are shown in Fig. 4 and summarized in Table II. From the analysis of such data, we observe that (1) the dissolution profiles indicated that ABZ incorporated in SD and PM was released very fast compared to ABZ alone; (2) the proportion of P 188 incorporated in SDs had a noticeable influence on ABZ

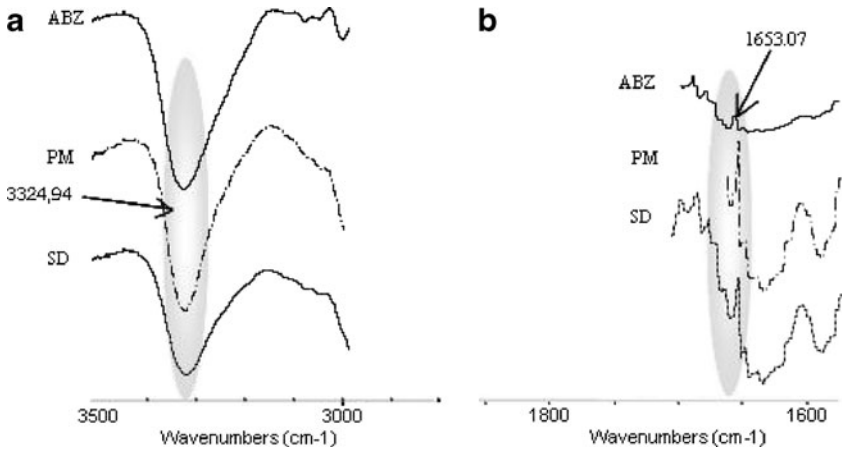

Fig. 2. FTIR for SDs and PMs. **a** Stretching vibration at 3324,94 cm^{-1} **b** bending vibration at 1653,07 cm^{-1}

release during the initial stage (5 min) of the dissolution process; (3) this behavior was not observed for PMs, being the amount of ABZ released very similar for all PMs (no significant differences were found for PMs, $p>0.05$), and (4) the dissolution rate was significantly higher for SDs than for PMs ($p>0.05$).

Although this increase of dissolution rate is usually observed at high surfactant polymer proportions, in this particular study we observed an opposite behavior for SDs as well as for PMs. In the case of SDs, systems with lower P 188 percentage (SD4, SD3) seemed to be more effective in increasing ABZ dissolution rate Fig. 5.

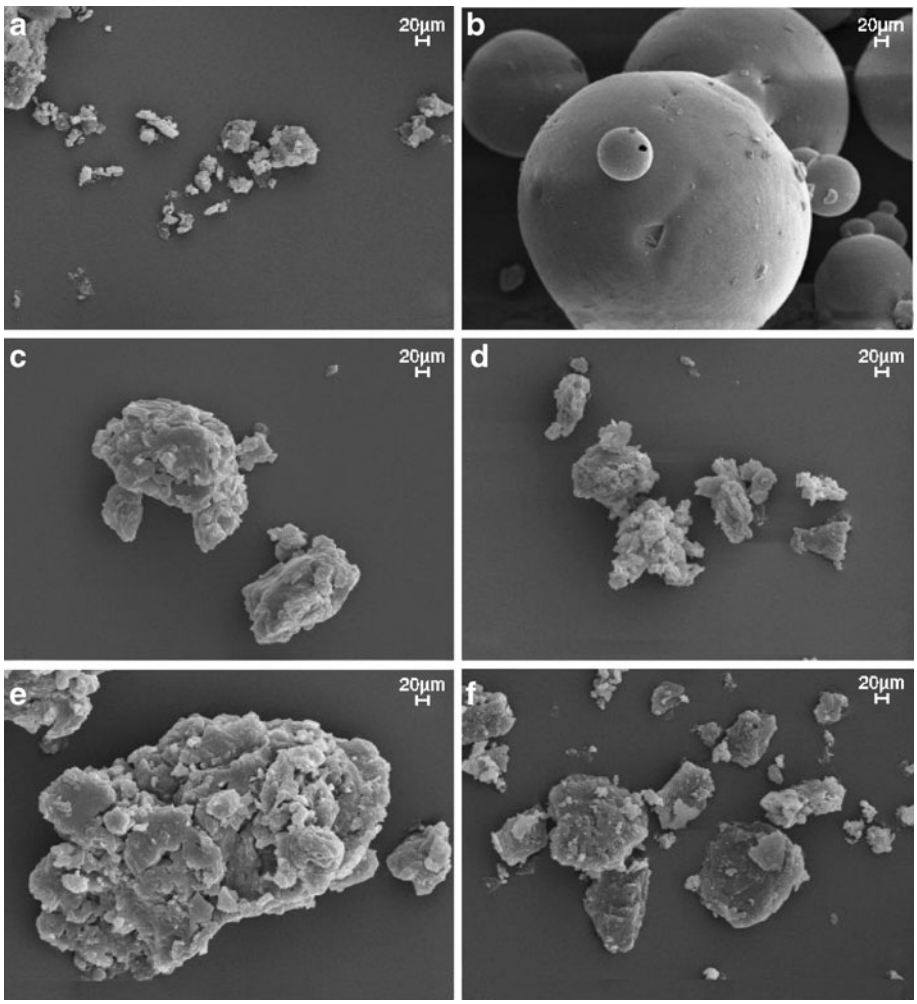

Fig. 3. SEM microphotographs. **a** ABZ 6000× **b** P 188 400×, **c** SD3 6000×, **d** PM3 6000×, **e** SD4 6000×, **f** PM4 6000×

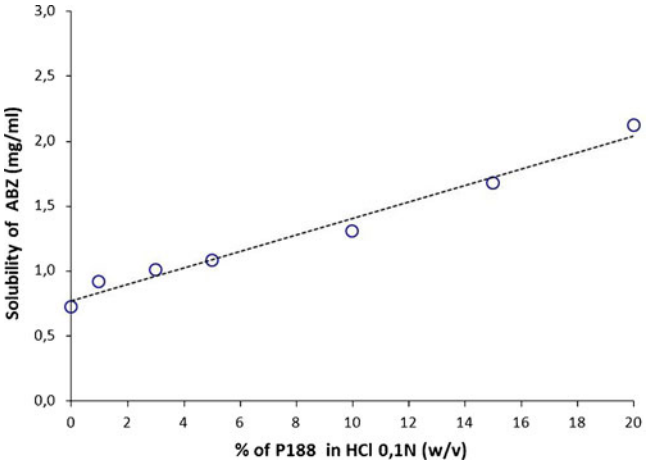

Fig. 4. ABZ solubility curve

A possible explanation of these results would be found analyzing the physical–chemical properties of P 188. It is well known that concentrated aqueous solutions of P 188 can form thermoreversible gels. The gelation mechanism of poloxamer solutions has been investigated extensively, although it is still under discussion (36).

At a sufficiently high concentration and temperature (higher than LCST, lower critical solution temperature), the Poloxamer micelles pack in an order that results in a transition of sol to a gel state called thermo-sensitive gel (37).

Numerous researchers have examined the thermo-sensitivity of P 188 gels with an interest in their potential use in various pharmaceutical applications taking into account that the surfactant solution is a free-flowing liquid at ambient temperature but gels at body temperature. Such a system would be easy to administer into a desired body cavity.

Specifically in this case, the thermosensibility of P 188 can help to explain the unusual dissolutions profiles. When SDs is placed in water at 37°C, gel formation on the microenvironment of the particle surface may be expected. In our opinion, the relative influence of drug dissolution/diffusion and the polymeric chain relaxation on the polymeric "gel layer" will define the release mechanism, according to the classical theory of drug release from matricial systems (38,39).

Aiming to clarify these observations, we calculated the diffusional coefficient n, whose numerical values are indicative of the delivery mechanism of the system according to the following equation (power law):

$$\mathbf{Mt/M_\infty = kt^n} \quad (1)$$

where M_t and M_∞ are the corresponding drug concentration at time t and $t=\infty$, respectively. k is a constant that include some device characteristics such as structure and geometry. The n values depend on device geometry and may be calculated by plotting the logarithmic form of Eq. 1 ($\log M_t/M_\infty$ *vs.* $\log t$, for $0.0 M_t/M_\infty 0.6$). This mathematical model may be applicable to film (tablets), cylinders, and spheres (38–40). In the case of spheroid particulates, n~0.43 indicates Fickian release (diffusionally controlled release) and n~0.85 indicates a purely relaxation controlled delivery which is referred as case II transport. Moreover, intermediate values indicate an anomalous behavior (non-Fickian kinetics corresponding to coupled diffusion/polymer relaxation) (38,39).

We assayed the applicability of power law to release data obtained from the dissolution test for SDs and PMs. In these assays, the results showed an excellent data correlation to this equation (r^2, Table II).

A value of n=0.9 for SD1 evidenced a mechanism of drug delivery ruled mainly by polymeric relaxation as consequence of polymer gelation. The opposite phenomenon was obtained for percentages of P 188 lower than 75%, where diffusion controlled mechanism (Fickian) was observed (n values for SD3 and SD4: 0.3). When analyzed SD2 (P 188 90%) some influence of polymeric chain relaxation process

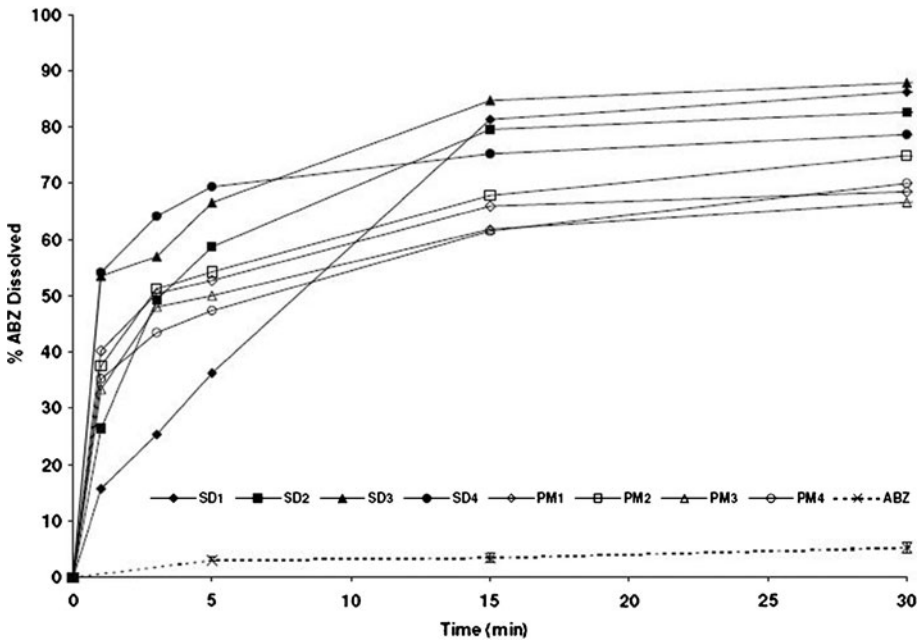

Fig. 5. Dissolution profiles

Table II. Amount of ABZ Dissolved and Diffusional Coefficient "n"

Percentage of ABZ disolved													
SD-P 188	1 min	3 min	5 min	15 min	n	r^2	PM-P 188	1 min	3 min	5 min	15 min	n	r^2
1	15.70	25.36	36.29	81.31	0.9	0.99	1	40.28	50.38	52.75	65.91	0.4	0.98
2	26.41	49.31	58.73	79.59	0.6	0.99	2	37.57	51.21	54.28	67.79	0.4	0.97
3	53.55	56.95	66.55	84.67	0.3	0.81	3	33.37	48.03	50.01	61,84	0.3	0.99
4	54.13	64.13	69.40	75.22	0.3	1.00	4	35.25	43.46	47.36	61.53	0.4	0.99
ABZ	–	–	3.01	3.44			ABZ	–	–	3.01	3.44		

was evidenced by an anomalous mechanism of drug release (n=0.6). On the other hand, the influence of P 188 percentages observed for PMs in the blends had negligible influence over the mechanism of drug release, since a similar value of n~0.4 was calculated for all PMs.

The first question arisen from these observations is why increasing of P 188 decrease the ABZ release, particularly at the beginning of the process. In the framework of this investigation, we could hypothesize that a higher efficiency in dissolution rate by decreasing the amount of the surfactant polymer are the result of a "different" physical state of ABZ in SDs. Thus, the drug is dispersed/dissolved into a P 188 melted solution. This means that the active compound ABZ is "entirely" dispersed in the solid material after crystallization. Consequently, any particle or molecule of drug is totally surrounded by the surfactant polymer which will build a homogeneous gel layer around the SD particle after thermal gelation in aqueous media. Therefore, as P 188 is increased, a thicker layer of polymeric film around the particle will be formed and polymeric chain relaxation process will rule kinetic drug release.

The second question is why SDs seem to be more effective as dissolution improver compared to PMs.

We infer that there is certain probability of a partial non-homogeneity in the randomized blend of ABZ and P 188 (PM). Consequently, some ABZ particles probably are not "perfectively" surrounded by P 188. In our opinion, this arrangement would allow the process of drug dissolution/diffusion across P 188 gel layer to regulate drug release kinetic. This fact would be the reason by which the variation of P 188 percentage in the PMs did not significantly affect the amount of ABZ released. Besides, and in agreement with this, ABZ release was lower in the case of PMs because the low wettability and solubility of isolated particles were not effectively overcome by the surfactant properties of P 188.

Another way to interpret the dissolution profiles is using the surfactants aggregation theories. The ethylene oxide (EO) and propylene oxide (PO) blocks in P 188 results in an amphiphilic structure, which has the properties to self-assemble into micelles or other aggregates in aqueous solution (41). Following this line, the hydrophobic core (PO block) could function as ABZ reservoir while the hydrophilic portion (EO) acts as interface between the aqueous medium and the drug. At relative low P 188 concentrations, the surfactant is present as monomer or monomolecular micelles and for this reason its effect acting of dissolution rate promoter can be attributed only to interfacial phenomena.

At higher concentration, these monomolecular micelles may associate to form aggregates of varying size and conformation, which have the ability to solubilize drugs and to increase the stability of solubilized agents with the consequent relative delay in the dissolution rate (42).

Finally, the physical–mechanical properties (flow, compressibility, and compactibility) have to be also evaluated if SDs are intended for solid dosage forms. Such properties (angle of repose, Carr Index, and Hausner Ratio) were measured and the results are shown in Table III.

There exist referential values for angle of repose, Hausner ratio and Carr index (43). In this way, values higher than 30º, 1.25, and 21, respectively, are indicatives of inadequate flow properties. From Table III, it is clear the differences between SD4 and PM4, where the former showed good properties whereas the later showed bad physical–mechanical properties.

For PM4 such properties were really unfavorable and this material could not be used for tablet manufacturing by direct compression processes.

SDs seem to be advantageous over PMs for manufacturing of acceptable quality solid dosage forms. Besides, tablet design would have to consider the influence of the "key properties" such as disintegration. Hence, rapid disintegration tablets would be the more appropriate formulation for ABZ SDs and they will be the new target of further studies.

Table III. Physical Mechanical Properties

	Angle of repose (°)	Carr' index	Hausner Ratio	Comp force (mPa)	Hardness (kg/cm2)
SD4	34.04±1.79	7.82	1.08	3,000	2.53±0.62
				3,500	4.93±0.51
				4,000	4.10±0.71
				4,500	5.03±1.31
PM4	56.99±1.41	33.86	1.51	3,000	4.08±0.47
				3,500	4.19±0.42
				4,000	4.56±0.61
				4,500	4.33±0.24
ABZ	52.62±1.11	34.78	1.54	–	–

CONCLUSIONS

The present study reveals that addition of P 188 as carrier in solid dispersions containing ABZ markedly improves its dissolution properties. This can be attributed to an increase on the dissolution surface area, in combination with improved wetting and ABZ solubilization as consequence of the dissolution of the carrier.

The proportion of P 188 incorporated in SDs had a noticeable influence on ABZ release during the initial stage (5 min) of the dissolution process. Nevertheless, this behavior was not observed for PMs being the amount of ABZ released was for all the PMs assayed. During the first 15 min of the test, the dissolution rate was significantly higher for SDs than for PMs ($p>0.05$). Systems with lower P 188 percentage (SD4, SD3; PM4, PM3) seemed to be more effective in increasing the ABZ dissolution rate.

SDs has shown to have better flow and compaction properties compared to PMs. Therefore, solid dispersions seem to be advantageous over physical mixtures for manufacturing of acceptable quality solid dosage forms.

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