



Dissolution parameters for sodium diclofenac-containing hypromellose matrix tablet

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ABSTRACT

Sodium diclofenac (SD) release from dosage forms has been studied under different conditions. However, no dissolution method that is discriminatory enough to reflect slight changes in formulation or manufacturing process, and which could be effectively correlated with the biological properties of the dosage form, has been reported. This study sought to develop three different formulae of SD-containing matrix tablets and to determine the effect of agitation speed in its dissolution profiles. F1, F2 and F3 formulations were developed using hypromellose (10, 20 and 30%, respectively for F1, F2 and F3) and other conventional excipients. Dissolution tests were carried out in phosphate buffer pH 6.8 at 37 °C using apparatus II at 50, 75 or 100 rpm. Dissolution efficiency (DE), T_{50} and T_{90} were determined and plotted as functions of the variables agitation speed and hypromellose concentration. Regarding DE, F2 showed more sensitivity to variations in agitation speed than F1 and F3. Increasing hypromellose concentration reduced DE values, independent of agitation speed. Analysis of T_{50} and T_{90} suggests that F1 is less sensitive to variations in agitation speed than F2 and F3. Most discriminatory dissolution conditions were observed at 50 rpm. Results suggest that the comparison of dissolution performance of SD matrix tablets should take into account polymer concentration and agitation conditions.

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1. Introduction

The development of controlled or sustained release delivery systems is a tool for optimizing therapeutic effect, by maximizing the bioavailability of conventional drugs and reducing side effects. These systems include matrix tablets, which considered being the easiest strategy for controlled-release systems (Lachman et al., 2001).

Matrix tablets can be formulated by using hydrophilic polymers, as an example of the controlled-release material. This group includes cellulose derivatives, such as hydroxypropylmethylcellulose (HPMC) or hypromellose, which is the carrier of choice for the preparation of hydrophilic matrices (Siepmann and Peppas, 2001; Lopes et al., 2005). Release of drugs from HPMC systems is influenced by polymer concentration, drug:polymer ratio, polymer particle size, and polymer degree of substitution (Li et al., 2005).

Drug release from different dosage forms, including matrix tablets, can be evaluated by means of dissolution testing (Azarmi

et al., 2007). Dissolution testing is a very important tool in drug products development and as a quality control procedure in pharmaceutical production. In quality control, dissolution test results can lead to approval or rejection of batches. In product development, it supports formulation selection, enables analysis of combined effects, such as drug, excipient or process properties, in order to evaluate the effect of these changes on biopharmaceutical characteristics, and is used in comparative studies of formulations (Pillay and Fassihi, 1998; Marcolongo, 2003; Siewert et al., 2003; Graffner, 2006).

Recently, considering the relationship between drug dissolution and bioavailability, several dissolution approaches have been proposed for estimating oral absorption (Dokoumetzidis and Macheras, 2006) and establishing biowaivers. Sensitive and reproducible dissolution data from predefined conditions are needed in order to compare *in vitro* dissolution results, and to allow its use for *in vitro*–*in vivo* correlations and as surrogates for *in vivo* bioavailability and bioequivalence testing (Pillay and Fassihi, 1998).

Methods to compare dissolution profiles have been proposed, which can be classified into: (a) methods based on analysis of variance, (b) model-independent methods and (c) model-dependent methods. Analysis of variance assesses the differences between the averages of two drug release data sets. Fit factors f_1 (difference factor) and f_2 (similarity factor) are the prime example of model-independent methods, and are used by many regulatory agencies

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Table 1
Studies that evaluated sodium diclofenac release from matrix systems.

Apparatus	Dissolution medium	Agitation speed	Reference
Paddle	Phosphate buffer pH 6.5 (with 0.2% Polysorbato 80)	100 rpm	Kiortis et al. (2005)
Basket	Distilled water	50 rpm	Velasco et al. (1999)
Paddle	Phosphate buffer	50 rpm	Bravo et al. (2002)
Basket	Phosphate buffer pH 6.8	50 rpm	Reza et al. (2004)
Paddle	Phosphate buffer pH 6.8	50 rpm	Samani et al. (2003)
Paddle	Phosphate buffer pH 7.4	100 rpm	Rani and Mishra (2004)
Paddle	Change pH until to 7.5	50 rpm	Savaser et al. (2005)
Paddle	Phosphate buffer pH 6.8	100 rpm	Avachat and Kotwal (2007)

to compare dissolution profiles. Model-dependent methods involve the application of mathematical models that can reveal the physical and chemical phenomena involved in drug release (Costa and Lobo, 2001).

Several factors influence dissolution test results, namely those related to the physical and chemical characteristics of the drug, to the drug product formula, to the dosage form, and to the parameters of the dissolution testing itself. The latter, such as dissolution medium (composition, pH, and viscosity), agitation speed, apparatus, and sampling, among others, can be evaluated by performing dissolution assays with drug units of the same drug product (Banakar, 1992). Thus, during the development of the dissolution test, it is necessary to define dissolution parameters, in order to ensure a discriminatory method that is able to identify changes in processes and/or formulations and can be used to establish a possible *in vitro*–*in vivo* correlation.

Sodium diclofenac (SD) is a potent non-steroidal anti-inflammatory drug with analgesic and antipyretic properties. It has an unpleasant taste, and causes gastric irritation (Savaser et al., 2005). The properties of SD liberation from matrix system have been widely studied, either as a model drug or as an effective candidate for controlled-release systems. In these studies, different dissolution conditions are employed, such as apparatus, agitation speed, and type and volume of dissolution media (Table 1). However, no dissolution method that is discriminatory enough to reflect slight changes in formulation or manufacturing process, and which could be effectively correlated with the biological properties of the dosage form, has been reported.

Considering dissolution studies as a tool for *in vitro*–*in vivo* correlation, and that the dissolution parameters may influence the performance of the dosage form, this study sought to develop different formulae of SD-containing matrix tablets and determine the effect of agitation speed in dissolution profiles and kinetic analysis.

2. Materials and methods

2.1. Materials

Hydroxypropylmethylcellulose K4M (hypromellose, HPMC) (Colorcon, Brazil), partially pre-gelatinized corn starch (Starch 1500®) (Colorcon, Brazil), microcrystalline cellulose type 101® (Blanver Farmacoquímica, Brazil), lactose (Purifarma, Brazil), magnesium stearate (All Chemistry, Brazil), polyvinylpyrrolidone K30 (PVP) (Valdequímica, Brazil) and sodium diclofenac (SD), batch Ds/05/05/096 (Henrifarma, Brazil), were used.

2.2. Preparation of sodium diclofenac tablets

Three different formulations of SD-containing matrix tablets were developed. Tablets were prepared by wet granulation, using 100 mg of SD per tablet, HPMC at concentrations of 10, 20 or 30%, magnesium stearate (1.5%) as lubricant, PVP as binder, and micro-

crystalline cellulose and lactose as diluents, in sufficient quantities to obtain a final mass of 350 mg per tablet. The composition of the matrix tablets is described in Table 2.

Powders were sieved through a 0.710 mm mesh screen and, except the lubricant and half of the HPMC, mixed manually. A PVP solution in water was added while mixing the powder blend in a planetary mixer, to obtain the desired consistency of the mass. The wetted mass was then granulated by passing it through a 1.0 mm mesh screen. Granules were dried in a hot air oven (Marconi, MA 037, Brazil) at 40 °C for 1 h, and the final moisture content was determined using an infrared moisture analyzer (Mettler, LJ16 Greifensee, Switzerland). Although HPMC is activated by the water used in the wet granulation, the drying process restores its original characteristics. The dried granules (moisture 3–5%) were passed through a 1.00 mm mesh screen. At the end, 1.5% (w/w) of the lubricant magnesium stearate and the second part of the HPMC were added, and mixed manually. The 350 mg tablets were obtained in a rotary tableting machine (Lawes, 10 PSC, Brazil), with 9 mm concave punches.

2.3. Characterization of tablet formulation

Tablets were characterized by weight, hardness and friability. The average weight was obtained for at least 20 units, according to pharmacopeial limits (United States Pharmacopeia, 2008; Farmacopeia Brasileira, 1988). Hardness was determined for at least 10 tablets using a Hardness Tester (Erweka, TBH 20, Germany), and adopting a minimum hardness of 3 kgf as the acceptance criterion (United States Pharmacopeia, 2008; Farmacopeia Brasileira, 1988). For each formula, friability was evaluated for a sample of 20 tablets, using the acceptance criterion of a maximum loss of 1.5% of the initial weight (United States Pharmacopeia, 2008; Farmacopeia Brasileira, 1988).

The SD quantification assay was carried out using an UV spectrophotometric method adapted from the United States Pharmacopeia chromatographic method (2008). Tablets were crushed and a mass correspondent to 100 mg of SD was transferred to a volumetric flask of 100 mL. The material was diluted in methanol:water (7:3) by sonication during 30 min. The mixture was filtered and properly diluted to 25 µg/mL, with the same solvent. SD concentration was determined by UV spectrophotometry at 281 nm (Shimadzu, UV-160 1PC, Japan), using the equation:

Table 2
Composition of sodium diclofenac matrix tablets.

Components	Amount (mg/tablet)		
	F1	F2	F3
Sodium diclofenac	100	100	100
Magnesium stearate	5	5	5
PVP K30	17.5	17.5	17.5
HPMC ^a	35	70	105
Lactose: microcrystalline cellulose (70:30)	q.s.p. 350	q.s.p. 350	q.s.p. 350

^a Added in two stages (before and after granulation).

$y = 0.0394x - 0.0091$ ($r^2 = 0.9999$), obtained from a standard curve of SD ($n = 3$).

2.4. Dissolution assay

Drug release studies from matrix-tablets were performed in a dissolution system (Erweka, DT80, Germany) for 480 min, using 900 mL of pH 6.8 phosphate buffer 0.68% (w/v) as dissolution medium and the USP paddle apparatus. Dissolution medium was kept at $37 \pm 0.5^\circ\text{C}$ and stirred at rotation speeds of 50, 75 or 100 rpm. At predetermined time intervals, aliquots of 10 mL of medium were withdrawn, filtered through 0.22 μm membranes and assayed by UV spectrophotometry at 276 nm to determine SD concentrations using the equation: $y = 0.028x + 0.0083$ ($r^2 = 0.9939$), obtained from a standard curve of SD. Aliquots withdrawals were followed by medium replacement.

2.5. Data analysis

Sodium diclofenac release kinetics was evaluated according to the following models:

- Zero order:

$$Q_t = Q_0 + K_0t$$

- First order:

$$\log Q_t = \log Q_0 + \frac{K_1t}{2.303}$$

- Higuchi:

$$Q_t = K_H\sqrt{t}$$

- Hixson–Crowell:

$$\sqrt[3]{Q_i} - \sqrt[3]{Q_r} = K_S t$$

- Korsmeyer–Peppas:

$$\frac{M_t}{M_\infty} = K_K t^n$$

where Q_t is the amount of drug dissolved in time t ; Q_0 is the initial amount of drug in the solution (most times $Q_0 = 0$); Q_i is the initial amount of drug in the pharmaceutical dosage form; Q_r is the amount of drug remaining as a solid state at time t ; M_t/M_∞ is the fractional drug release; K_0 , K_1 , K_H , K_S and K_K are, respectively the zero order, the first order, the Higuchi's, the Hixson–Crowell's and the Korsmeyer's release constants; and n is an exponent which characterizes the drug release mechanism (Hixson and Crowell, 1931; Higuchi, 1963; Korsmeyer and Peppas, 1981; Costa and Lobo, 2001; Tanaka et al., 2005).

The model which gave the highest coefficient of determination (r^2) was considered to be the most suitable kinetic model for describing the release of SD from the matrix tablets. It was carried out the statistical analysis of variance (ANOVA) followed by the *a posteriori* (Tukey's) test using Statistica 6.0 software and considering a significance level of 0.05. The equation of the kinetic model was used to determine T_{50} (time to dissolve 50% of the drug in the pharmaceutical dosage form) and T_{90} (time to dissolve 90% of the drug in the pharmaceutical dosage form) values.

Dissolution efficiency (DE) was also determined. DE is defined as the area under the dissolution vs. time curve at time t , expressed as a percentage of the area of the rectangle that would correspond to 100% dissolution at time t ($DE = 100AUC_{0-t}/TA_{100\%t}$) (Khan and Rhodes, 1975). DE values were submitted to statistical analysis of variance (ANOVA) followed by the *a posteriori* (Tukey's) test to compare the different formulations. Statistical analysis was performed using Statistica 6.0 software and considering a significance level of 0.05.

Correlation between parameters DE, T_{50} and T_{90} and variables agitation speed and polymer concentration was investigated by plotting these parameters as a function of the variables. From these graphs, the coefficients of determination (r^2) and slope (a) were determined.

3. Results

Tablets average weight, hardness, friability, and assay results are shown in Table 3.

Dissolution profiles and DE values for each formulation (F1, F2 and F3) at three different agitation speeds (50, 75 and 100 rpm) are presented in Fig. 1 and Table 4, respectively.

Dissolution data were analyzed in order to assess drug release kinetics according to zero order, first order, Higuchi, Hixson–Crowell and Korsmeyer–Peppas models. Coefficients of determination (r^2) for each model are described in Table 5. The model which gave the highest r^2 value for each formulation and agitation speed was used to determine T_{50} and T_{90} (Table 6).

Figs. 2 and 3 present the correlations between parameters DE, T_{50} and T_{90} , and variables agitation speed or polymer concentration. For each correlation, coefficient of determination (r^2) and slope (a) were determined (Table 7).

4. Discussion

Average weight, hardness, friability and assay of all prepared tablets were within pharmacopeial specification (United States Pharmacopeia, 2008; Farmacopeia Brasileira, 1988).

In vitro drug release from tablets is influenced by testing conditions, such as apparatus, agitation speed, and volume, composition and temperature of the dissolution fluid (Abdou, 1989). Swellable matrix tablets, such as HPMC tablets, are activated by water, and drug release is controlled by the interaction between water, polymer and drug. Hydration of polymer results in the formation of a gel layer that controls the drug release rate (Colombo et al., 2000).

Table 3
Characteristics of sodium diclofenac tablets [average \pm SD (CV)].

Test	Formulations		
	F1	F2	F3
Weight average (mg) ^a	364.9 \pm 7.3 (2.0%)	365.2 \pm 7.8 (2.1%)	365.5 \pm 5.4 (1.45%)
Hardness (N) ^a	62.4 \pm 7.5 (12.0%)	72.7 \pm 9.0 (12.4%)	68.2 \pm 9.0 (13.1%)
Friability (%) ^a	0.29	1.07	0.12
Assay (%) ^b	101.6 \pm 2.2 (2.1%)	90.1 \pm 5.3 (5.9%)	92.12 \pm 5.6 (6.1%)

^a $n = 10$.

^b $n = 3$.

Table 4
Dissolution efficiency (DE) [average \pm SD (CV)] of F1, F2 and F3 using the USP paddle apparatus, pH 6.8 phosphate buffer at 37 ± 0.5 °C as dissolution medium, and different agitation speeds.

Agitation speed	Formulations		
	F1	F2	F3
50 rpm	93.1 \pm 2.1 ^b (2.2)	52.7 \pm 6.6 ^e (12.5)	29.8 \pm 1.6 ^g (5.3)
75 rpm	104.8 \pm 1.9 ^a (1.8)	72.8 \pm 4.4 ^d (6.1)	35.2 \pm 2.8 ^{fg} (7.9)
100 rpm	107.4 \pm 2.4 ^a (2.3)	83.2 \pm 5.2 ^c (6.3)	41.1 \pm 5.2 ^f (12.5)

Averages with different letters within the column shows significant difference ($p < 0.0001$) according to the Tukey's test.

Table 5
Coefficients of determination obtained from sodium diclofenac dissolution data analysis according to different mathematical models.

F	S (rpm)	Coefficient of determination and K										
		Zero order		First order		Higuchi		Hixson–Crowell		Korsmeyer–Peppas		
		r^2	K_0	r^2	K_1	r^2	K_H	r^2	K_S	r^2	K_K	n
F1	50	0.9947 ^a	0.4839	0.9489 ^a	0.0075	0.9845 ^a	9.1742	0.8338 ^b	0.0382	0.9921 ^a	3.5647	0.6473
	75	0.9848 ^a	0.7372	0.949 ^a	0.0093	0.9973 ^a	12.186	0.94 ^a	0.0749	0.9979 ^a	6.2749	0.6125
	100	0.750 ^c	0.4128	0.75 ^c	0.0041	0.8126 ^b	15.012	0.75 ^c	0.0771	0.8688 ^a	39.517	0.2408
F2	50	0.9701 ^b	0.154	0.8529 ^c	0.0036	0.9982 ^a	4.3818	0.9981 ^a	0.0041	0.9971 ^a	1.4448	0.6651
	75	0.9208 ^a	0.1414	0.7861 ^c	0.0021	0.9739 ^a	4.0909	0.8522 ^b	0.0094	0.9592 ^a	8.4675	0.4102
	100	0.9712 ^{a,b}	0.1481	0.9132 ^{b,c}	0.0018	0.9903 ^a	4.2084	0.9399 ^c	0.0151	0.9921 ^a	15.273	0.3279
F3	50	0.9905 ^b	0.0956	0.8842 ^c	0.0039	0.9959 ^a	2.6868	0.9982 ^a	0.0019	0.9999 ^a	0.6475	0.7073
	75	0.9893 ^b	0.1069	0.9054 ^c	0.0034	0.9973 ^{a,b}	3.0206	0.9981 ^{a,b}	0.0023	0.9994 ^a	1.245	0.636
	100	0.9841 ^a	0.1167	0.9166 ^b	0.0032	0.995 ^a	3.3023	0.9951 ^a	0.0027	0.9949 ^a	1.9324	0.573

F = formulae; S = speed agitation. Considering the same line, r^2 values with different letters within the column shows significant difference ($p < 0.05$) according to the Tukey's test. Underlined values indicate the highest r^2 values; the kinetic model associated to them was used to calculate T_{50} and T_{90} .

When the penetration of water in the gel-matrix exceeds a critical concentration (i.e. the concentration at which the interactions between water and polymer increase, with a consequent reduction of polymer–polymer interactions), the polymer chains begin to separate, extending the spaces where distribution of the drug occurs. At this stage, the erosion rate increases (Lopes et al., 2005).

Kavanagh and Corrigan (2004) studied the effect of dissolution medium composition and agitation speed on the swelling and erosion of HPMC matrix tablets, and concluded that the extent of swelling and the erosion rate increased with agitation rate.

In this study, it was observed, from the dissolution profiles and DE values (Fig. 1, Table 4), that F1 presents a greater extent and rate of release of the drug than F2 and F3, regardless of agitation speed. In fact, at the highest agitation speed (100 rpm), it has not even shown controlled drug release, since 85% of

sodium diclofenac was released in less than 30 min. This may be due to the gel layer responsible for controlling the release does not occur at low HPMC concentrations (Li et al., 2005), and the swelling and erosion rate can increase with agitation rate (Kavanagh and Corrigan, 2004). Accordingly, F2 and F3 present lower extents and rates of drug release, which increased with agitation rate.

The most suitable kinetic models for describing the release of SD from the matrix tablets were the zero order model for F1 at 50 rpm, the Higuchi model for F1 at 75 and 100 rpm and for F2 at 50, 75 and 100 rpm, and the Hixson–Crowell model for F3 at 50, 75 and 100 rpm (Table 5). The Higuchi model describes drug release through diffusion mechanism, and it has been used to describe drug dissolution from systems such as matrix tablets containing water soluble drugs (Costa and Lobo, 2001).

Table 6
Time in minutes to dissolve 50% (T_{50}) and 90% (T_{90}) of the drug in the pharmaceutical dosage form for F1, F2 and F3, at different agitation speeds.

Agitation speed	T_{50} %			T_{90} %		
	F1	F2	F3	F1	F2	F3
50 rpm	62.57078	197.0545	488.134	145.2325	536.6765	1367.62
75 rpm	29.8344	71.12555	362.9337	76.46703	331.6549	1042.852
100 rpm	11.09335	33.48659	285.5857	35.94247	233.8318	841.6992

Table 7
Coefficient of determination (r^2) and slope (a) from plots between parameters (DE , T_{50} and T_{90}) and variables (agitation speed and polymer concentration).

Variable	DE		T_{50}		T_{90}	
	a	r^2	a	R^2	a	r^2
Plots from agitation speed (x) vs. parameter (y) for each formulae						
F1	0.2852	0.8819	−1.0296	0.9759	−2.1858	0.9782
F2	0.6116	0.9674	−3.2714	0.9115	−6.0568	0.9599
F3	0.2248	0.9992	−3.4436	0.9889	−8.2144	0.9896
Plots from formula (x) vs. parameter (y) for each agitation speed						
50 rpm	−3.164	0.9745	19.934	0.9659	56.053	0.9706
75 rpm	−3.4795	0.9759	16.477	0.8423	47.398	0.9337
100 rpm	−3.3315	0.9978	13.899	0.81	40.982	0.9182

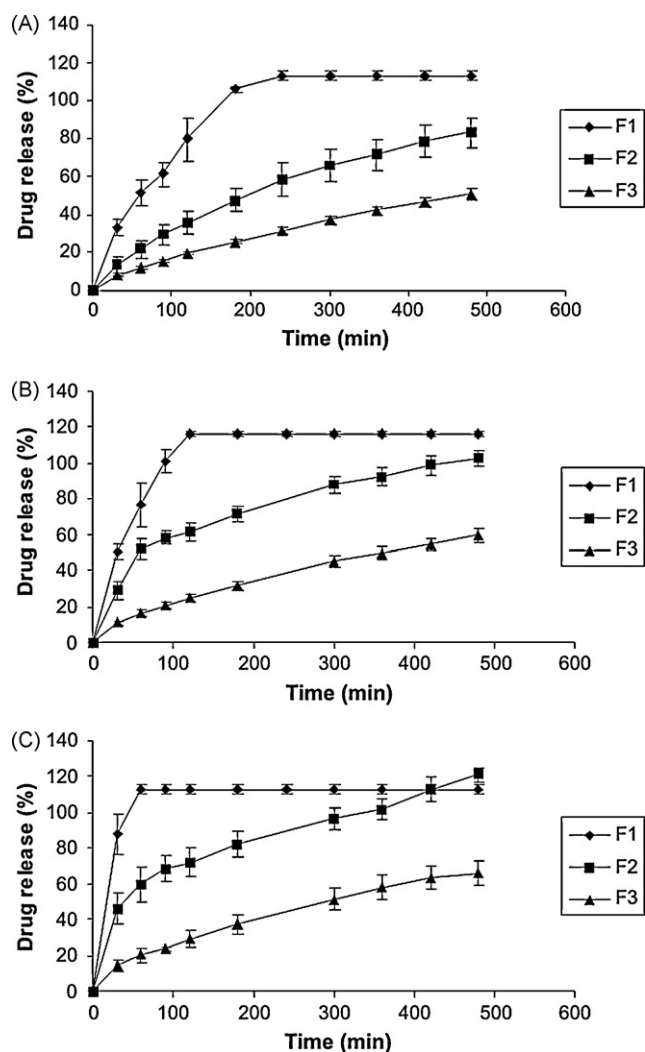


Fig. 1. Dissolution profiles of F1, F2 and F3 using the USP paddle apparatus, pH 6.8 phosphate buffer at $37 \pm 0.5^\circ\text{C}$ as dissolution medium, and different agitation speeds: 50 rpm (A), 75 rpm (B) and 100 rpm (C).

The Hixson–Crowell model assumes that the drug release is limited by the dissolution rate of the particles, and not by diffusion through the polymer matrix (Costa and Lobo, 2001). F3 dissolution data were better explained by the Hixson–Crowell model, but it can be pointed out that the coefficient of determination values obtained by applying Higuchi model to F3 data were also very high (greater than 0.99), which may also suggest diffusion mechanism for SD release from F3.

The n exponent from Korsmeyer–Peppas model can be used to characterize the drug release mechanisms as Fick diffusion, when $n=0.5$ and as a non-Fickian model if n is between 0.5 and 1.0 or $n=1.0$. When $n=0.5$, the drug release is controlled by diffusion and is time-dependent while when $n=1.0$, the drug release is controlled by swelling and is time-independent with zero order kinetics. Values of n between 0.5 and 1.0 indicate superposition of both phenomena, known as anomalous transport. It is necessary to consider that the exponent values are valid for certain slab geometry, and different values can be derived for spheres and cylinders (Siepmann and Peppas, 2001).

Sodium diclofenac release from the matrix tablets prepared in the present study can be explained by Fick diffusion or anomalous transport (matrix swelling and erosion) mechanisms (Table 5). Similar conclusions were obtained by Kiortis et al. (2005) in a study of SD release from HPMC and HPC matrices. A slight increase in

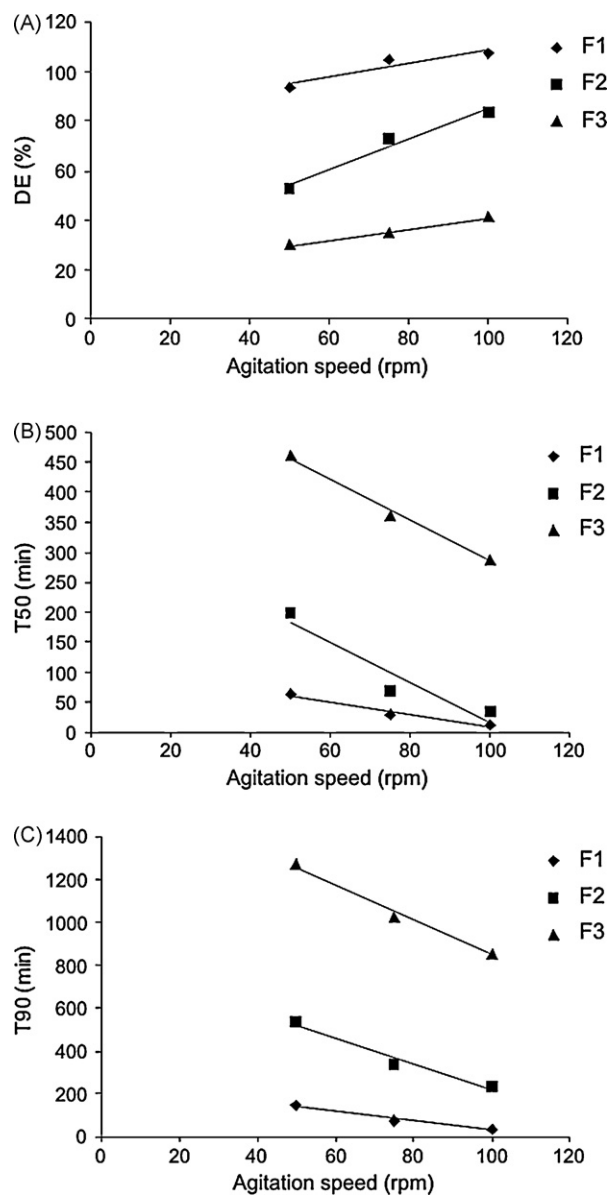


Fig. 2. Correlation between parameters DE (A), T_{50} (B) and T_{90} (C) and variable agitation speed for F1, F2 and F3.

n value is observed with the increase of polymer concentration at agitation speeds of 50 and 100 rpm, which is in accordance with the study of Velasco et al. (1999): these authors evaluated the effect of HPMC:SD ratio on drug release and demonstrated that the n exponent was statistically higher for the formula with the highest polymer concentration, indicating a greater role of erosion.

T_{50} (time to dissolve 50% of the drug in the pharmaceutical dosage form), T_{90} (time to dissolve 90% of the drug in the pharmaceutical dosage form), obtained from the most suitable kinetic model to explain SD release, and DE (dissolution efficiency), were the parameters used to compare the dissolution profiles. T_{50} and T_{90} values decreased with agitation speed increase and with polymer concentration increase in the formulation, being consistent with DE values. Correlation between DE, T_{50} and T_{90} (parameters), and agitation speed or polymer concentration (variables) was considered appropriate when coefficient of determination (r^2) values were greater than 0.9. Low slope (a) values indicate that variables changes has low-impact on dissolution performance.

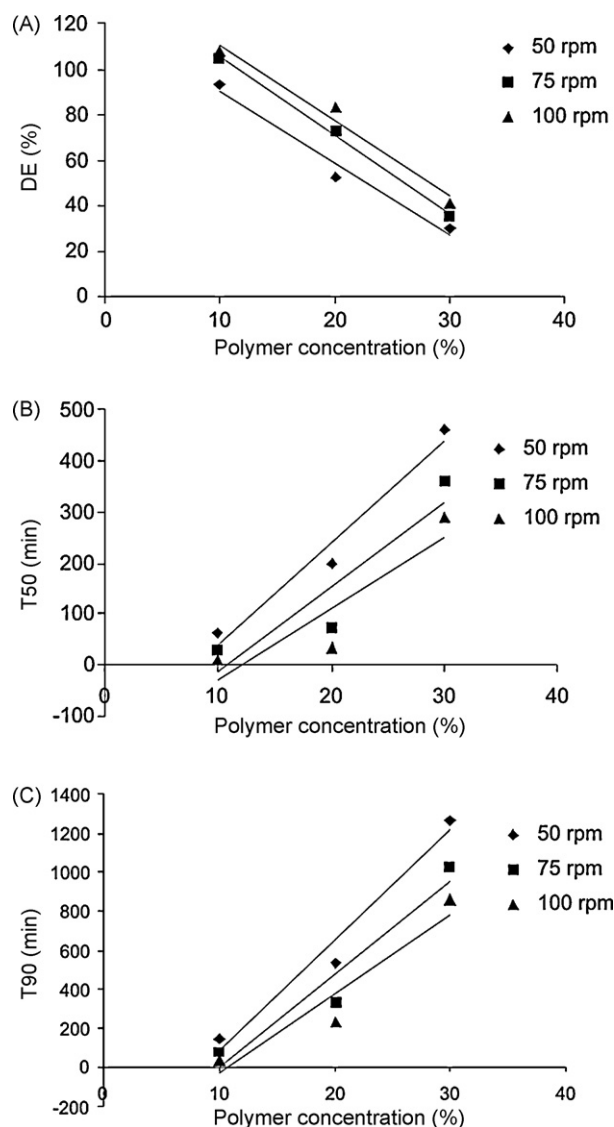


Fig. 3. Correlation between parameters DE (A), T_{50} (B) and T_{90} (C) and variable polymer concentration for F1, F2 and F3.

Considering DE, it was observed that F2 was more sensitive to variations in agitation speed, since it presented the highest a value (Fig. 2, Table 7). However, increasing polymer concentration has the same impact on DE at all agitation speeds, as can be concluded by similar a values for correlations between DE and polymer concentrations at 50, 75 and 100 rpm (Fig. 3, Table 7). In addition, DE is closely correlated with both agitation speed and polymer concentration, with r^2 values greater than 0.9, except for F1 in analysis of DE correlation with agitation speed ($r^2 = 0.8819$). The influence of agitation speed on kinetic parameters T_{50} and T_{90} , is lower for F1 than for F2 and F3, and the agitation speed of 50 rpm is more discriminating for formulation changes, since it presented the highest a values for both T_{50} and T_{90} (Figs. 2 and 3, Table 7). Regarding parameter T_{50} , a low correlation ($r^2 < 0.9$) with polymer concentration was observed at agitation speeds of 75 and 100 rpm, suggesting that these speeds are not adequate to differentiate between formulations (Fig. 3, Table 7).

It can be concluded that *in vitro* drug dissolution from matrix tablets is significantly influenced by the amount of polymer in the formulation and by the medium agitation speed. Low HPMC concentrations may be insufficient for drug release control, while formulae containing high concentrations of HPMC may no longer

present differences between them, regardless of agitation speed. It is needed to carefully extrapolate these findings to other matrices, since it should be considering the mechanism of drug delivery and the factors that affect it.

Also important is the choice of the parameters for comparing dissolution profiles. In this study, the parameter DE (dissolution efficiency) highly correlated with both agitation speed and polymer concentration. As expected, the rate of 50 rpm is more appropriate for assessing the impact of formula changes on dissolution performance. However, this needs to be confirmed through a bioavailability study, and an *in vitro*–*in vivo* correlation.

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