BIOPHARMACY

DETERMINATION AND MODELLING OF *IN VITRO* RELEASE KINETICS OF MEBENDAZOLE IN SIMULATED INTESTINAL FLUID FROM SOLID DISPERSION FORMULATIONS AS INFINITE RESERVOIRS

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Abstract: Mebendazole (MBZ) is a wide-spectrum antihelmintic drug and, more recently, has proven to be active in various types of cancer. In both cases, its efficacy is limited by insufficient bioavailability due to its very low solubility and inadequate release kinetics. This paper presents the preparation and *in vitro* availability of solid dispersions of MBZ and polyethylene glycol (PEG) 6000, which were combined with Ludiflash as a disintegrant and croscarmellose as a superdisintegrant in tablets, by direct compression processing technology. The release was determined in simulated intestinal fluid, and the kinetics were analyzed using square root, Noyes-Whitney, Peppas, and Weibull models. An improvement of release in a simulated intestinal medium has been achieved due to the formation of solid dispersion and presence of disintegrants, leading to tablet disintegration in about 15 min in the case of 1 : 1 solid dispersion and between 30 min and 1 h in the case of 1 : 2.5 solid dispersion. The amount of MBZ released was approximately 60% in 3 h for the 1 : 1 dispersion, 100% for the 1 : 2.5 dispersion, and only 6% for the tablets without PEG. The release was described well and unitary by square root laws in both pre- and post-disintegration phases. The square root model was argued to describe the release from an "infinite reservoir" (i.e., a generalized square root law, similar to those applied in heat transfer) and not released under the conditions of the Higuchi model.

Keywords: Mebendazole, solid dispersions, release kinetics, square root models, infinite reservoir

Mebendazole (MBZ) is known mainly as a broad-spectrum antihelmintic drug that produces high cure rates in infestations by *Ascaris*, threadworms, hookworms, and whipworms. Human echinococcosis is caused by the larval form of the parasite *Echinococcus granulosus* or *E. multilocularis*, which enter the blood and contaminate internal organs (1, 2). The main treatment is surgical, but this doesn't solve the problem of secondary alveolar echinococcosis. Thus, in addition, continuous treat-

ment with MBZ for at least 2 years and patient monitoring for 10 years are necessary (3). In veterinary medicine, MBZ is administered orally to horses at a target dose of 8.8 mg/kg body weight and to sheep and goats at a target dose of 15 mg/kg body weight, as presented in the European Medicines Agency (EMA) report (4). MBZ has also been used in game birds, pigs, deer, poultry, and cattle. More recently, MBZ has been shown to be active in various types of cancer, including non-small cell lung cancer (5),

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adrenocortical carcinoma (6), colon cancer (7), gastric tumors (8), and brain tumors (9).

The development of MBZ for indications requiring systemic availability remains to be elucidated (10). The low and insufficient bioavailability attributed to the poor water solubility of drugs, especially for those of biopharmaceutical classification system class II (which exhibit low solubility but high permeability), can be improved by increasing the solubility or the dissolution rate of the active pharmaceutical ingredients in gastrointestinal fluids. Several practical methods have been applied to increase the solubility and availability of MBZ, such as preparation of solid dispersions (11, 12), crystal engineering (13), self-microemulsifying drug delivery systems (14), micronization (15), N-substitution (10), etc. Many published research papers suggest that the bioavailability of MBZ is indeed an important issue. The problem of predicting bioavailability following *in vitro* and *in vivo* correlations is not yet satisfactorily resolved (16, 17), as well as problems connected with the bioequivalence and therapeutic equivalence of different MBZ formulations (18, 19). Besides, following the new pharmacodynamic effects highlighted in various types of cancer, it is clear that the management of release kinetics is necessary to ensure optimal concentrations at the site of action and the balance between the efficacy and safety of treatment with MBZ.

The objectives of this study were to prepare tablets based on solid dispersions of MBZ with polyethylene glycol (PEG) 6000 by melting method, to evaluate the release kinetics in a fasting state simulated intestinal fluid (FaSSIF), and to find a mathematical model appropriate for the analysis of experimental data. An insufficient and low release leads to low bioavailability. A rapid and massive release leads to precipitation and highly variable bioavailability.

The second objective was an analysis of the applicability of the models in the correlation between phenomenological conditions of the processes and initial and boundary conditions of the mathematical equations of the models.

EXPERIMENTAL

Materials

Mebendazole was a gift sample from the Iraqi Pharmaceutical Industry (IPI) Company (Baghdad, Iraq). Polyethylene glycol 6000 was purchased from Merck Schuchardt - Germany, AC-DI-SOL® Crosscarmellose from FMC Biopolymers, and Ludiflash from BASF. HPLC gradient grade ace-

tonitrile and methanol were purchased from Merck KGaA (Darmstadt, Germany), whereas HPLC grade methyl tert-butyl ether was acquired from Sigma-Aldrich (Taufkirchen, Germany). HPLC grade tri-fluoroacetic acid was obtained from Honeywell-Fluka (Buchs, Switzerland). Physiological compounds - granular Lecithin, (Acros Organics, Geel, Belgium) and sodium taurocholate min 98% (Carl Roth, Karlsruhe, Germany) were used in the preparation of the simulated intestinal fluids. Ultrapure water (resistivity $18.2 \text{ M}\Omega \cdot \text{cm}$ at 25°C , TOC < 5ppb) was obtained from a Milli-Q (Millipore, Milford, MA, USA) water purification system. All other reagents were of analytical grade, purchased from different commercial suppliers, and used without further purification.

Preparation of mebendazole solid dispersions (MSD)

In order to evaluate the effect of the ratio between active substance and polymer on mebendazole release kinetics, formulations based on two different ratios between MBZ and PEG, namely 1 : 1 and 1 : 2.5, respectively, were prepared and evaluated. The preparation of solid dispersions was carried out using the melting method, and included the following steps:

- obtaining of the powder containing active substance and polymer (PEG 6000) in different mass ratios (1 : 1 and 1 : 2.5 respectively);
- heating of the mixture at a temperature of about $70 \pm 2^\circ\text{C}$ (approximately 10°C higher than the melting point of the polymer) for 5 min under continuous stirring;
- rapid solidification of the melted mixture on an ice bath, followed by maintaining the resulted solid mass in a freezer at -20°C for 24 h;
- milling of the obtained solid mass using a hammer mill with a forward-oriented knife and the sifting of resulted powders through a 1.00 mm sieve.

Particles of less than 1 mm in diameter were separated from those with a diameter greater than 1 mm to further investigate the impact of particle size on release kinetics.

Preparation of tablets

Tablets were obtained by direct compression after mixing the prepared solid dispersion with Ludiflash, croscarmellose, talcum, and magnesium stearate. In the case of 1 : 2.5 MBZ:PEG 6000 ratio, tablets were prepared in two variants: with solid dispersion particles having a size < 1 mm and with particles having a size in the 1-1.5 mm range. The next

step was lubricating the resulting powder with magnesium stearate for 3 min. This 3-minute time interval is a critical parameter because, in the case of a longer time, segregation of the mixture occurs in the supply funnel of the tableting machine. Tablets were obtained by compression with a 12 mm diameter punch. A "control" formulation containing crystalline MBZ was used to assess the impact of the solid dispersions on the release kinetics of MBZ, as shown in Table 1.

To study the influence of the mean diameter of the solid dispersion particles on the release kinetic profile of MBZ from the obtained tablets, two different formulation batches of MSD 1 : 2.5 were prepared. The former was prepared using the MBZ:PEG 6000 solid dispersion with a particle diameter < 1 mm and the second batch using the 1-1.5 mm fraction of the same dispersion.

HPLC analysis of MBZ samples

Instrumentation

MBZ was quantified by using an RP-HPLC method, with UV detection at 254 nm. The analyses were performed on a Waters liquid chromatographic system (Waters, Milford, MA, USA) composed of a 600 E Multisolvant Delivery System, Waters AF inline degasser, 486 UV tunable absorbance detector, and Waters 717 plus autosampler. The system control and data acquisition were performed using Empower software (Milford, MA, USA).

Chromatographic conditions

The separation was performed on an Hypersil Gold (4.0 × 150 mm, 5 µm) reverse phase C18 column (Thermo Fisher Scientific, Bellefonte, PA, USA), maintained under constant temperature (35°C). The mobile phase was composed of an isocratic mixture of 0.1% trifluoroacetic acid (A) and

acetonitrile (B) in a 63 : 37 (v/v) ratio, delivered with a flow rate of 1 mL/min. The injection volume was 5 µL.

Preparation of standard and test solutions

The MBZ stock solution was prepared at 0.5 mg/mL level, by transferring an accurate weight of 25 mg of MBZ reference standard into a 50 mL volumetric flask, adding approximately 5 mL formic acid for MBZ solubilization, and completing to the mark with methanol. Six calibration standards, with the concentrations 1.25, 2.5, 5, 10, 20 and 40 µg/mL were subsequently prepared by serial dilution of the stock solution with the mobile phase.

For the test solutions, to 100 µL of each dissolution sample, 100 µL methanol was added under continuous vertexing, in order to disrupt the bile salts-lecithin-MBZ mixed micelles present in the dissolution medium. The resulting sample was subsequently diluted with 800 µL mobile phase, and 5 µL were analyzed by HPLC.

Analytical method validation

The HPLC procedure was fully validated following the International Conference on Harmonization (ICH) regulations Q2(R1) [ICH 2005] for specificity, linearity, range, sensitivity, accuracy, precision (repeatability and intermediate precision), robustness and system suitability.

Selectivity was performed against both components of the tablet matrix and against the components of the dissolution media.

The linearity assessment was performed for the concentration range 1.25-40 µg/mL (Fig. 1, Fig. 2) by using triplicate injections of each of the six MBZ calibration standards. The detection limit and quantitation limit were calculated based on the signal-to-noise (S/N) ratio. The concentrations yielding S/N

Table 1. Composition of the prepared experimental tablets.

Formulation	MSD 1 : 1		MSD 1 : 2.5		PEG 0	
	mg/tablet	%	mg/tablet	%	mg/tablet	%
Mebendazole:PEG 6000 1 : 1	200	33.3	-	-	-	-
Mebendazole:PEG 6000 1 : 2.5	-	-	350.0	58.3	-	-
Mebendazole	-	-	-	-	100	16.7
Ludiflash (BASF)	376	62.7	226.0	37.7	476.0	79.3
Sodium croscarmellose	12.0	2	12.0	2	12.0	2
Talcum	6	1	6.0	1	6.0	1
Magnesium stearate	6	1	6.0	1	6.0	1
Total	600	100	600	100	600	100

ratios of 3 : 1 and 10 : 1 were taken as the limit of detection (LOD) and limit of quantification (LOQ), respectively.

The accuracy of the method was evaluated by the standard addition method, spiking appropriate amounts of MBZ stock solution of the pure drug into dissolution medium, in order to obtain low (QC_{low} : 3.75 $\mu\text{g/mL}$), medium (QC_{med} : 15 $\mu\text{g/mL}$) and high (QC_{high} : 30 $\mu\text{g/mL}$) concentration levels and was expressed as MBZ mean percentage recovery (%) after five injections of each concentration level.

Precision was tested for the intra-day (repeatability) and inter-day (intermediate) variations. Intra-day precision was tested by analyzing five replicates from each of the three QC levels of concentrations within a single experimental session, while intermediate precision was determined by analyzing the same concentrations on five different days.

To assess the robustness of the methods, small but deliberate changes were made in some parameters of the chromatographic methods, with the results being expressed as RSD (%) of the peak area

Figure 1. MBZ calibration curve in the 1.25-40 $\mu\text{g/mL}$ range. Each point is the mean of three determinations.

Figure 2. Chromatogram containing overlapping signals obtained from the standard sample analysis used to construct the calibration curve (concentration range: 1.25-40 $\mu\text{g/mL}$).

Table 2. Accuracy and precision data for the determination of MBZ.

	Nominal conc. (µg/mL)	Measured conc. (Mean ± SD, µg/mL)	Precision RSD (%)	Mean recovery (%) [range]
Intra-day (Repeatability)				
QC _{low}	3.75	3.73 ± 0.02	0.52	99.52 [98.67-100.00]
QC _{med}	15	15.15 ± 0.14	0.90	100.97 [100.00-101.93]
QC _{high}	30	29.76 ± 0.14	0.47	99.19 [98.67-99.60]
Inter-day (Intermediate precision)				
QC _{low}	3.75	3.76 ± 0.08	2.05	100.28 [97.6-102.45]
QC _{med}	15	15.19 ± 0.24	1.61	100.9 [99.07-103.27]
QC _{high}	30	29.78 ± 0.32	1.06	99.19 [97.73-100.40]

of the analyte. The system suitability parameters, including retention factor, separation factor, resolution, number of theoretical plates, height equivalent to theoretical plates, and tailing factor, were also evaluated. The benchtop stability of the samples was assessed for 24 h at room temperature ($25 \pm 2^\circ\text{C}$), and after overnight storage in the refrigerator ($4 \pm 1^\circ\text{C}$), it was evaluated.

Dissolution experiments

In vitro release assays were performed in simulated intestinal media. Due to the low solubility of MBZ and the importance of intestinal surfactants on the bioavailability of poorly soluble drugs, a FaSSIF (20) containing physiologically relevant surface-active agents (3 mM sodium taurocholate and 0.75 mM phosphatidylcholine) was selected. The release was performed using the USP 2 (paddles) apparatus at 75 rpm (DT800. HH, Erweka, Germany). Samples (2 mL) were taken at 5, 10, 15, 30, 45, 60, 90, 120, and 180 min after the start of the test. The resulting samples were appropriately diluted and analyzed by HPLC. Six units of each MBZ formulation were evaluated.

Applied release theoretical models

For describing the evolution over time of the cumulative amount of MBZ released and to predict behavior beyond the measuring time interval, several mathematical models were applied and compared. All models were used in linearized forms as previously described (21, 22) to permit a global, naked eye analysis.

Noyes-Whitney model (NW)

Delivery is considered across a limit stationary layer of thickness (δ). The concentration gradient is considered constant in this limit layer. Furthermore, the concentration of molecules in the immediate

neighborhood of pharmaceutical formulation is considered equal to its maximum solubility value, c .

Initial and boundary conditions corresponding to phenomenological conditions for $c(x,t)$ are:

$$c(0,t) = c, \text{ and } c(\delta,t) = c_s(t) \text{ for } x \geq \delta$$

A solution of Fick's first law, with these conditions, can be written in the linear form:

$$-\ln(1 - r(t)) = kt$$

where $r(t)$ is the fraction released at time t .

Higuchi square root law (H)

The Higuchi model describes the dissolution and diffusion of an active substance in the solvent, which dissolves slowly into the permeating fluid phase in the pharmaceutical matrix (23).

Since the assumptions of the model are valid only in the first part of the release process, the application of this law only describes the first 60% of the released drug amount satisfactorily. The law concludes a linear dependence of the released amount on the square root of time.

The Power-Law model (S-P)

The release profile from a degradable polymer matrix was analyzed using a power-law equation by Peppas and Siepmann (24), which supposes swelling, erosion, and diffusion effects, in the form:

$$r(t) = at^\beta$$

or in the linearized form:

$$\ln(r(t)) = \ln a + \beta \ln t.$$

Weibull model (W)

The Weibull model (25) is one of the most general models in science, applying to processes running in several steps with a constant rate of inter-transfers. The time course of released fraction $r(t)$ can be described by the Weibull distribution in the implicit form:

$$\ln(-\ln(1 - r(t))) = \ln\alpha + \beta \ln t$$

where α and β are empirical constants.

The model was first time applied in describing the dissolution of drugs from pharmaceutical formulations (26) and was subsequently extended to a deep analysis of dissolution in homogeneous and heterogeneous media (27, 28).

RESULTS

Validation of the HPLC method

The method was linear in the concentration range of 1.25–40 $\mu\text{g/mL}$ ($R^2 = 0.9999$) (Fig. 1). The LOQ, estimated based on a 10 : 1 S/N ratio, was 0.7412 $\mu\text{g/mL}$, whereas the LOD, corresponding to a 3 : 1 S/N ratio, was 0.2204 $\mu\text{g/mL}$.

Repeatability and intermediate reproducibility experiments resulted in RSD % values ranging from 0.47% to 0.90% for repeatability and from 1.06% to 2.05% for intermediate precision. The overall recovery was between 97.6% and 103.27% (Table 2), confirming no interference from the excipients. All these results indicated that the precision and accuracy of the assay were satisfactory.

The samples were stable for the investigated benchtop stability time frame (24 h at room temperature) and overnight in the refrigerator. System suitability parameters calculated to assess the effectiveness and suitability of the method (theoretical plates, resolution, and tailing factor) were all within acceptable limits.

The method proved to be appropriate for multiple assays that required quantitative determination

of MBZ (i.e., determining the drug content of the tablets obtained from solid dispersions) and assessing the in vitro release kinetics of MBZ.

Release of MBZ from tablets

Two-phase release of MBZ

Regardless of the composition of the formulations and the release medium, two distinct phases correspond to most of the immediate release formulations, namely pre- and post-disintegration (29). In the first phase, the tablets underwent concomitant swelling and erosion. An increase of their volume to approximately double was visible with the naked eye. In the second phase, the tablets disintegrated into small particles, forming a coarse suspension.

Dependence of the release kinetics in FaSSIF on PEG proportion

Results concerning the release kinetics of MBZ in FaSSIF from MSD 1 : 1 and MSD 1 : 2.5 are presented in Figure 3.

In the release, a time delay of at least 10 min occurs in the case of the 1 : 1 formulation and at least 15 min for the 1 : 2.5 formulation, which corresponds to the first release step before the disintegration of the tablets.

As can be seen in Figure 3C, the increase of the PEG proportion didn't lead to an increase in the rate and extent of release in the first hour. Significant differences appeared in the 1–3 h timeframe, a result similar to that reported in the literature (11), in the case of an increase of MBZ:PEG proportion from 1 : 1 to 1 : 5.

Figure 3. The kinetics of MBZ release in FaSSIF, mean release curves for the two solid dispersion-based formulations (MSD 1 : 1 and MSD 1 : 2.5) as compared to the control crystalline MBZ formulation (PEG 0).

Figure 4. Influence of the particle diameter of MBZ PEG6000 solid dispersion on the release of MBZ from tablets in FaSSIF (mean $\pm$ SD).

Influence of the mean diameter of the solid dispersion particles on the release profile

The mean release curves and standard deviations at all samplings for the two 1 : 2.5 formulations are given in Figure 4. Data suggest that the use of higher size particles of solid dispersions in the formulation increases the dissolution rate of MBZ. Similarity factor f_2 was found 49.94 i.e. exactly on the frontier between similar and non-similar.

Differences appeared mainly in the second part of the release process. In the first hour, differences between curves appear to be randomly distributed. After this time, the release curves of MBZ from tablets were significantly different.

Effect of formulation as SD on the extent of release at 3 hours

Given that the site of action/absorption of MBZ is at the intestinal level, as well as the fact that it tends to precipitate in the passage from the gastric level to the intestine (having a weak basic structure), the time evolution of MBZ concentration in an intestinal fluid determines its bioavailability and final therapeutic effect. Due to the formulation as a solid dispersion, an obvious improvement of bioavailability occurred after 3 h.

As can be seen in Figure 4, in the simulated intestinal medium, MBZ was available approximately 60% from the 1 : 1 dispersion and 100% from the 1 : 2.5 dispersion (compared with only 6% in the absence of PEG). So, improving the solubility of MBZ due to its incorporation into solid dispersions was significant.

Modeling the release kinetics in FaSSIF

As a rule, applied models worked in all cases starting after 15 or 30 min. The first points couldn't

be included in the regression lines of the linearized models. These first three or four points approximately corresponded to the pre-disintegration phase.

Formulation MBZ:PEG 1 : 1

Both Higuchi and Siepmann-Peppas models assume that the matrix is swollen by the solvent, and the release occurs in this solvent, which penetrates the matrix, so the 15-min time delay corresponds to the inflating step. It should be noted that, in the case of the Higuchi model, the release is absent in the first 15 min. The Siepmann-Peppas model provided evidence that there was a release in the same interval, but the values were very small. Normally, if the Higuchi model works, the Siepmann-Peppas model must also work, with $n = 0.5$, but in Figure 5 it appears that the slope of regression line modeling the $\ln r - \ln t$ dependence, $n = 0.86$, was significantly greater than 0.5. It is noteworthy that the Higuchi model approximated the last point (3 h) better than the Siepmann-Peppas model. Apparently, the fitting worked well with the Noyes-Whitney model, but the last point (3 h) was deviant from the regression line. A more in-depth analysis revealed that better fitting was obtained using two different regression lines: one corresponding to the initial time interval and another, with a somewhat higher slope, in the second phase. The Noyes-Whitney model described the release from the surface of the matrix to the external medium. The model worked in both release phases, suggesting a release through the surface of the tablet followed by a release from the surface of the particles resulting after disintegration. The slope increased in the second phase due to the increase in the total surface of particles following disintegration. The model no longer worked at the end, perhaps

because the release into channels and pores of particles in suspension cannot be neglected. Given diffusion, with or without swelling, we tested the Weibull model, which considers the processes in successive stages with an approximately equal probability of transition between successive steps.

Since the model has two parameters, the fitting was expected to be better. This happened and the regression line approximated the point corresponding to 15 min and the final point (3 h), but the first two points still remained outside the model. Finally, the erosion observed with the naked eye seems to have a lower influence on the total release kinetics.

Formulation MBZ:PEG 1 : 2.5

The experimental points and regression lines corresponding to linearized patterns for the formulation MSD 1 : 2.5 are depicted in Figure 6.

The fittings were good with all the models for the whole range of time, except the NW model, which worked well only from 30 min to 2 h. In the case of larger particles, the pattern suggests an acceleration of the release in the interval from 2 h to 3 h. Both the Higuchi model and Siepmann-Peppas model applies to diffusion-controlled release inside

the tablet matrix. Both advocate for release in channels and pores within matrices or fragments of matrices and not for a direct release into the dissolution medium.

DISCUSSION

Formulation effects

MBZ is known chemically as methyl-5-benzoyl benzimidazole-2-carbamate. Its partition coefficient is $cLogP = 3.1$, but despite this optimum value and due to its very low solubility in water (71.3 mg/L at 25°C) (31), its bioavailability remains very low (32).

Its formulation as tablets based on solid dispersions of MBZ in PEG, networking polymers and superdisintegrants resulted in a great increase of release surface following the formation of a network of channels, pores, and cavities filled with water after the swelling and erosion of soluble polymers. These processes favor extended dissolution and diffusion (33, 34). In the first phase, the transformations of the tablet matrix and release kinetics are controlled by croscarmellose and Ludiflash excipients. Croscarmellose is an excipient used in the preparation of tablets for its action as a superdisintegrant (35). It was

Figure 5. Experimental results and regression lines for release kinetics of MBZ from MSD 1 : 1 a. Higuchi model; b. Siepmann-Peppas model; c. Noyes Whitney model; and d. Weibull model.

Figure 6. Experimental results and regression lines for release kinetics of MBZ from MSD 1 : 2.5. a. Higuchi model; b. Siepmann-Peppas model; c. Noyes Whitney model; and d. Weibull model.

reported that the association of croscarmellose sodium (7.5%) with other superdisintegrants led to an increase in the release of loratadine (5%) (36) and hydrochlorothiazide (37). Our previous research proved an increase of the extent of release of MBZ as a function of croscarmellose concentration, both in simulated gastric fluid (38) and in FaSSIF (39).

Ludiflash® is comprised of 90% mannitol, a fast-dissolving filler; 5% Kollidon® CL-SF (crospovidone), a disintegrant; and 5% Kolli-coat®SR 30 D (polyvinyl acetate), a hydrophobic binder. It promotes swelling and absorption of at least two times its weight in water (40), becoming a hydrogel (41). In the absence of a disintegrant in the tablet formulation, the dissolution is governed by the erosion-diffusion process. Even for a highly soluble drug, a superdisintegrant is needed in the formulation to overcome the limitations due to the diffusion layer and changes the dissolution mechanism from erosion-diffusion to disintegration (42).

In vitro drug release in 0.1 N HCl showed 80.35% in 60 min for the best solid dispersion (MBZ and poloxamer 338 ratios 1 : 2), but it was not performed in *in vivo* determinations (43).

Solid dispersions of MBZ prepared with PVP K30, PEG 8000, and pregelatinized starch had a better release at pH 1.2 compared with pH 7.4 at the end of three hours. *In vitro*, antihelminthic studies showed the effectiveness of formulations (44).

It should be underlined that a moderate increase in the release rate and extent (to 60-70% at four hours) in 0.1 N HCl can assure a significant increase in bioavailability of MBZ formulated as a solid dispersion, as was obtained, for example, by its inclusion in low-substituted hydroxypropyl cellulose (45).

Finally, increasing the *in vitro* release kinetics depends on the biorelevance of the method and an increase of bioavailability and effect doesn't necessarily result.

Modeling of release kinetics

Usual models

To compare the performances of the models, it is useful to examine the phenomenological suppositions of the models. The usual models presented above can be classified into three categories:

- swelling and diffusion controlled release, which includes the Higuchi and Siepmann-Peppas models;

- diffusion-controlled release, which includes the NW model;
- empirical Weibull model, based only on the hypothesis of successive steps with equal probabilities of the transfer.

The Higuchi model supposes that the solvent front is moving slowly inside the tablet and washes the matrix layer by layer, so it is a model of the "moving boundary" type. An essential difference between the Higuchi and Noyes-Whitney models is that the latter considers the release in the limit layer attached to the interface in the part of the solvent (Fig. 7). The concentration gradient is again constant, such as in the Higuchi model. The concentration in bulk is considered constant as a function of space, equal to the concentration at the outer face of the limit layer. As a common feature, the low solubility of MBZ implies that, at the release interface, its concentration is equal to the saturation value. The Siepmann-Peppas model supposes two moving boundaries (53, 54): the external surface modified by erosion and the waterfront inside the matrix. Higuchi's law can be considered as a particular case of the Siepmann-Peppas law when the external surface is moving more slowly than the internal solvent front. So, it is to be expected that, if the Higuchi model is applicable, the same is true with the Siepmann-Peppas model. In the first phase of release, as was observed by the naked eye, the swelling was significant and the application of the Siepmann-Peppas and Higuchi model was an expected result. Maybe the same phenomena also appear in the second phase, but this is not visible with the naked eye. In the second phase, once the tablets disintegrate, a subsequent release occurs on a much larger surface (i.e., the total surface area of the particles resulting from the disintegration), and the acceleration of release is the expected result.

A very good fit with the Noyes-Whitney model and a good fit with the Higuchi model means that diffusion is a determining factor, regardless of the shape and integrity of the tablets. On the other hand, the contradiction between the two types of mechanisms remains, and their simultaneous application needs an explanation, following a more in-depth analysis.

Keeping in mind the concomitant time course of swelling and diffusion, it was considered necessary to also try fitting with the power-law model of Siepmann-Peppas. Neither in the first phase nor in the second phase was a better linear correlation obtained than that in the case of square root laws, so apparently, the Higuchi model remains the preferred model.

The more general model introduced by Weibull (25) is based on the assumption that the process is carried out in several independent stages, and the cumulative probability of an event observed in step n is conditioned of probabilities to observe the event at the previous stages $(1-P_n) = (1-P)^n$.

In the case of dissolution, P is the probability that the MBZ molecule will not be released (26). The Weibull model worked excellent on both types of formulations, but this remains a more or less empirical approach.

Infinite Reservoir-Semi-infinite Medium (IR-SIM) model

A square root law similar to the Higuchi equation was proposed to describe the release kinetics of drugs from pharmaceutical formulations, which can be assumed as an infinite reservoir, at the interface with a semi-infinite solvent medium (21, 46, 47). Since MBZ has low solubility, at the pharmaceutical matrix-solvent interface, its concentration is for a long time constant (saturation value), acting as a reservoir. Mathematical analysis of the results suggested that the release kinetics could be described by the model "release from an infinite reservoir in a semi-infinite medium", the model initially applied in heat transfer phenomena (48).

The concentration of drugs inside the solution can be, in this case, expressed using the following equation (21): $c(x,t) = c_s(1 - \text{erf}(x/\sqrt{4Dt}))$ where x is the distance from the interface and $\text{erf}(z)$ is the error function

$$\text{erf}(z) = \int_0^z \frac{2}{\sqrt{\pi}} e^{-x^2} dx$$

which provided the following square root equation:

$$m(t) = 2/\sqrt{\pi} A c_s \sqrt{Dt}$$

Where A is the area of interface between the reservoir and diffusion medium and D is the diffusion coefficient.

This is a square root law, but it should be noted that the phenomenological conditions are very different and much more general in form than in the Higuchi model, similar to laws from the theory of mass diffusion. Here, the law describes the release at the matrix-solvent interface in the limit layer. When the interface is fixed, the solvent doesn't swell the matrix.

The state of the formulations had three evolution phases: a first phase, as was mentioned, swelling and increase in volume; a second phase when disintegrated tablets formed a coarse suspension; and the third phase of a fine suspension. Such a partition is suggested both by the examination of the direct release curves and modeled after transformation and linearization.

In these conditions, a reliable mechanism of release phenomena could be the following:

- in the first phase, a release across the interface of the tablet and a slow release into the channels;
- in the second phase, a release across the entire surface of the particles in suspension;
- finally, a dissolution from the fine suspension.

Most probably these mechanisms are intricate, but in each phase, one of them is predominant. In the second phase, both the square root model and NW model work well (Fig. 5). The NW model and IR-SIM model suppose transfer across the interfaces. Both H and IR-SIM lead to a square root law, but the applicability of the NW model is an argument for the IR-SIM model. In the last 60 years, the square root law has been used often in describing release from solid pharmaceutical formulations (21). Authors considered in all cases that it was proved the application of the Higuchi model. In fact, in almost all cases, the systems in connection with the phenomenological conditions used in deriving the Higuchi square root law were not evaluated. Maybe, in many cases, the IR-SIM model was applicable, which has the same final expression.

Comparison of performances of models

The release kinetics of active components depends on their physicochemical properties, formulation, dissolution media, and dissolution methods. As was presented above, a lot of methods for improving the solubility of MBZ and development of complex polyphasic formulations were attempted, the present paper being one of these. Dissolution media were sought to be as similar as possible to gastrointestinal fluids. Dissolution methods and applied models for the analysis of the result are designed to be "biorelevant" in order to allow an estimation of *in vivo* dissolution and pharmacokinetics (29, 30, 46, 49, 50). On the other hand, from the mathematical considerations (51, 52) connected with the stability of the predictions, a model with a lower number of parameters is preferable, in our case the square root model. The fact that better results were obtained using the Higuchi and Noyes-Whitney models appeared to be contradictory behavior, as one model is based on the hypothesis of moving solvent inside the matrix and the other on the hypothesis of diffusion outside the matrix surface. A possible explanation could be that the linear dependence of the cumulative amount of drug released on the square root of time is the mathematical expression of a release from an infinite reservoir in a semi-infinite medium across the matrix-solvent interface.

Dependence of release kinetics on particle size

Experimental results indicated that the inclusion of dispersion particles of greater size in tablets favors the dissolution of MBZ. This aspect, seemingly surprising, could be explained by the fact that smaller particles led to a more compact powder and to a lower disintegration rate.

"It was checked if the mechanism of release is dependent on the proportion between components. Some of the results were essentially similar and others somewhat different. Qualitatively, the release was described by the same models but appeared quantitative differences. An increase in the PEG proportion led to an increase of time-lag from 15 min to approximately 30 min. The slopes of linear regressions increased, suggesting a more rapid release in the post-disintegrating phase.

CONCLUSIONS

Formulations developed with MBZ as the active substance, Ludiflash as the disintegrant, and croscarmellose as the superdisintegrant allowed for a direct compression technology process. The presence of disintegrants led to the disintegration of tablets in approximately 15 min in the case of a 1 : 1 solid dispersion and between 30 min and 1 h in the case of a 1 : 2.5 solid dispersion. So, the release occurred in different conditions connected with the two phases: pre-disintegration and post-disintegration, and the results were different.

An improvement of release in simulated intestinal medium following the formulation as a solid dispersion occurred, with MBZ being released in about 60% in 3 h from the 1 : 1 dispersion and 100% from the dispersion of 1 : 2.5 (vs. only 6% in the absence of PEG).

In both phases (pre- and post-disintegration), despite the very different initial and boundary conditions, the release was described very well by the square root law. Performance of the square root model, rather than the application of the Higuchi law, in both cases, was considered to be the release from a "reservoir" (i.e., the generalized square root law). The model is based on initial and boundary conditions compatible with the supposed physicochemical properties and structures of many MBZ formulations.

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Conflict of interest

The authors declare no conflict of interest.

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