Research Article

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Therapeutic Delivery

Dissolution profiles of fenbendazole from binary solid dispersions: a mathematical approach

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Aim: Understanding a drug dissolution process from solid dispersions (SD) to develop formulations with predictable *in vivo* performance. **Materials & methods:** Dissolution data of fenbendazole released from the SDs and the control physical mixtures were analyzed using the Lumped mathematical model to estimate the parameters of pharmaceutical relevance. **Results:** The fit data obtained by Lumped model showed that all SDs have a unique dissolution profile with an error of ±4.1% and an initial release rate 500-times higher than the pure drug, without incidence of drug/polymer ratio or polymer type. **Conclusion:** The Lumped model helped to understand that the main factor influencing the fenbendazole release was the type formulation (SD or physical mixture), regardless of the type or amount of polymer used.

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Keywords: dissolution efficiency • drug release • fenbendazole • initial release rate • lumped model • mathematical model • poloxamer • solid dispersions

In recent years, the number of drug candidates associated with low water solubility has increased dramatically [1–6], posing a significant challenge for the pharmaceutical industry. These types of compounds, categorized as class II by the biopharmaceutical classification system [7], have adequate membrane permeability, so the dissolution process becomes the rate-limiting step during oral absorption. That is why research groups have designed new technologies to overcome the problems associated with low bioavailability and erratic absorption [8], having a direct impact on both the rate and extent of absorption in the gastrointestinal tract [9–12].

For many years, the strategy of formulating active pharmaceutical ingredients using solid dispersions (SD) has been widely studied and has reached great interest due to its ability to modify the physicochemical properties of poorly water soluble compounds. This allows better drug dissolution rates and oral bioavailability, besides its use as a drug-repositioning strategy [13–15]. It has been deeply discussed how SD technology collaborates to improve drug dissolution rate and extent: from altering solid-state properties of the materials such as porosity and wettability to reducing particle size, even up to a molecular level, including the possibility of converting drug crystalline particles into an amorphous state [16,17]. When a SD is orally administered, the above mentioned advantages of this technology contribute to the formation of a saturated or supersaturated solution at the site of absorption, leading to the immediate dissolution of a fraction of the drug and its rapid absorption.

When the drug is part of a SD, its dissolution may be carrier mediated that forms a polymer-rich diffusion layer between the SD and the dissolution medium. The drug must permeate through this layer to reach the dissolution medium. In those cases, in which the permeability of the membrane is not a limitation of the absorption of the

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drug, the extension and maintenance of the state of supersaturation of the drug that can be achieved by the SD will be decisive for its bioavailability. In this sense, information on the incidence of formulation and process parameters on the *in vivo* performance of a SD can be obtained from thoughtfully designed dissolution tests at each stage of development [18].

The key factors in the development of SDs are driven by two considerations: biopharmaceutical relevance (in terms of greater solubility and dissolution) and commercial viability (in terms of scaling and shelf-life stability) [19]. This has led to evolution since the 1960s, when SDs were first reported [20], with four generations already described to the present [21] and numerous methods available for their preparation. However, there are still <30 commercialized formulations prepared by this technology [17]. In this context, research must continue to gain a deeper understanding of these systems and their drug release mechanisms, which will directly impact their practical use, helping to make more precise decisions during the formulation steps [22].

Mathematical models are a valuable tool to evaluate the processes involved in the dissolution of drugs, and in general, to devise and optimize the design of new systems. Knowing how to use the equations generated in mathematical modeling will allow us to understand the different factors that affect the dissolution kinetic process and how the stages of this phenomenon can vary and influence the efficacy or dosage of the drug. Therefore, the mathematical evaluation of the dissolution kinetics of the drug is an added value, which guarantees an optimal design of the drug delivery systems, as well as the knowledge of the mechanisms that operate in the dissolution process through experimental verification [23–25].

The mathematical models applied in the area of pharmaceutical science and reported in the scientific literature are diverse. Mathematical models can be of two different types: empirical or theoretical. An empirical model is nothing more than a mathematical equation capable of describing the experimental trend of a quantity of interest (e.g., drug concentration in blood against time) adopting appropriate values for its parameters. As this model is not a real mathematical metaphor for all the phenomena that concur with the experimental evidence, its parameters have no physical significance. For this reason, an empirical model does not imply an improvement in the theoretical knowledge of the physical phenomenon under study but allows a more objective comparison between the different sets of experimental data on based on variations in the model parameters. In this sense, Ritger and Peppas described a simple and empirical equation, suitable for adjusting the values corresponding to the first 60% of the release curve of a drug, which makes it possible to elucidate the drug release mechanism according to the value of the diffusional exponent that comes from statistical mathematics [26,27]. Another empirical equation that is widely used in reliability, statistics and survival analysis, is the Weibull model [28,29]. The Weibull parameter a_W defines the time scale of the process and b_W characterizes the shape of the profile. Values of $b_W > 1$ characterize sigmoid-shaped curves, while values of $b_W < 1$ fit concave profiles. The Weibull model fits the release data of different systems very well, but the parameters of the equation have not a physical meaning.

On the contrary, a theoretical model represents a possible mathematical schematization of all the concurrent phenomena to the experimental evidence to be studied. Consequently, as its parameters have physical meaning (e.g., the diffusion coefficient of the drug in a membrane), by configuring them appropriately, the model can be used to predict the experimental trend corresponding to the different conditions. The Higuchi model, which was initially conceived for plane geometries, but later extended to different geometries and porous systems [30], is one of the most successful theories that predict drug release from a stable monolithic system where only the diffusion step within the matrix is considered; with constant diffusion coefficient and slab geometry. Nevertheless, this model is far from solving the complex system found in more real systems.

However, due to the complexity of reality, it is sometimes impossible to have a theoretical model and the constitution of mixed theoretical-empirical models called semi-empirical is necessary. The so-called power law or Korsmeyer–Peppas equation describes the release of drugs from polymeric systems. Another model, which takes into account the coupled effect of Fick-type diffusion and the contribution of polymer relaxation, is the one proposed by Peppas–Sahlin [31]. Based on this, the Lumped model derived from a second-order kinetic expression [32,33], groups the main stages involved in the drug release or dissolution processes. This new model allows fitting all the experimental data from $t = 0$ to $t \rightarrow \infty$. The proposed mathematical model satisfactorily describes the processes in which the phenomena of diffusion and transfer to the dissolution medium occur, or when there is only an external transfer to a fluid medium in which the concentration of the drug is constantly increasing.

In our previous work, we reported the preparation of fenbendazole (FBZ) and poloxamer SDs together with the extensive characterization performed [34]. This work aims to analyze the dissolution data of FBZ to achieve a deep understanding of the *in vitro* dissolution properties. This is a decisive factor that allows selection between alternative

Table 1. Solid dispersions and physical mixtures of fenbendazole and poloxamer 188 and poloxamer 407 composition.

SD	PM	FBZ (w/w%)	P188 (w/w%)	SD	PM	FBZ (w/w%)	P407
SD11	PM11	5	95	SD21	PM21	5	95
SD12	PM12	10	90	SD22	PM22	10	90
SD13	PM13	25	75	SD23	PM23	25	75
SD14	PM14	50	50	SD24	PM24	50	50

FBZ: Fenbendazole; P188: Poloxamer 188; P407: Poloxamer 407; PM: Physical mixture; SD: Solid dispersion.

dosage forms for better formulation development. In this context, the Lumped mathematical model [29–32] was used that allowed us to understand and predict the behavior of SDs and calculate the parameters of pharmaceutical relevance such as the initial release rate (RR_0), the dissolution efficiency (DE) and the mean dissolution time (MDT) [35].

Materials & methods

Materials

FBZ (pharmaceutical grade) was kindly donated by Laboratorio Uruguay S.A. (LUSA, Montevideo, Uruguay). Poloxamer 188 (P188) and Poloxamer 407 (P407) were provided by BASF (Ludwigshafen, Germany). All other reagents were of analytical grade.

Preparation of SDs & dissolution tests

The preparation of FBZ SDs and physical mixtures (PM) were described in our previous work in conjunction with the dissolution tests of FBZ performed [34]. Briefly, FBZ SDs were prepared by dispersing the drug in the melted poloxamer at 65°C, using different proportions of P188 or P407. After dispersing the drug, the mixtures were rapidly cooled and pulverized. For the PMs, the appropriate amount of FBZ and poloxamer were mixed manually. Table 1 shows the different compositions of SDs and PMs analyzed in this work.

Data analysis

The data obtained from the dissolution tests were analyzed using the Lumped mathematical model [22–26]. To compare the different dissolution profiles, the RR_0, DE, dissolution time, sampling time and MDT were calculated. Likewise, the profiles were statistically compared using an independent model approach by calculating the difference factor (f_1) and similarity factor (f_2) between the profiles.

Results & discussion

Dissolution data analysis

An integral part of pharmaceutical development is drug dissolution testing, which enables a batch quality assessment to ensure product safety, efficacy and reproducibility. During the formulation development process, drug dissolution testing guides the design, optimization and selection of the leading formulation to be used for subsequent clinical studies. On the other hand, it is one of the indicator tests that are carried out in the stability studies to evaluate the useful life of the drug during the product development phase.

The dissolution of the drug is a relevant property of a pharmacotherapeutic system, being a prerequisite for the absorption of the active agent, playing a preponderant role in the rate and degree of bioavailability in the body.

To establish specific predetermined dissolution profiles, it is necessary to understand in depth the mass transport mechanisms involved in the drug dissolution process and to quantitatively predict the dissolution kinetics of the drug.

It is feasible, in some cases, to develop a mathematical expression that adequately describes the dependence of dissolution as a function of time. The application of this tool is very useful to predict the dissolution kinetics of systems before their actual development. This analytical solution can lead to several models that can be used in the design stage of simple and complex drug delivery devices, in addition to predicting the general behavior of the dissolution process.

In this sense, the Lumped model makes it possible to find a simple relationship between the released/dissolved mass and the release/dissolution rate as a function of time over the entire range of values obtained from a release/dissolution profile, as well as to calculate different parameters of pharmaceutical relevance. This model

makes it possible to adequately adjust the experimental data of immediate, sustained or extended-release dosage forms to predict the *in vitro* dissolution properties as well as comparisons between different formulations or design variables.

Under this framework, the *in vitro* dissolution of FBZ samples containing P188 and P407 were modeled using the Lumped model [33,36,37] recently developed and validated [32,38]. This semi-empirical model is based on second-order kinetics (Equation 1) where the driving force is the difference between the maximum amount of drug that the sample can release (M_∞)(t $\rightarrow \infty$) and the amount release at time t (M_t).

The pseudo-second-order kinetic expression for the drug-release rate is Equation 1.

$$\frac{dM_t}{dt} = k(M_\infty - M_t)^2 \quad \text{(Eq. 1)}$$

where the kinetic constant k considers all the steps involved in the release process.

The model is obtained considering the initial condition $M_t = 0$ at t = 0 and allows to calculate M_∞ (Equation 2).

$$M_t = \frac{kM_\infty^2 t}{1 + kM_\infty t} \quad \text{(Eq. 2)}$$

The Lumped model is represented in Equation 3, and expresses the percentage of drug release as a function of time. Considering that k and M_∞ are constant

$$M_t\% = \frac{at}{1 + bt} \quad \text{(Eq. 3)}$$

where $M_t\%$ is referred to M_∞ according to Equation 4.

$$M_t\% = \frac{M_t 100}{M_\infty} \quad \text{(Eq. 4)}$$

From Equation 3 it follows that the parameters a and b have no physical meaning and they are expressed by Equations 5 & 6, respectively.

$$a = kM_\infty^2 \quad \text{(Eq. 5)}$$

$$b = kM_\infty \quad \text{(Eq. 6)}$$

Furthermore, from Equation 3 it is possible to calculate the release rate ($RR\%$) which is given by Equation 7:

$$RR\% = \frac{dM_t\%}{dt} = \frac{a}{(1 + bt)^2} \quad \text{(Eq. 7)}$$

Therefore, the initial release rate ($RR_0\%$) is given by Equation 8.

$$RR_0\% = \frac{dM_t\%}{dt}|_{t=0} = a \quad \text{(Eq. 8)}$$

The Lumped model parameters in percent amount of drug release, under this condition (Equation 3), must obey the Equation 9,

$$\frac{a}{b} = 100 \quad \text{(Eq. 9)}$$

which is an interesting internal consistency test. Table 2 shows the model parameters a and b, M_∞, correlation coefficient (R^2), and standard deviation ($s\%$) calculated for the SD and PM samples studied, with P188 and P407, respectively. The $s\%$ is defined by Equation 10,

$$s = \sqrt{\frac{(SSD)}{(n-1)}} \quad \text{(Eq. 10)}$$

where SSD is the sum of the square of the difference between the experimental value and that calculated by the model, and n is the number of samples taken in an experimental run.

We use an $s\%$ because it is calculated on values in percentages.

As shown in Table 3, the SD and PM samples with P188 represented the same release process, as well as the samples containing P407. Therefore, the release profile for the SD and PM samples in each poloxamer could be

Table 2. Parameters of the kinetic model.

Carrier polymer	Sample	Lumped model parameter				
		a (%/min)	*b* (min^{-1})	M_∞ (mg)	R^2	*s*%
P188	SD11	20.344	0.2034	5.00	0.9981	1.43
	SD12	17.238	0.1724	4.68	0.9964	1.96
	SD13	25.089	0.2509	4.79	0.9993	0.84
	SD14	22.324	0.2232	5.54	0.9968	1.80
	Average profile	21.249	0.2125	–	–	–
	PM11	10.011	0.1001	3.60	0.9972	1.70
	PM12	9.940	0.0994	3.37	0.9960	2.04
	PM13	8.933	0.0893	3.78	0.9929	2.69
	PM14	6.979	0.0698	5.46	0.9944	2.43
	Average profile	8.966	0.0897	–	–	–
P407	SD21	28.939	0.2894	4.87	0.9990	0.9
	SD22	29.129	0.2903	4.44	0.9979	1.48
	SD23	21.068	0.2107	4.59	0.9995	0.68
	SD24	32.435	0.3844	4.54	0.9931	2.63
	Average profile	29.393	0.2939	–	–	–
	PM21	12.020	0.1202	3.62	0.9954	2.19
	PM22	10.004	0.1012	3.15	0.9966	1.86
	PM23	10.002	0.1000	3.08	0.9914	2.94
	PM24	8.061	0.0806	3.53	0.9902	3.12
	Average profile	10.022	0.1005	–	–	–

a and *b*: Lumped model parameters; M_∞: Maximum amount of drug that the sample can release; P188: Poloxamer 188; P407: Poloxamer 407; PM: Physical mixture; R^2: Correlation coefficient; *s*%: Standard deviation; SD: Solid dispersion.

Table 3. Difference and similarity factor of solid dispersion and physical mixture samples based on the poloxamer 188 and poloxamer 407 as carrier vehicles.

Carrier polymer	Sample	Factor	
		f_1	f_2
P188	SD11	1.030	87.82
	SD12	4.295	70.06
	SD13	3.094	78.02
	SD14	1.140	93.12
	PM11	3.050	83.47
	PM12	2.596	85.62
	PM13	1.352	86.06
	PM14	7.079	74.05
P407	SD21	0.258	95.84
	SD22	0.146	99.79
	SD23	5.705	63.19
	SD24	4.104	69.26
	PM21	5.008	72.63
	PM22	0.728	96.86
	PM23	0.182	99.75
	PM24	5.211	69.71

f_1: Difference factor; f_2: Similarity factor; P188: Poloxamer 188; P407: Poloxamer 407; PM: Physical mixture; SD: Solid dispersion.

represented by the Lumped model with the average parameters depicted in Table 2. Note that the percentage of FBZ in the SD and PM samples is 5, 10, 25 and 50% w/w for both poloxamers.

That is, the FBZ concentration in the samples varies almost tenfold, nevertheless, all samples, according to US FDA and European Medicines Agency criteria, presented the same dissolution profile. In addition, when

Table 4. Comparison of the average release profile of solid dispersions and physical mixtures between samples with poloxamer 188 and poloxamer 407 and parameters of the general model equation.

Sample	Factor		Lumped model parameter	
	f_1	f_2	a_G (%/min)	b_G (min^{-1})
SD	5.550	63.75	25.321	0.2532
PM	2.787	83.14	9.494	0.0951

a_G and b_G: Parameters of the general model equation; f_1: Difference factor; f_2: Similarity factor; P188: Poloxamer 188; P407: Poloxamer 407; PM: Physical mixture; SD: Solid dispersion.

comparing the average profiles of the percentage amount released for the SD and PM samples in any of the poloxamers, the f_1 and f_2 shown in Table 4, were obtained.

Figures 1 & 2 depict the experimental data (symbols) and the Lumped model fit (solid line) of the SD and PM samples with P188 and P407, respectively. Figure 3 shows the goodness of fit of the model.

Furthermore, Figure 4 shows the ratio (M_∞/total amount loaded [M_o]) as a function of the compositions of the samples. As can be seen, the average maximum percentage amount of FBZ released (M_∞ 100/M_o) by the SD and PM samples, referred to as the M_o, were 95.3 and 73% for the samples containing P188. While for the SD and PM samples prepared with P407, these values were 91.6 and 66.7%, respectively.

The fit was quite good with R^2 better than 0.99 and an s% of <2% for the SD samples and 3% for the PM samples. Furthermore, the results showed that the percentage amount released for the SD and the PM samples could be represented by a single curve (average). Although the amount of drug loaded to the system was 5 mg, the samples have 5, 10, 25 and 50% w/w of FBZ in poloxamer. That is, the FBZ concentration in the samples varies almost tenfold, but all the samples presented the same dissolution profile.

To consider that all profile corresponded to a single equation (average), the model-independent statistical analysis approaches were used to validate the significance of the difference and similarity between profiles by calculating the f_1 and f_2 using Equation 11 & 12, respectively.

$$f_1 = \frac{\sum_1^n |R_i - D_i|}{\sum_1^n R_i} 100 \qquad \text{(Eq. 11)}$$

Where R_i and D_i are the percentage of drug dissolved of the reference and test samples at the time i and n is the number of experimental samples taken during the entire release test.

$$f_2 = 50 \log \left\{ \left[1 + \left(\frac{1}{n} \right) \sum_1^n (R_i - D_i)^2 \right]^{-0.5} 100 \right\} \qquad \text{(Eq. 12)}$$

The Center for Drug Evaluation and Research of the FDA and the European Medicines Agency have established as criteria that two or more dissolution profiles are similar when the values of f_1 are <15 and the values of f_2 are >50. Table 3 shows the values of both factors taking as reference the data obtained with the value of the parameters of Table 2 for the average profile. According to the established criteria, it can be concluded that the profiles of the different SD and PM samples for each poloxamer studied were indeed similar and the differences were not significant. Therefore, both formulations could be represented by the average equation for each polymer.

However, comparing the average profile equations for the amount released by the SD samples in P188 and P407, and those corresponding to the PM samples in both poloxamers; the f_1 and f_2 values depicted in Table 4, were found.

According to the criteria established for f_1 and f_2 values, the FBZ release profiles of the SD samples with P188 and P407 were similar and the difference was not significant. Therefore, a general Lumped model equation was able to predict the FBZ% released by all SD samples, regardless of the drug/polymer ratio and poloxamer type. In the same way, a general Lumped model equation for the PM samples was obtained. The parameters of the general model equation for the SD and PM samples are depicted in Table 4.

These general Lumped model equations obtained to predict the FBZ release amount with an error of ± 4.1% for SD samples and ± 9% for PM samples.

Comparing the general release profile of the SD and PM samples, the values of f_1 and f_2 obtained were 19.678 and 38.47, respectively. Therefore, these profiles did not meet the criteria indicated above, and consequently, were considered not similar, representing two different release phenomena. Figure 5 shows the general profiles of the

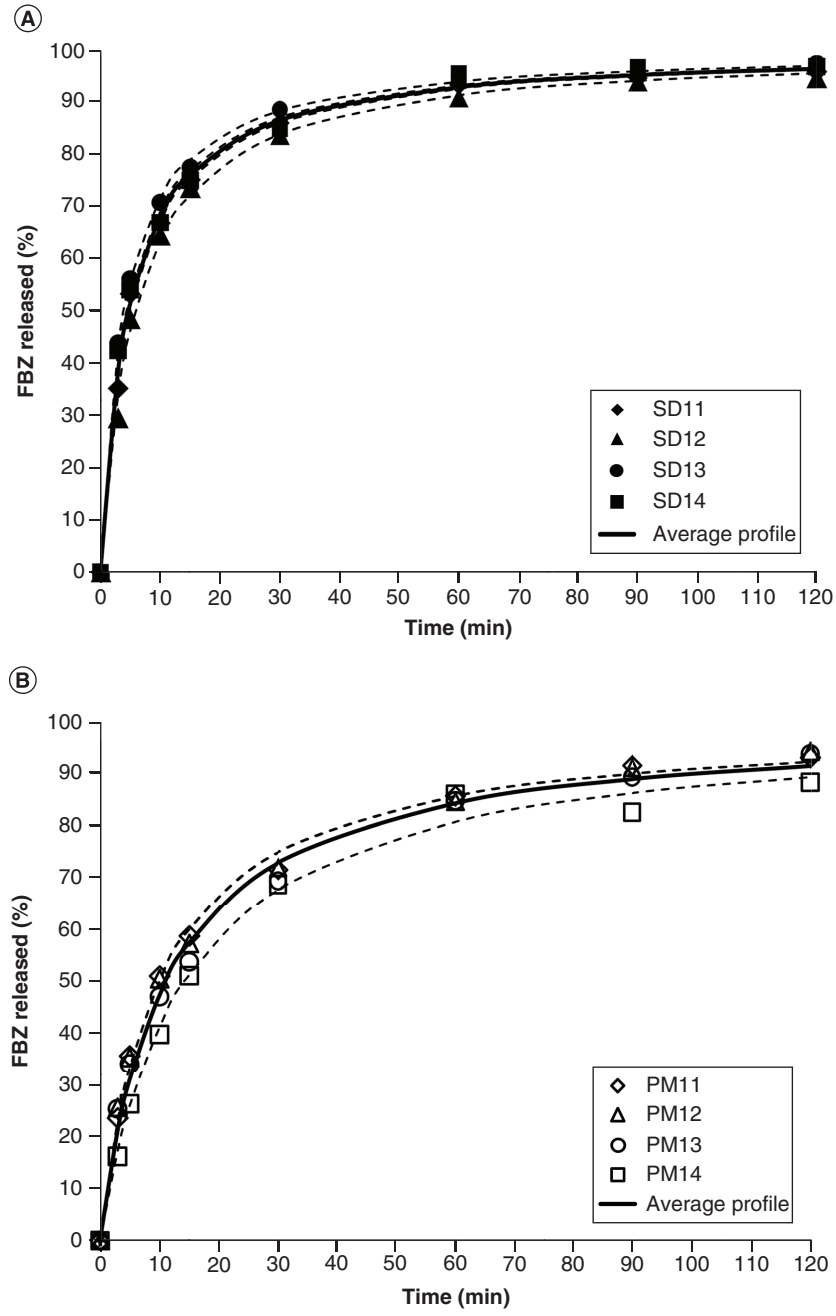

Figure 1. Fenbendazole release profiles from (A) solid dispersions and (B) physical mixtures, using polymer poloxamer 188 as a carrier. Error bars have been omitted for clarity purposes.
FBZ: Fenbendazole.

Lumped model for the SD and PM samples. In Figure 5, the experimental data (points) of all the samples with P188 and P407, are indicated.

The experimental dissolution test with pure FBZ showed that the amount of drug released after 60 min was 2.9%. Up to 15 min, the presence of FBZ was detected but not is quantifiable. The results showed that the amount released at 60 min was increased 30-times by the SDs with poloxamer compared with pure FBZ, regardless of the drug/carrier ratio and the type of poloxamer. Making the same comparison, the PM samples increased the release of the drug by 20-times. It was also possible to compare the RR_0. Considering a linear relationship of the amount released by the pure FBZ (zero-order kinetics mechanism), the RR_0 of the pure drug was 0.05%/min. Then, the

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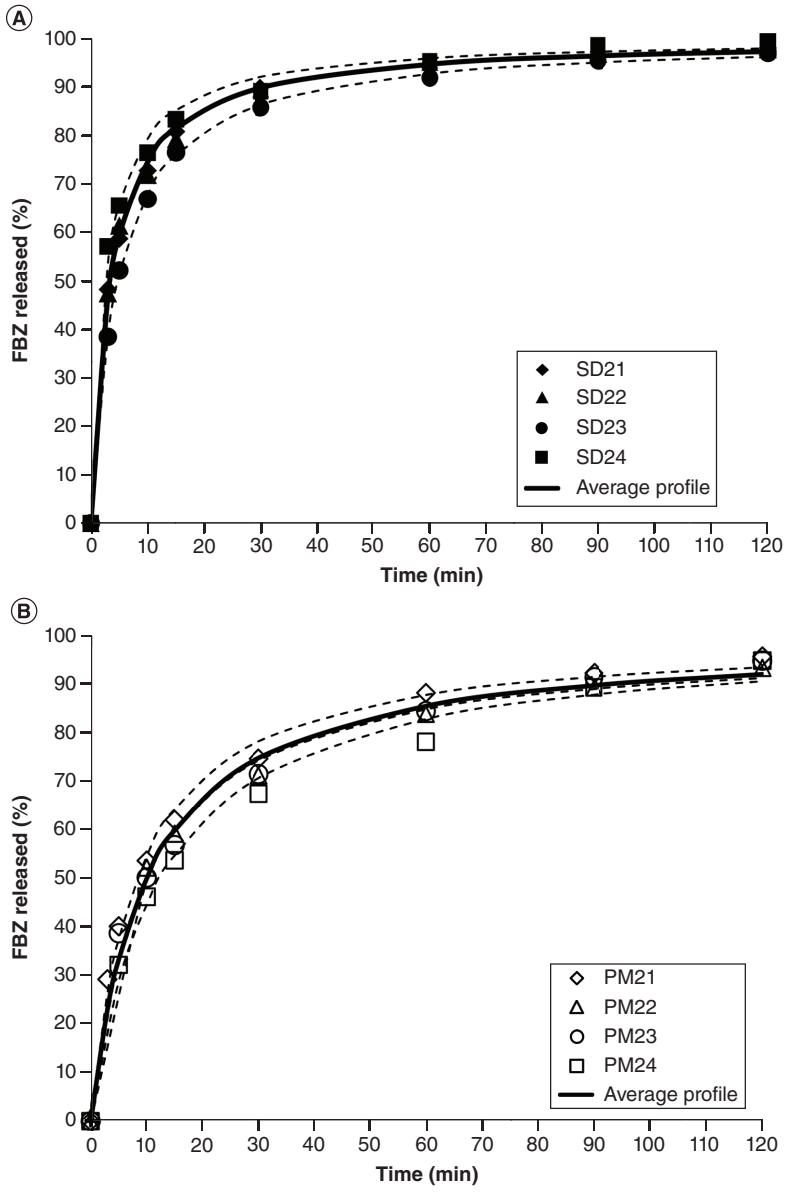

Figure 2. Fenbendazole release profiles from (A) solid dispersions and (B) physical mixtures, using polymer poloxamer 407 as a carrier. Error bars have been omitted for clarity purposes.
FBZ: Fenbendazole.

RR_0 of the SD samples was 500-times greater than that of the pure drug, while the RR_0 of the PM samples was 200-times faster than the RR_0 of the pure FBZ. Thus, poloxamer polymers facilitate the release of FBZ. All SD samples showed an improved release amount of FBZ, compared with the corresponding PM.

To compare the behavior of the SD and PM samples, the characteristic parameters of the samples such as the time point $t_{X\%}$ (min), the *DE* (%), the *MDT* (min) and the time sampling t_F (%) were calculated. The $t_{X\%}$ time point is the time required to reach X% drug release. In general, it is estimated at X% = 80%. The *DE* is defined as the surface area under the profile up to a given end time t_e divided by the total surface area of the rectangle 100 t_e. The *MDT* is the first moment of the profile up to the $T_{X\%}$ time point. Finally, the sampling time t_F is the percentage of drug released for each sample at a given time.

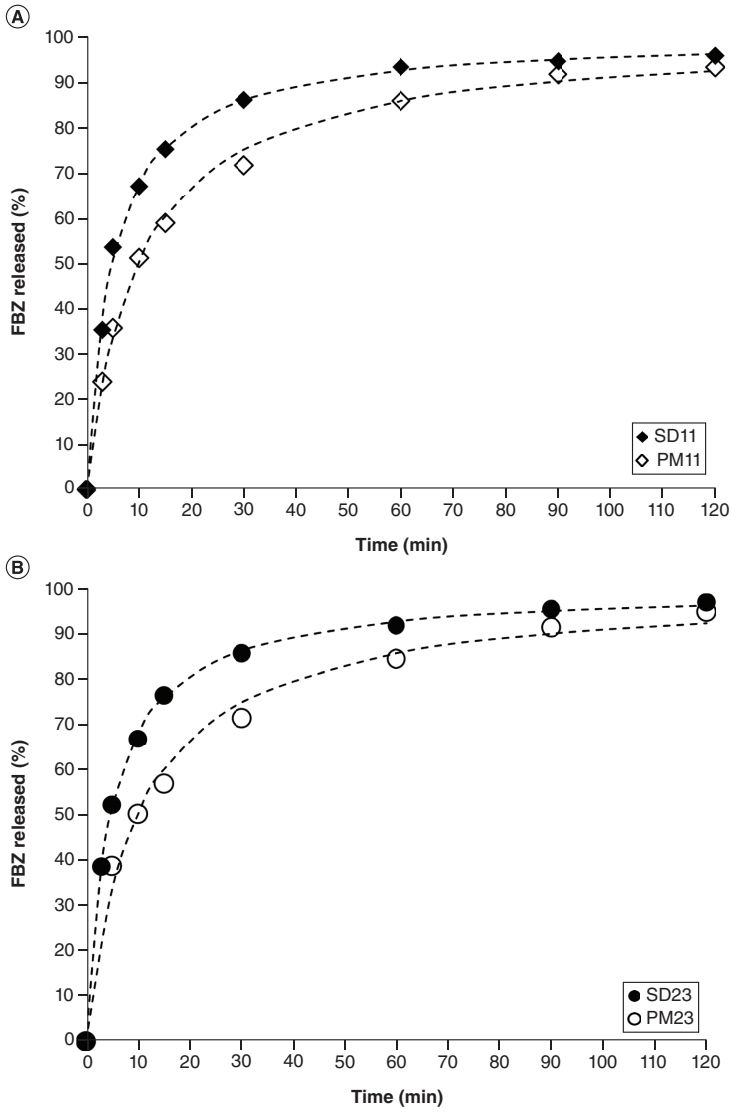

Figure 3. Example of fenbendazole release data fit using the Lumped model applied to samples based on polymer (A) poloxamer 188 and (B) poloxamer 407. Error bars have been omitted for clarity purposes.
FBZ: Fenbendazole.

According to the Lumped model, each of the characteristic parameters of the profile is calculated by Equations 13, 14 & 15.

$$t_{X\%} = \frac{X\%}{(a_G - b_G * X\%)} \quad \text{(Eq. 13)}$$

$$DE = \left(\frac{a_G}{b_G^2}\right) \frac{[b_G * t_e - \ln(1 + b_G * t_e)]}{t_e * 100} * 100 \quad \text{(Eq. 14)}$$

$$MDT = \frac{a_G}{b_G^2} \frac{[ln(1 + b_G * t_{X\%}) - \frac{b_G * t_{X\%}}{(1+b_G * t_{X\%})}]}{M\%(t_{X\%})} \quad \text{(Eq. 15)}$$

While t_F is the value of $M_t\%$ of the corresponding average profile equation at the final time of the experiment run.

The values of the characteristic parameters obtained from the general profiles of the SDs and PMs are reported in Table 5.

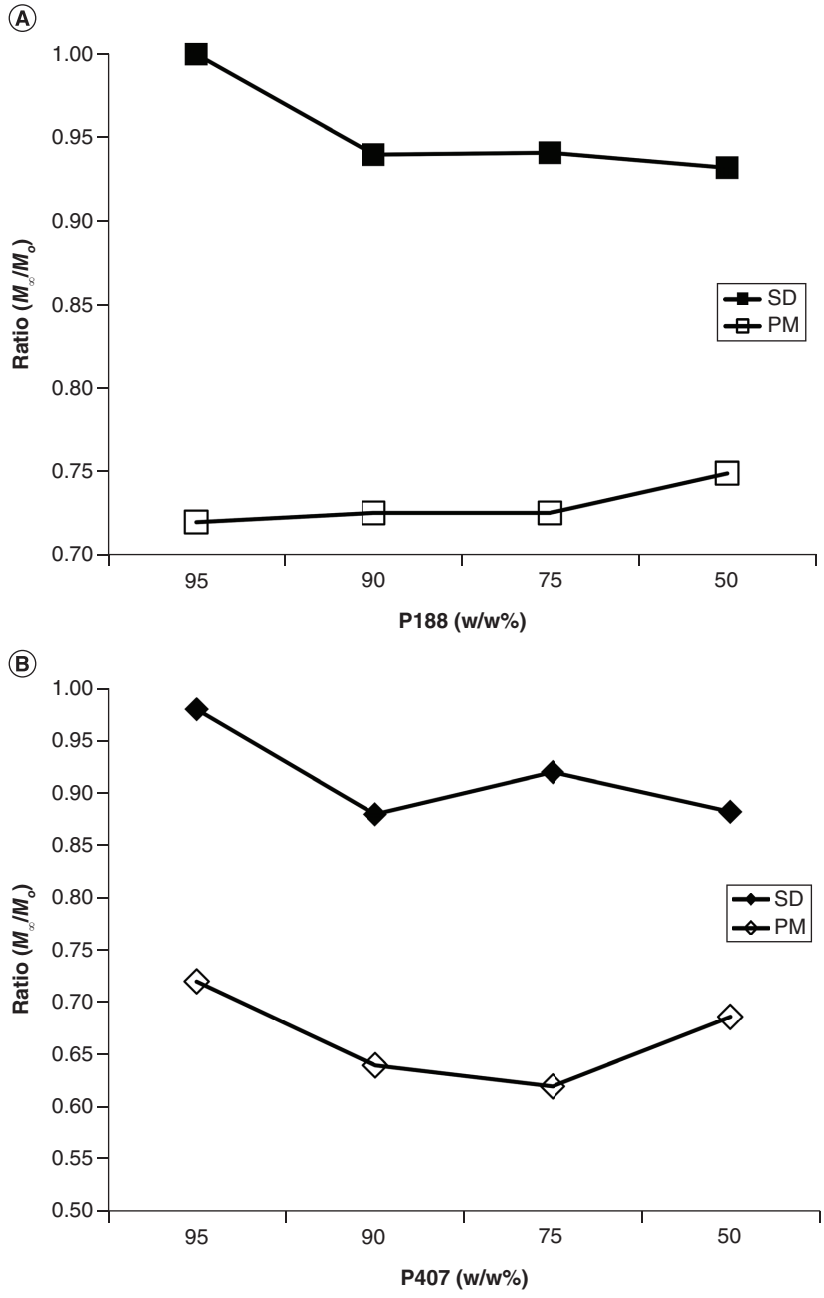

Figure 4. The ratio (maximum amount of drug that the sample can release/sample dose of fenbendazole changes as a function of the compositions of the samples of polymer (A) poloxamer 188 and (B) poloxamer 407.FBZ: Fenbendazole; M_o: Total amount loaded; M_∞: Maximum amount of drug that the sample can release.

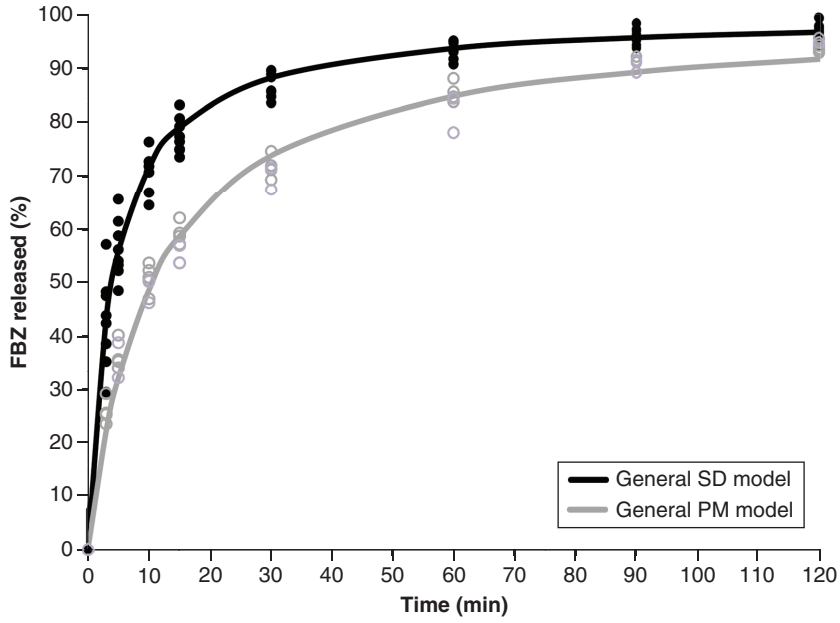

Figure 5. Fitting of the general Lumped model including all the points taken from the release profiles of the samples evaluated as solid dispersions and physical mixtures.
FBZ: Fenbendazole; PM: Physical mixture; SD: Solid dispersion.

Table 5. Characteristic parameters and initial release rate of solid dispersions and physical mixtures.

Sample	$t_{80\%}$ (min)	*DE* (%)	*MDT* (min)	t_{120} (%)	RR_0 (%/min)
SD	15.79	88.66	3.99	96.81	25.32
PM	42.40	77.80	10.69	91.80	9.49

DE: Dissolution efficiency at 120 min; M_∞: Maximum amount of drug that the sample can release; *MDT*: Mean dissolution time; PM: Physical mixture; RR_0: Initial release rate; SD: Solid dispersion; $t_{80\%}$: Time point at 80%, referred to M_∞; t_{120} (%): % Released at 120 min referred to M_∞.

When comparing RR_0, the SD samples were 2.5-times faster than the PMs. No significant influence of the FBZ/poloxamer ratio on RR_0 was found.

As indicated above, the R^2 and *s%* values were indicative of the goodness of fit of the Lumped model.

The values of the f_1 and f_2 of the samples with P188 and those with P407 validated the consideration that the profiles were represented by a general profile equation for the SD or PM samples.

Note that the profiles, as well as the characteristic parameters, have taken M_∞ as a reference, not the total drug loading in the sample. However, considering the maximum percentage of release referred to the total dose of the drug in the sample is not complicated, since it is easy to obtain through the value of the ratio (M_∞/M_o). The general ratio (M_∞/M_o) for the SD and PM samples was 0.935 ± 0.034 and 0.698 ± 0.025, respectively, regardless of the drug/polymer ratio and the type of poloxamer.

The internal consistency of the model can be verified using the relation (a/b) that must be equal to 100. Observing the values of a and b in Tables 2 & 4, the relation previously indicated was perfectly obeyed.

The main factor influencing the release rate of FBZ was the type of formulation (SD or PM). On the other hand, the type of poloxamer used (P188 or P407) and the drug/polymer ratio did not affect it significantly. Finally, Lumped's mathematical model could become an important tool for designing pharmaceutical formulations by evaluating the dissolution/release process of the drug *in vitro*, contributing to the optimal design of new systems. The Lumped model allowed the determination of important pharmaceutical parameters (e.g., *MDT*, *DE* and RR_0) with an excellent fit of the experimental drug release data.

Conclusion

In this work, we tried to elucidate the mechanisms involved in the dissolution process of FBZ, a drug with limited water solubility. This could help overcome the recognized problems of formulating this kind of drugs and its related

issues as the poor bioavailability. This was verified under the experimental conditions in which the dissolution tests of the different formulations were carried out; determining that for a time of 90 min only approximately 6% of the pure drug was dissolved.

The equations derived from the Lumped model can help to understand the different factors that affect the dissolution rate, as well as the variations in dissolution behavior that could influence the efficiency or the therapeutic regimen of patients. The mathematical equations were developed to allow the quantitative interpretation of the values obtained from the FBZ dissolution test. The main factor influencing the release rate of the drug was the type of FBZ formulation (SD or PM), regardless of the type of poloxamer used (P188 or P407) and the drug/polymer ratio.

FBZ SDs using P188 or P407 as a carrier represent a promising alternative to confer an apparent advantage in solubility and dissolution rate. This would facilitate development at an early stage, to achieve a potentially scalable optimal formulation with adequate dissolution profiles suitable for the oral route.

Future perspective

In the coming years, *in vivo* studies of the formulations developed would be necessary to complement the information obtained in these studies. In this sense, future pharmacokinetic and efficacy studies would be decisive to choose the most suitable formulation for FBZ and other similar benzimidazole carbamates, and thus, to develop new commercially SD-based products. Additionally, the preparation of stable SDs using novel vehicles to avoid recrystallization, together with the design to obtain adequate drug dissolution kinetics will allow satisfying the pre-established requirements of the patient.

Summary points

- Solid dispersion (SD) technology statistically improved the dissolution rate of a biopharmaceutical classification system class II compound as fenbendazole (FBZ).
- The equations derived from the Lumped model helped to understand the different factors that affect the dissolution rate of the prepared formulations.
- The mathematical equations developed allowed the quantitative interpretation of the values obtained from the FBZ dissolution test.
- The obtained correlation coefficient and standard error values showed a good fitting with the Lumped model.
- The main factor influencing the release rate of FBZ was the type of formulation (SD or physical mixture).
- The type of poloxamer used (poloxamer 188 or poloxamer 407) and the drug/polymer ratio does not significantly affect FBZ release.
- The Lumped model allows the determination of important pharmaceutical parameters (e.g., mean dissolution time, dissolution efficiency and initial release rate) with an excellent fit of the experimental drug release data.
- A general Lumped model equation can predict the FBZ% released by SD or physical mixture samples, irrespective of the drug/polymer ratio and poloxamer type.

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