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Research Article

Bio-Dis and the Paddle Dissolution Apparatuses Applied to the Release Characterization of Ketoprofen from Hypromellose Matrices

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Abstract. The purposes of this work were: (1) to comparatively evaluate the effects of hypromellose viscosity grade and content on ketoprofen release from matrix tablets, using Bio-Dis and the paddle apparatuses, (2) to investigate the influence of the pH of the dissolution medium on drug release. Furthermore, since direct compression had not shown to be appropriate to obtain the matrices under study, it was also an objective (3) to evaluate the impact of granulation on drug release process. Six formulations of ketoprofen matrix tablets were obtained by compression, with or without previous granulation, varying the content and viscosity grade of hypromellose. Dissolution tests were carried out at a fixed pH, in each experiment, with the paddle method (pH4.5, 6.0, 6.8, or 7.2), while a pH gradient was used in Bio-Dis (pH1.2 to 7.2). The higher the hypromellose viscosity grade and content were, the lower the amount of ketoprofen released was in both apparatuses, the content effect being more expressive. Drug dissolution enhanced with the increase of the pH of the medium due to its pH-dependent solubility. Granulation caused an increase in drug dissolution and modified the mechanism of the release process.

KEY WORDS: apparatus 3; Bio-Dis; dissolution; hypromellose matrix; ketoprofen.

INTRODUCTION

Matrix tablets are among the simplest and least expensive extended-release dosage forms, being widely explored in the pharmaceutical industry. Although many materials can be used to modulate drug release from these systems, hydrophilic polymers are the most employed, especially the cellulose derivative hypromellose (1–4).

When developing hydrophilic matrix tablets, it is pertinent to meticulously evaluate the release characteristics of the formulations by applying dissolution methods which simulate the pH, ionic strength, viscosity, motility, or other relevant gastrointestinal conditions, as means of improving the possibility of correlation between *in vitro* and *in vivo* performances (5–8).

In this context, US Pharmacopeia dissolution apparatus 3 (Bio-Dis) offers important advantages over apparatuses 1 (rotating basket) and 2 (paddle) since it shows a superior hydrodynamics and allows the exposure of the dosage form to different conditions of pH, composition of the medium and agitation, in a single test (9,10).

The use of apparatus 1 to evaluate the dissolution characteristics of hydrophilic matrices that swell after hydration is discouraged since the matrix clogs the holes in the rotating basket, disrupting the hydrodynamics of the test (6). But, interestingly, according to the bibliography review carried out for the elaboration of this work, just a few papers report the use of Bio-Dis for the elucidation of drug release from hydrophilic matrices in comparison with the paddle apparatus, although the former method seems to be more appropriate for this application.

Considering the above-mentioned aspects, the purposes of the present work were: (1) to study the release characteristics of ketoprofen from hypromellose matrix tablets, comparatively evaluating the influence of polymer viscosity grade and content on the dissolution profiles obtained with Bio-Dis and the paddle apparatuses and (2) to investigate the effect of dissolution medium pH on drug release. Furthermore, since direct compression had not shown to be appropriate to obtain the matrices under study, it was also an objective of this work (3) to evaluate the impact of granulation on drug release process.

MATERIALS AND METHODS

Materials

Materials used to prepare tablets were: hypromellose (Methocel® K4M CR and K100M CR, Colorcon, Cotia, SP, Brazil), microcrystalline cellulose (Blanver, Cotia, SP, Brazil), polyvinylpyrrolidone (Henrifarma, São Paulo, SP, Brazil), ketoprofen, colloidal silicon dioxide, and magnesium stearate (SP Farma, São Paulo, SP, Brazil). All other chemicals and reagents used were of analytical grade.

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Table I. The 2^2 Factorial Design Which Generated FM1–FM4 and the Composition of the Formulations (%)

	Factors			Composition (%)			
Formulation	A	B	Ketoprofen	Methocel®	MC	CSD	MS
FM1	−	−	40	10 (K4M)	48.5	0.5	1.0
FM2	+	−	40	10 (K100M)	48.5	0.5	1.0
FM3	−	+	40	20 (K4M)	38.5	0.5	1.0
FM4	+	+	40	20 (K100M)	38.5	0.5	1.0

Factors: (A) hypromellose viscosity grade and (B) hypromellose content. Levels of A: (−) 4,000 mPa s and (+) 100,000 mPa s; levels of B: (−) 10% and (+) 20%
MC microcrystalline cellulose, *CDS* colloidal silicon dioxide, *MS* magnesium stearate

Dissolution Media

The dissolution media used were simulated gastric fluid without enzymes (pH1.2), pH4.5, pH6.0, and pH7.2 phosphate buffer solutions, and simulated intestinal fluid without enzymes (pH6.8) (11,12).

Solubility Tests

Excess of ketoprofen was added to the dissolution medium in a plastic flask, which was closed and maintained under controlled agitation and temperature (200 rpm, 37°C) for 72 h (Tecnal TE 420 shaker, Piracicaba, SP, Brazil). Then, filtered samples were spectrophotometrically assayed at λ_{max}= 260 nm (spectrophotometer DU 640, Beckman Instruments, Fullerton, CA, USA). The equilibrium solubility of the drug was tested in each dissolution medium in duplicate.

Factorial Design and Preparation of Tablets

Four formulations (FM1–FM4) of matrix tablets containing 200 mg of ketoprofen were obtained according to a 2^2 factorial design (Table I), aiming at elucidating the influence of hypromellose viscosity grade (factor A: levels 4,000 or 100,000 mPa s) and content (factor B: levels 10% or 20%) on drug release, which was evaluated as the drug dissolved at 6 and 12 h ($Q\%_{6\ h}$ and $Q\%_{12\ h}$). Matrices were prepared by direct compression in a tablet machine (Lawes 14 PSC, São Paulo, SP, Brazil), equipped with 11-mm punches and dies. Besides ketoprofen and hypromellose (Methocel®), other formulation's components were microcrystalline cellulose, colloidal silicon dioxide, and magnesium stearate, as shown in Table I.

Two additional formulations (FM5 and FM6), the compositions of which are exhibited in Table II, were prepared by wet granulation. A 10% polyvinylpyrrolidone aqueous solution was added to ketoprofen and the resulting mass was granulated using a 2.38-mm sieve. Granules were dried at 45°C and calibrated in a 1.19-mm sieve. Then, they were mixed with the other components (hypromellose, microcrystalline cellulose, colloidal silicon dioxide, and magnesium stearate) and compressed in a tablet machine (Fabbe-Primar, São Paulo, SP, Brazil), producing matrices with 11 mm of diameter.

Table II. Composition of Ketoprofen Granules and FM5–FM6 (%)

Granules	Component (%)	
Ketoprofen	93.8	
PVP	6.3	
Tablets:	FM5	FM6
Granules	42.7	42.7
MC	35.8	35.8
Methocel K 4 M CR	20.0	–
Methocel K 100 M CR	–	20.0
CSD	0.5	0.5
MS	1.0	1.0

PVP poly(vinyl pyrrolidone), *MC* microcrystalline cellulose, *CDS* colloidal silicon dioxide, *MS* magnesium stearate

Evaluation of Tablets Physical Properties

Weight variation was verified in an analytical balance (Sartorius BL 210 S, Göttingen, Germany) using 20 tablets. Thickness, diameter, and crushing strength were determined in an automatic instrument (Logan Instruments HDR-300, Somerset, NJ, USA) using ten tablets. Friability was measured as the weight loss (%) of 20 tablets after 100 revolutions in a friabilator (Nova Ética, Vargem Grande Paulista, SP, Brazil).

Dissolution Tests

Paddle Method

An SR8 Plus dissolution tester (Hanson Research Corp., Chatsworth, CA, USA) was used in the following conditions: 50 rpm, 900 mL of dissolution medium at 37°C, during 12 h. At previously defined time points, 10-mL samples were manually collected and filtered. Dissolved ketoprofen was spectrophotometrically assayed at λ_{max}=260 nm (Beckman Instruments DU 640 spectrophotometer, Fullerton, CA, USA). Tests were carried out in triplicate (except FM2), using dissolution media with pH values of 4.5, 6.0, 6.8, and 7.2. FM2 was tested in duplicate since bulk's unsatisfactory flow and compaction properties made production difficult and, as a consequence, just a few tablets were obtained.

Bio-Dis

A Bio-Dis III extended-release tester (Vankel, Cary, NC, USA) was used, employing an agitation of 8 dips per minute and 250 mL of dissolution medium at 37°C. Each tablet was placed

Table III. Weight Variation, Crushing Strength, Friability, Thickness, and Diameter of FM1–FM6

Tests	Mean±standard deviation (relative standard deviation %)				
	FM1	FM3	FM4	FM5	FM6
Weight variation (mg)	0.4626±0.0281 (6.1)	0.4566±0.0169 (3.7)	0.4490±0.0182 (4.0)	0.5081±0.0044 (0.9)	0.5034±0.0046 (0.9)
Diameter (mm)	11.0±0.0 (0.2)	11.0±0.0 (0.1)	11.0±0.0 (0.1)	11.1±0.0 (0.1)	11.1±0.0 (0.2)
Thickness (mm)	5.9±0.1 (1.2)	5.5±0.1 (1.2)	5.4±0.0 (0.8)	6.1±0.1 (0.9)	5.8±0.1 (1.3)
Friability (%)	3.9	2.8	1.5	0.8	0.6
Crushing strength (Kgf)	5.0±1.7 (34.7)	6.9±2.9 (41.6)	9.8±5.1 (51.4)	6.0±0.4 (7.2)	7.0±1.9 (27.4)

Tests were not performed for FM2

in a dipping tube with a polypropylene bottom screen of 420-μm mesh size, the mesh size of the top screen being also 420 μm. The pH values and dosage form residence times in each medium were selected to simulate the human gastrointestinal tract in fasted conditions: pH1.2–1 h; pH4.5–0.5 h, pH6.0–2.5 h, pH6.8–6 h, pH7.2–2 h (8,9). Dipping tubes were drained for 1 min before moving to the following media. At defined time intervals, 3-mL samples were automatically collected and filtered. Keto-

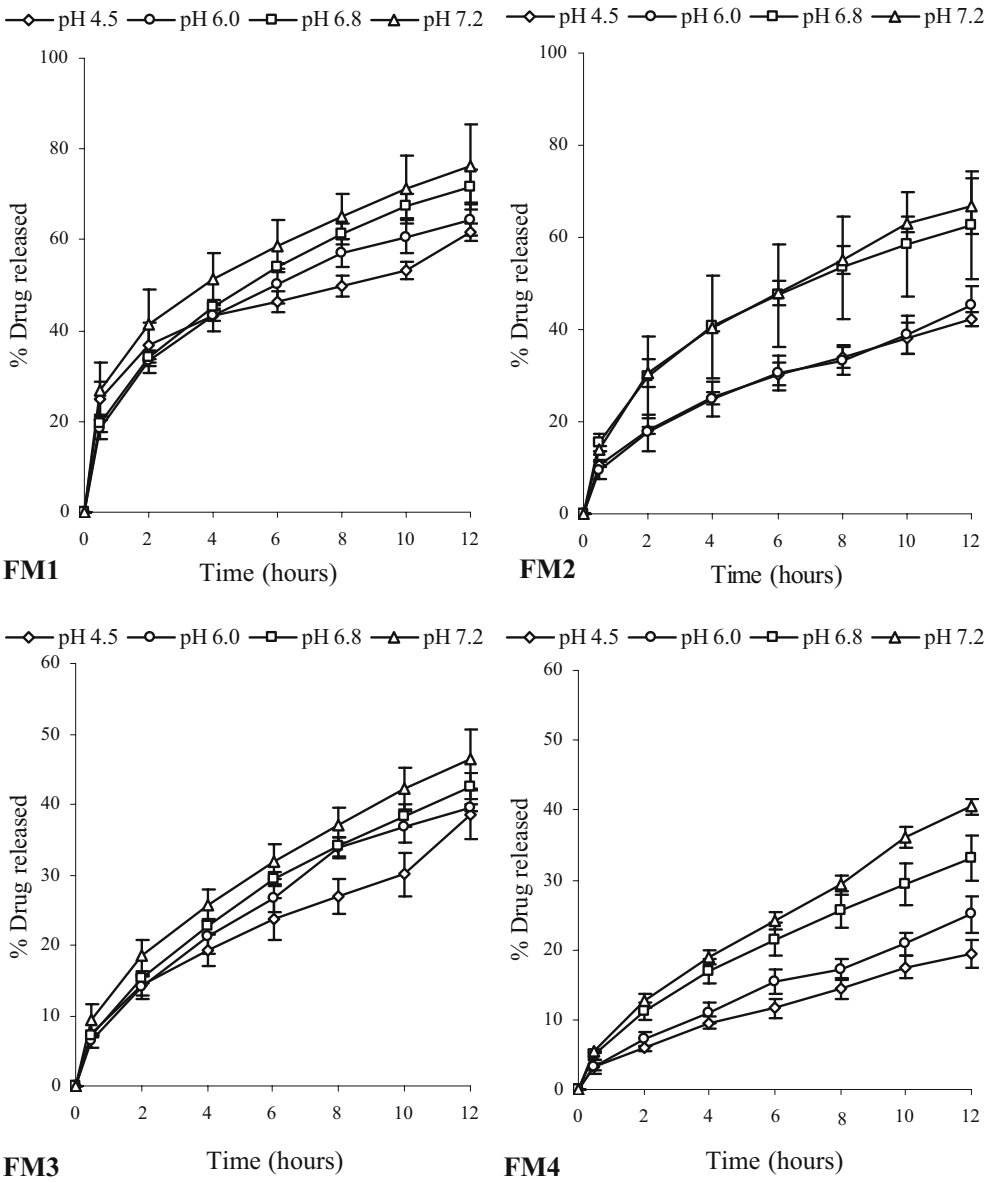

Fig. 1. Dissolution curves of FM1–FM4 at pH4.5–7.2 obtained with the paddle method: comparison among ketoprofen release profiles from the same formulation at different pH values

profen was spectrophotometrically assayed at λ_{max}=260 nm (Beckman Instruments DU 640 spectrophotometer, Fullerton, CA, USA). All experiments were performed in triplicate.

Statistical/Mathematical Treatment of Results

The percentages of drug dissolved at 6 and 12 h ($Q\%_{6\,h}$ and $Q\%_{12\,h}$) and at 7 and 12 h ($Q\%_{7\,h}$ and $Q\%_{12\,h}$) were established as responses (2^2 factorial design, Table I) for the paddle and Bio-Dis apparatuses, respectively. The effects of hypromellose viscosity grade and content on the responses were estimated and the statistically significant effects was established by analysis of variance (ANOVA; α=0.05%) (13,14). Calculations were carried out using Microsoft Office Excel® software.

One-way ANOVA and Tukey's test (α=0.05%) were used to compare the mean percentages of drug dissolved at 2, 6, and 12 h ($Q\%_{2\,h}$, $Q\%_{6\,h}$, and $Q\%_{12\,h}$), registered at pH values from 4.5 to 7.2 using the paddle apparatus. The purpose was to evaluate if altering the pH of the dissolution medium would modify the drug release profile of the formulation. Calculations were performed using GraphPad Prism® version 4.00 software.

A comparison was established between the Bio-Dis dissolution profiles of FM3/FM5 and FM4/FM6 by the application of the Weibull equation, with the determination of b (shape parameter) and T_d (the time required for 63.2% of the drug present in the dosage form to get dissolved) (15–17). Besides, the two-sample paired t test was used to compare couples of mean T_d values. The objective was to elucidate if granulation influenced drug release. Calculations were carried out using Microsoft Office Excel® software.

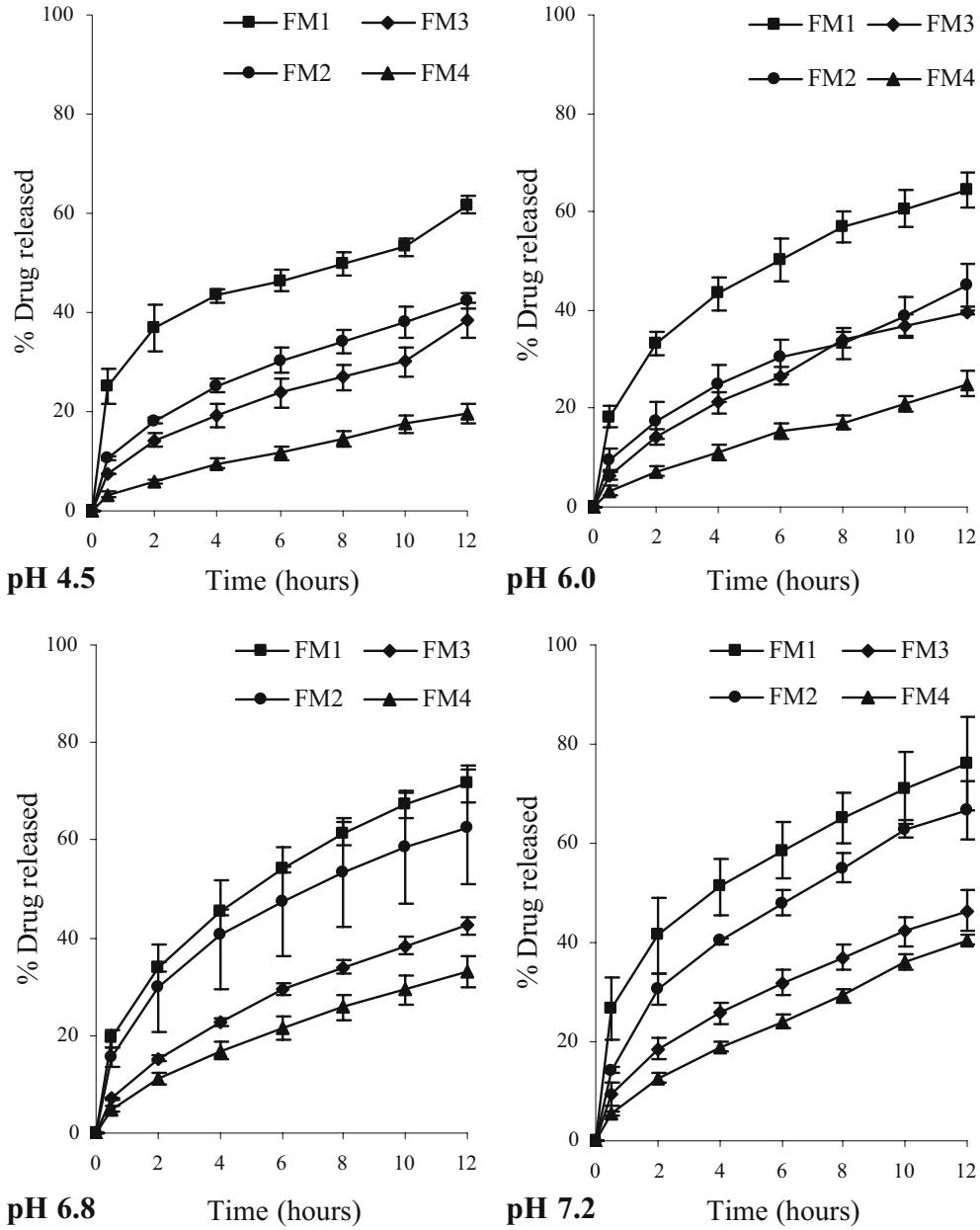

Fig. 2. Dissolution curves of FM1–FM4 at pH4.5–7.2 obtained with the paddle method: comparison among ketoprofen release profiles from different formulations at the same pH value

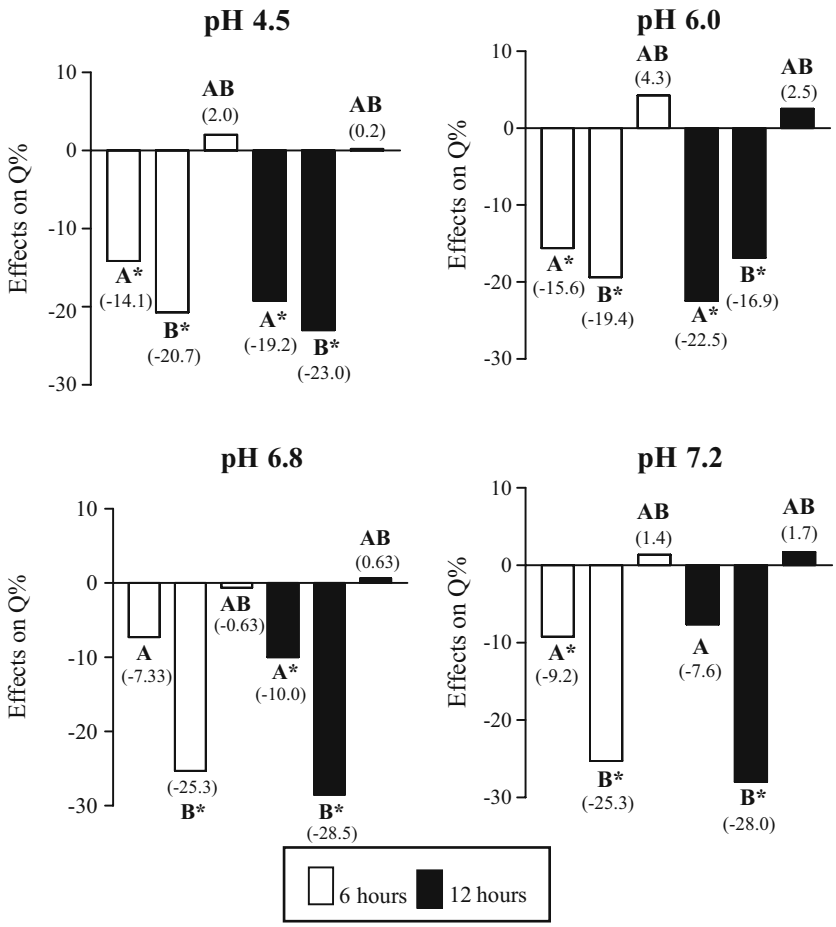

Fig. 3. Estimation of the effects of hypromellose viscosity grade (*A*) and content (*B*) on the percentages of drug dissolved (Q%) at 6 and 12 h in the paddle apparatus. *Statistically significant ($P<0.05$)

RESULTS

Ketoprofen solubility rose as the pH of the dissolution medium increased, this pattern being more expressive over the pKa of the drug (~4.6), as expected for acidic compounds. The maximum amount of drug dissolved varied from 0.11 mg/mL at pH1.2 to 9.23 mg/mL at pH7.2 and it implied that when using 250 mL of dissolution medium (Bio-Dis) the sink conditions were satisfied at pH6.8 and 7.2, while they were obeyed at pH 6.0, 6.8, and 7.2 with 900 mL of medium (paddle apparatus).

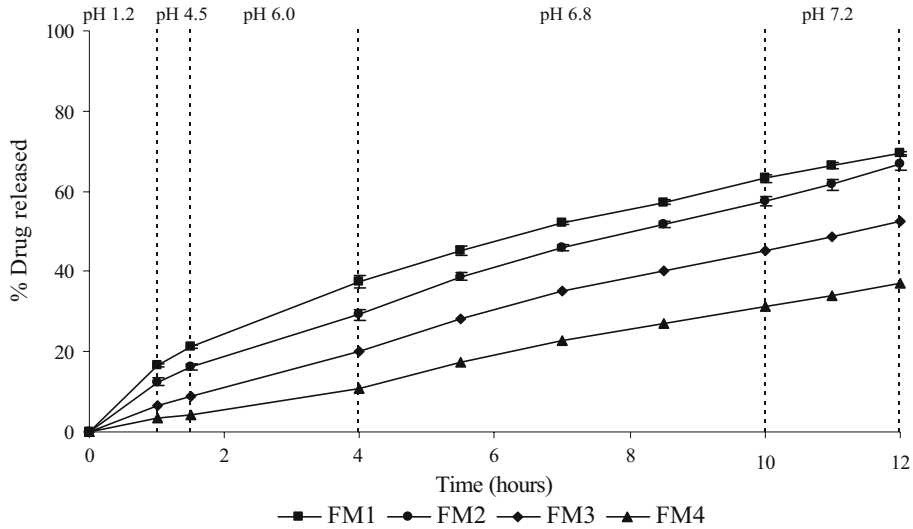

Fig. 4. Dissolution profiles of FM1–FM4, using the Bio-Dis apparatus

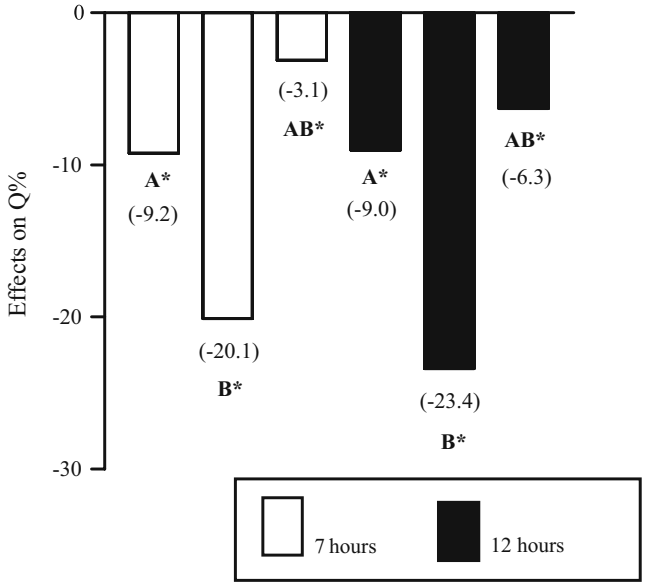

Fig. 5. Estimation of the hypromellose viscosity grade (*A*) and content effects (*B*) on Q% values at 7 and 12 h in the Bio-Dis apparatus. *Statistically significant ($P<0.05$)

Weight variation, crushing strength, friability, thickness, and diameter of tablets are presented in Table III. FM1, FM3, and FM4 showed high friability, while FM5 and FM6 presented satisfactory physical properties, with lower weight variation and friability. Due to the preparation problems mentioned above, physical tests were suppressed for FM2 to make possible its evaluation in all desired dissolution conditions.

The Effect of the pH of the Dissolution Medium on Drug Release from the Formulations

Figure 1 shows the dissolution curves of formulations FM1 to FM4 at pH4.5, 6.0, 6.8, and 7.2, obtained with the paddle method. Aiming at establishing the influence of the pH of the medium on the amount of ketoprofen released from each formulation, the results of Q% at 2, 6, and 12 h extracted from the dissolution curves were statistically compared.

In the case of FM1 and FM2, the pH of the medium did not influence the amount of ketoprofen released at 2 h ($P>0.05$). FM3 showed the same $Q\%_{2\ h}$ at pH4.5, 6.0, and 6.8 ($P>0.05$); however, drug release was superior at pH7.2 ($P<0.05$). For FM4, $Q\%_{2\ h}$ obtained at pH4.5 and 6.0 were similar ($P>0.05$) and these values were inferior to those determined at pH6.8 and 7.2 ($P<0.05$), which were equal ($P>0.05$).

The pH of the medium exerted the same effect on Q% at 6 h for FM1 and FM3, i.e., the same amount of the drug was released from the matrix tablet at pH4.5, 6.0, and 6.8 ($P>0.05$). However, from a statistical point of view, Q% at pH4.5 was inferior to that at pH7.2 ($P<0.05$), but there was no difference among Q% at pH6.0, 6.8, and 7.2 ($P>0.05$). For FM2 and FM4, the same influence was exerted by pH on $Q\%_{6\ h}$ and this influence was equal to that observed for FM4 at 2 h.

At 12 h, the influence exerted by pH on drug release from FM1 and FM3 was the same observed for these formulations at 6 h. In the case of FM2, $Q\%_{12\ h}$ at pH4.5 and 6.0 were equal ($P>0.05$), these values being inferior to that at pH7.2 ($P<0.05$). Nevertheless, statistically, Q% at pH4.5 was inferior to that at pH6.8 ($P<0.05$), while the latter value was equal to that observed at pH6.0. In the same manner, Q% at pH6.0 was inferior to that at 7.2 ($P>0.05$), but the latter value was equal to that observed at pH6.8. For FM4, the results of $Q\%_{12\ h}$ were similar at pH4.5 and 6.0 ($P>0.05$), but in the other established comparisons the increase in the pH of the medium resulted in a higher amount of drug released.

Comparative Evaluation of the Effects of Hypromellose Viscosity Grade and Content on Ketoprofen Release from Matrix Tablets Using Bio-Dis and the Paddle Apparatuses

Figure 2 illustrates the comparison among the dissolution profiles of formulations FM1–FM4 at each pH condition (pH 4.5–7.2) using the paddle apparatus. The differences among the formulations' performances, observed in all dissolution media, occurred because of the adoption of distinct hypromellose viscosity grade and/or content in each of them. Figure 3 shows that both hypromellose viscosity grade and content main effects were negative on Q% at 6 and 12 h in all tested dissolution media. Besides, with the exception of pH 6.0 results at 12 h, hypromellose content was the main factor that influenced drug release in the remaining conditions. There was no significant effect of the interaction between the factors on drug release.

FM1–FM4 Bio-Dis dissolution profiles are shown in Fig. 4. Figure 5 shows that the effects of hypromellose viscosity grade and content on drug release ($Q\%_{7\ h}$ and $Q\%_{12\ h}$ extracted from the dissolution curves) were negative in the Bio-Dis apparatus, as observed for the paddle apparatus. Also, hypromellose content was the main factor which has influenced drug release. There was significant effect of the interaction between the factors on drug dissolution.

The Impact of Granulation on Drug Release

Results of parameters b and T_d, obtained from the comparison between the dissolution profiles of FM3/FM5 and

Table IV. Results of b, T_d, and Coefficient of Correlation Obtained for the Comparison of the FM3–FM6 Dissolution Profiles using the Weibull Method

	Mean±SD (RSD %)			
Variables	FM3	FM4	FM5	FM6
Correlation	0.9965±0.0013 (0.1)	0.9965±0.0004 (0.0)	0.9970±0.0005 (0.1)	0.9976±0.0010 (0.1)
b	0.8±0.0 (6.2)	0.9±0.0 (2.5)	1.4±0.0 (0.5)	1.3±0.0 (0.1)
T_d (hours)	17.0±1.1 (6.2)	25.2±0.4 (1.7)	12.7±0.3 (2.1)	21.8±0.3 (1.5)

FM4/FM6 using the Weibull equation, are presented in Table IV. The statistical comparison between T_d values demonstrated that granulation process modified ketoprofen dissolution rate from FM5 in relation to FM3 and from FM6 in relation to FM4 since there was a reduction in the time required to release 63.2% of the drug ($P<0.05$). FM3 and FM4 *b* values indicated that these formulations showed parabolic dissolution curves, while FM5 and FM6 *b* values indicated a sigmoid format.

DISCUSSION

The Effect of the pH of the Medium on Drug Release from the Formulations

Drug release from hypromellose matrices occurs by diffusion of the drug through the hydrated polymer and/or erosion of the dosage form. Diffusion is limited by drug solubility since nondissolved drug present in the matrix is unavailable for diffusing (18).

Results showed that drug release from all formulations suffered the influence of the pH of the dissolution medium to some extent and that, in general, drug dissolution enhanced as the pH increased because ketoprofen solubility is higher in such condition, causing the improvement of the diffusivity through the matrix.

FM1 (lower in both hypromellose content and viscosity grade) was the less susceptible to the medium pH, in terms of dissolution properties, while the most susceptible was FM4 (higher in both hypromellose content and viscosity grade). When results of formulations with the same type of hypromellose were analyzed (FM1 and FM3 or FM2 and FM4), it was seen that differences between the dissolution profiles of the same formulation at distinct pH values started before, early at 2 h, for FM3 and FM4, respectively (higher content of the polymer). Between formulations with the same hypromellose content (FM1 and FM2 or FM3 and FM4), a more accentuated pH effect occurred on the dissolution curves of FM2 and FM4, respectively (highest viscosity grade of the polymer).

Since ketoprofen has pH-dependent solubility and diffusion requires previous dissolution of the drug, the susceptibility of the formulation to pH variations revealed the mechanism by which drug release occurred. So, results also indicated that erosion had preponderated over diffusion in the case of FM1, while diffusion was the main mechanism of drug release from FM4. Between formulations with the same hypromellose type, there was a more expressive contribution of diffusion for drug release from that with the highest content of the polymer (the contribution of diffusion was greater for FM3 and FM4 in relation to FM1 and FM2, respectively). On the other hand, between the same hypromellose content formulations, there was a more expressive contribution of diffusion for drug release from the formulation with the highest viscosity grade hypromellose (the contribution of diffusion was more important for FM2 and FM4 in relation to FM1 and FM3, respectively).

Comparative Evaluation of the Effects of Hypromellose Viscosity Grade and Content on Ketoprofen Release from Matrix Tablets Using Bio-Dis and the Paddle Apparatuses

The paddle is the most used apparatus to evaluate the release characteristics of matrix tablets, while there are evidences that Bio-Dis is the most appropriate one for sustained-release oral dosage forms since it can more efficiently simulate *in vivo* conditions. So the question to be answered was how the formulation variables (hypromellose viscosity grade and content) would impact on drug release in these two very different dissolution apparatuses.

Despite the fact that dissolution equipment differ with respect to the agitation system type, intensity of agitation, volume of media per dissolution vessel, and shape of the vessels, resulting in very distinct hydrodynamics, and despite the paddle method having been operated with the same medium during the whole test, while a gradient of pH had been used in Bio-Dis, the effects of the formulation variables

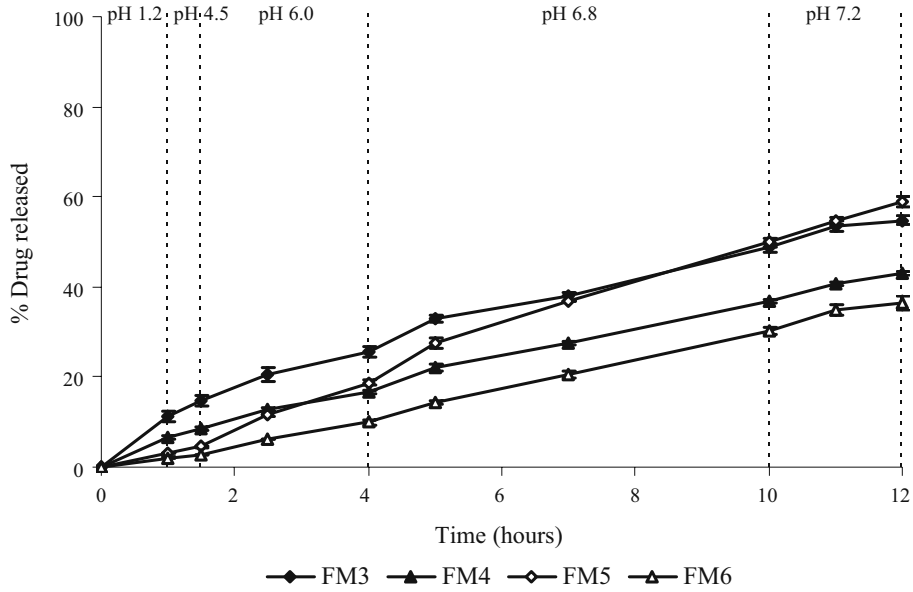

Fig. 6. Dissolution profiles of FM3–FM6, using the Bio-Dis apparatus

were negative in both apparatuses: the higher the hypromellose content and/or viscosity grade were/was, the slower the rate of ketoprofen release was. Furthermore, in both dissolution equipment, hypromellose content was the main factor which has influenced drug release.

The negative effects of the studied formulation variables on drug dissolution curves obtained using the paddle method are well known. However, the reason that led to the realization of this study was our previous experience with hypromellose matrices containing another drug of pH-dependent solubility, which displayed completely different results when submitted to the dissolution methods described in this paper. The same formulation that was able to sustain drug release over a period of 12 h using the paddle apparatus and dissolution medium of pH6.8 (under sink conditions) suffered disintegration in the first hours of the experiment using Bio-Dis and a gradient of pH (data not yet published). This experience associated with the results of the present work indicate that the qualitative and quantitative composition of hypromellose matrix tablets can led to very distinct results when the paddle apparatus and Bio-Dis are used and scrutiny needs to be used in order to evaluate the significance of *in vitro* data.

Although establishing the most appropriate apparatus for evaluating the dissolution characteristics of hydrophilic matrices was out of the scope of this work, results showing the influence of the pH of the medium on ketoprofen release rate suggest that Bio-Dis can provide a better approximation of the dissolution *in vivo* performance of hypromellose matrix tablets containing drugs with pH-dependent solubility.

The Impact of Granulation on Drug Release

Besides the release characteristics of the formulation, powder mixture flow and compactability are also important. FM5 and FM6, obtained with previous granulation, showed a superior performance during compression and generated tablets with better physical characteristics than FM1–FM4. However, rate and mechanism of drug release have changed from FM5 and FM6 in comparison with the respective formulations obtained by direct compression.

According to T_d values, granulation improved the rate of ketoprofen release and it seems to be contradicted for the dissolution profiles of FM4 and FM6 (Fig. 6) since FM6 showed inferior amounts of drug dissolved during the 12 h of the test. However, ketoprofen release was superior for FM3 in comparison with FM5 until 7 h and, after this, the dissolution profile of FM3 was achieved and exceeded (at 12 h) by FM5, suggesting that 63.2% of drug released would be reached earlier for this last formulation if the test would not be interrupted, in agreement with T_d parameter. So, considering that FM5 and FM6 contained the same amount of hypromellose and that FM6 was prepared with the highest viscosity grade of the polymer, it is possible that the improvement in the rate of drug dissolution observed for FM5 could have happened later for FM6, confirming the behavior predicted by T_d.

Although the Weibull function has been empirically used for the analysis of dissolution and release data, a link between the values of b and the mechanism of drug release was provided. It was established that values of b in the range 0.75–1 indicate a diffusion-controlled mechanism combined with another release pathway (19). This interpretation is in agreement with the inference above made about the contribution of diffusion and erosion for ketoprofen release from FM3 and FM4: diffusion has preponderated over erosion in both formulations, the contribution of diffusion being even more expressive for FM4. It is interesting to note that b=0.8 for FM3 and b=0.9 for FM4, i.e., the mechanism of drug release from FM4 is closer to pure diffusion according to the value of b since b=1 is compatible with first-order release obeying Fick's first law of diffusion.

On the other hand, $b>1$ indicates sigmoid dissolution curves, S-shaped, denoting that a complex mechanism governs the release process (19). Considering FM5 and FM6, it can be caused by the presence of ketoprofen granules, which did not contain hypromellose. This way, at the beginning of the dissolution test, when the pH of the medium was lower, the rate of drug release was slower. Over the course of the experiment, ketoprofen granules dissolved in contact with higher pH media, creating pores through the polymer matrix, which altered the equilibrium between drug diffusion/matrix erosion and improved the rate of drug release. This change in the rate of ketoprofen release conferred the sigmoid format to the dissolution curves.

CONCLUSION

The higher the hypromellose viscosity grade and content used in the formulation were, the lower the amount of ketoprofen released was in both the paddle and Bio-Dis apparatuses. The content of the polymer had a more expressive impact on sustaining drug release than viscosity grade. Dissolution medium pH influenced drug release due to ketoprofen pH-dependent solubility. In general, drug dissolution was more accentuated in the higher pH media, but the susceptibility to pH variations changed among formulations. The more expressive the contribution of diffusion to drug release was, the more susceptible the release from the formulation to pH variations was. Granulation caused an increase in drug dissolution and modified the mechanism of drug release in comparison with the formulations prepared by direct compression.

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