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Influence of the viscosity grade and the particle size of HPMC on metronidazole release from matrix tablets

María Elena Campos-Aldrete, Leopoldo Villafuerte-Robles *

National Polytechnic Institute, Department of Pharmacy, Carpio y Plan de Ayala, Col. Santo Tomas, D.F. Mexico, México

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Abstract

Matrix tablets of metronidazole with hydroxypropyl methylcellulose (HPMC) were prepared by granulation with water and compaction at 127 MPa in a hydraulic press. The release profile of the obtained tablets was evaluated with the USP 23 apparatus 2 (paddle) at 100 rpm and using 0.1 N HCl as the medium. The influence of the HPMC viscosity grade and particle size on the release profile of metronidazole was evaluated at viscosity grades of 15, 860, 5000, 20 000 and 30 000 cP and at particle sizes of 163, 213, 335 and 505 μm. The results showed a linear relationship between the inverse of the release rate ($Q/t^{1/2}$) and the viscosity grade of HPMC, at a HPMC ratio of 10%. A linear relationship between the release rate and the cube of the diameter of the HPMC particles was also observed. Higher HPMC ratios (20 and 30%) showed no difference on release rate when the viscosity and the particle size were changed. An increasing burst effect occurred with increasing viscosity grades and increasing particle sizes of HPMC. © 1997 Elsevier Science B.V.

Keywords: Metronidazole; Hydroxypropyl methylcellulose; Viscosity; Particle size; Release rate and matrix tablets

1. Introduction

Common adverse effects of metronidazole involve the gastro-intestinal tract and the neurological system, especially with high doses. The adverse effects of metronidazole are generally dose-related [1]. Because of this, reduction of side effects of metronidazole (plasma peak levels) while prolonging its action by using controlled release oral dosage forms is highly desirable.

Substances used to modify drug release from a dosage form include natural products such as gelatin and alginic acid, chemically modified natural products such as cellulose ethers and esters and synthetic polymers such as polyvinyl chloride and methacrylate [2]. The cellulose ethers group of semisynthetic cellulose derivatives has found wide applications in hydrophilic matrices. The non-ionic ones are among the most used, because of their gelling efficacy independent of the pH of the medium. Hydroxypropyl methylcellulose (HPMC) was found especially useful in this field [3].

The most important variable in hydrophilic matrix systems is the rate at which the drug substance is released. The release of drug is controlled by the formation of a hydrogel layer around the matrix following exposure to aqueous fluid [4]. When a hydrophilic matrix comes into contact with water the pores near the surface of the matrix are filled with water and drug release is initially controlled by the dissolution of the drug in the water filled pores and by its diffusion in water. The high viscosity of the polymer solution in the pores slows down the drug transport by forming a gel layer [5].

The factors influencing the release of drugs from hydrophilic matrices include, viscosity of the polymer, ratio of the polymer to drug, mixtures of polymers, compression pressure, thickness of the tablet, particle

* Corresponding author. National Polytechnic Institute, Department of Pharmacy, Carpio y Plan de Ayala, Col. Santo Tomas, C.P. 11340, D.F. Mexico, México. Fax: + 52 5 3412215.

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size of the drug, pH of the matrix, entrapped air in the tablets, molecular size of the drug, molecular geometry of the drug, solubility of the drug [6], the presence of excipients or additives and the mode of incorporation of these substances [4,5,7].

Regarding the polymer's physical properties, Alderman [8] has suggested that particle size affects release through its incidence on the rate of formation of the gel. The rate of release would be dependent on the rate and extent of tablet swelling and on the rate of drug diffusion.

The effect of viscosity on the overall release kinetics, as described by Kuu et al., can be seen from the Stokes–Einstein equation or the Wilke–Chang correlation. The diffusion coefficients are inversely proportional to the viscosity of medium [9]. However, substances like propanolol hydrochloride (26–64% of HPMC), aminophylline (16–54% of HPMC) and promethazine hydrochloride (55–86% of HPMC) have not shown significantly different release profiles with viscosity grades of HPMC of 850 cP and above (12 450 and 93 000 cP), when released from matrix tablets [10,11].

Different equations have been used to describe the relationship between drug release and time in hydrophilic matrix tablets. The most useful has been the Higuchi or square-root equation [7,10–13], although other equations like the empirical equation proposed by Peppas [14] and the zero and first order equations [7,14] have also been used.

In a previous study [13], the effects of moisture content, compaction pressure and HPMC ratio on the dissolution and mechanical properties of metronidazole tablets were evaluated. The influences on release rate of HPMC particle size, drug:HPMC ratio and HPMC viscosity grade are presented in this paper.

2. Materials and methods

2.1. Materials

The pharmaceutical excipient HPMC was obtained as Demacol® and Methocel®, both of pharmaceutical quality (producer: Derivados Macroquimicos S.A.-Mexico). Demacol® with viscosity grades of 15, 860, 5000, 20 000 and 30 000 cP, and with a nominal particle size of 420 μm was used. Methocel® having the viscosity grade of 4000 cP and with particle size range between 149 and 590 μm was used. The Methocel® particles were separated using sieves into four fractions with average particle sizes of 163, 213, 335 and 505 μm. Metronidazole was of the USP type and with a nominal particle size of 112 μm.

2.2. Methods

2.2.1. Granulation

Of each formula, 20 g, were prepared by mixing corresponding proportions of the components for 15 min (18 rpm) in a twin shell blender. Each mixture was moistened by aspersion, kneaded for 5 min and sifted using a No. 12 sieve. The mixture was again moistened, kneaded for 3 min and sifted through the same sieve. The resulting granulations were dried at 30°C in beds with a thickness of 1 cm, until a moisture content between 0.5 and 1.0% was achieved.

All tablets contained 400 mg metronidazole. The effects of the following variations in tablet formulae on dissolution rates were examined:

(a) viscosity grade of HPMC (Demacol®). Using each of the five viscosity grades of HPMC, tablets were made containing 44 mg HPMC (10%). For concentrations of 20% HPMC, tablets were made containing 100 mg HPMC of three different viscosity grades (860, 5000 and 20 000 cP) whereas for concentrations of 30% HPMC, tablets were made containing 171 mg HPMC of four different viscosity grades (860, 5000, 20 000 and 30 000 cP).

(b) particle size of HPMC (Methocel®). Using each of the four particle sizes of HPMC, tablets were made containing 44 mg of HPMC (10%). For concentrations of 20 and 30% HPMC, tablets were made containing 100 and 171 mg HPMC, respectively, under three different particle sizes (163, 213 and 335 μm).

2.2.2. Tableting

Flat-faced tablets of 12.7 mm diameter were compressed for 5 s on a hydraulic press adapted with a manometer at a compaction pressure of 127 MPa.

2.2.3. Metronidazole release curves

The release profiles were determined with USP 23 apparatus 2 (paddle) [15] at 100 rpm using 900 ml of 0.1 N hydrochloric acid at 37°C as a medium. Metronidazole solubility in water is 1.0 g/100 ml [16] and thus, the dissolution of 400 mg/900 ml can be considered under sink conditions. The effect of pH of the medium on the release profile and stability of the samples was studied earlier and no significant changes were observed. These dissolution conditions are similar to those used by Chemtob [17] for metronidazole microcapsules and by Baveja [18] for centperazine sustained release tablets. Filtered samples of dissolution medium, taken at different times, were determined for their metronidazole content through ultraviolet absorption at λ_{max} at 277 nm. Three repetitions were made for each determination and the results were registered as an average.

3. Results and discussion

3.1. Effect of the viscosity grade of HPMC

The dissolution data were plotted as the percentage of metronidazole dissolved against the square-root of time to give typical straight-line Higuchi type plots. The dissolution rates of these plots were determined by linear regression. The regression parameters and the determination coefficients of linear regression of the lines are given in Table 1. Fig. 1 depicts typical metronidazole release curves showing the additive effect of the viscosity grade and HPMC ratio on matrix tablets. The curve corresponding to 10% HPMC and a viscosity grade of 860 cP includes the calculated S.D. of the experimental points.

Most formulae were able to provide a stable matrix in the dissolution medium over the period of study and therefore, diffusion is assumed to be the most important factor controlling the rate of metronidazole release from the system. The formula containing 10% HPMC with a viscosity grade of 15 cP which dissolved completely, and the formula containing 30% HPMC with a viscosity grade of 30 000 cP which disintegrated the tablets, were the exceptions.

The release rate derived from the Higuchi equation predicts a zero intercept. However, all the release rate curves registered in Table 1 indicate either negative or positive effects. This represents a failure of the system to immediately attain the state of equilibrium diffusion (lag time) or the burst effect prior to the establishment of the diffusion controlled process.

Many matrix tablets in this part of the study presented a burst effect up to 20% of metronidazole. This burst effect shows differences according to the HPMC concentration (Table 1). For concentrations of HPMC of 20 and 30%, no relationship was found between these values and the HPMC viscosity type. This fact agrees with the findings of Ford et al. [10,11].

Table 1
Regression parameters of the metronidazole release curves for tablets made with HPMC

Viscosity (cP)	Slope (n = %/h$^{1/2}$)	Intercept (I = % metronidazole)	r^2
10% Hydroxypropyl methylcellulose			
15	71.93	−8.37	0.99
860	47.55	11.48	0.98
5000	38.14	8.24	0.98
20 000	31.80	20.2	0.98
30 000	25.94	69.8	0.85
20% Hydroxypropyl methylcellulose			
860	25.20	16.49	0.99
5000	25.07	15.92	0.99
20 000	23.25	14.42	0.99
30% Hydroxpropyl methlcellulose			
860	24.40	18.19	0.99
5000	28.79	−3.86	0.97
20 000	26.99	−0.275	0.98

$Q = n^* t^{1/2} + I$.

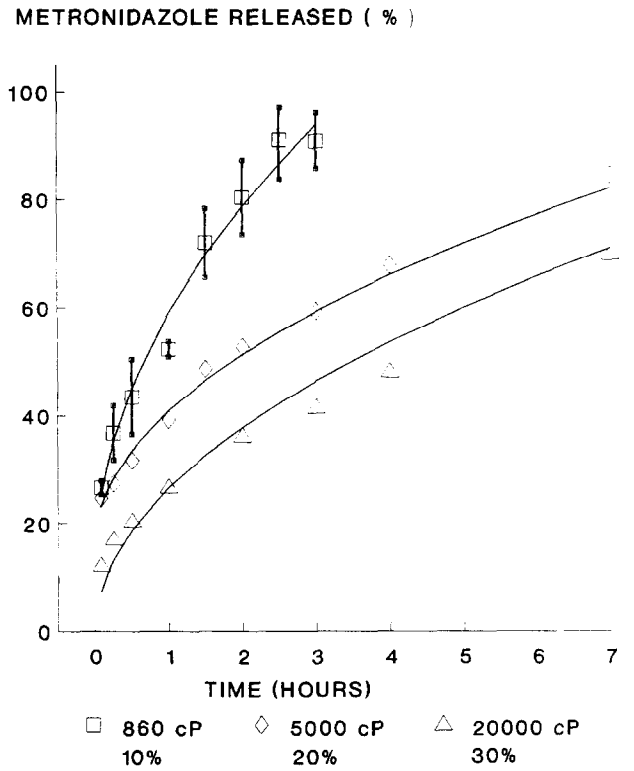

Fig. 1. Effect of viscosity grade and proportion of HPMC on the release profile of metronidazole from matrix tablets.

The data corresponding to 10% HPMC (Table 1) confirm the claim of Salomen et al. [10,11] that the lag time was dependent on the viscosity grade. Actually, higher viscosity grades (η) produced metronidazole–HPMC matrices with an increasing burst effect (% of metronidazole). This effect is depicted in Fig. 2 and described by the following equation:

$$1/\text{burst} = 0.1116 - 3.1183 \times 10^{-6} \times \eta \qquad r^2 = 0.82 \tag{1}$$

Several theories may account for this behavior. We assume for swellable systems like those made of HPMC which swell rather fast and with release kinetics controlled predominantly by the pore network rather than the polymer [19], that the continuous phase in the matrix will be formed by the metronidazole particles (90% of particles smaller than 10% of particles of HPMC) and that the gel barrier will be established only after the free dissolution of some metronidazole particles. This allows the swelled HPMC particles to come in a close contact to permit their adhesion. Further, the increasing burst effect produced by higher viscosity grades may be attributed to slower swelling rates with increasing viscosity grades, allowing greater time for the

free dissolution of metronidazole before the gel barrier is established.

For HPMC ratios of 20% or more, the HPMC particles are close enough to permit a faster establishment of the gel barrier, in a manner that the effect of different viscosity grades is minimized (Table 1 and Fig. 2).

Separating the burst effect by subtracting the intercepts from the percentage of metronidazole dissolved, the pure effect of the established gel barrier on the release rate can be observed. Fig. 3 depicts the effect of different viscosity grades on the calculated release profiles of metronidazole after the initial burst, under a HPMC ratio of 10%. Decreasing dissolution rates (n) are observed with increasing HPMC viscosity grades (η) (Table 1 and Fig. 4), as derived from Eq. (2):

$$1/n = \eta \times 5.466 \times 10^{-7} + 0.02169 \qquad r^2 = 0.96 \qquad (2)$$

The points in the graph are experimental and the line is the calculated regression with Eq. (2).

Following the assumptions made before and supposing that HPMC particles of increasing viscosity grades swell slower and produce swollen particles of smaller volumes [4], then matrices made of particles of HPMC with higher viscosity grades will contain pores of smaller diameters and will show slower release rates than those made of HPMC particles with lower viscosity grades, as has been observed in matrices with 10% HPMC.

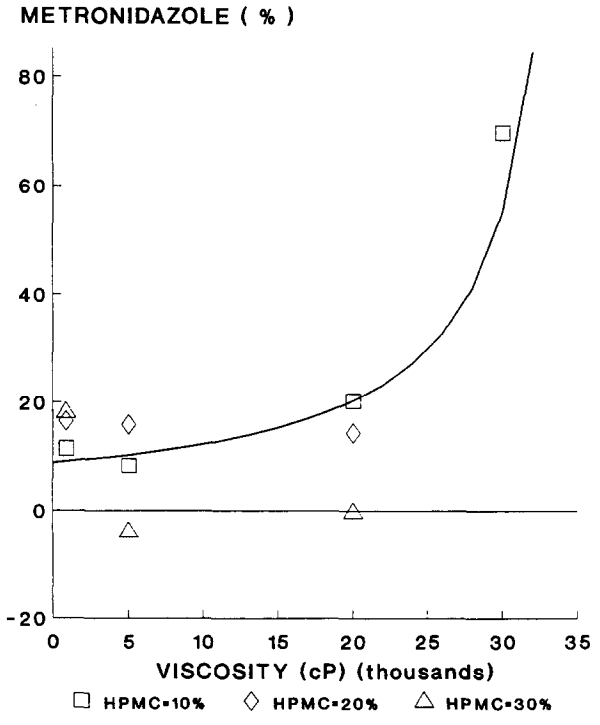

Fig. 2. Effect of viscosity grade of HPMC on the extrapolated concentration of metronidazole at zero time (lag time or burst effect), of matrix tablets made with different concentrations of HPMC.

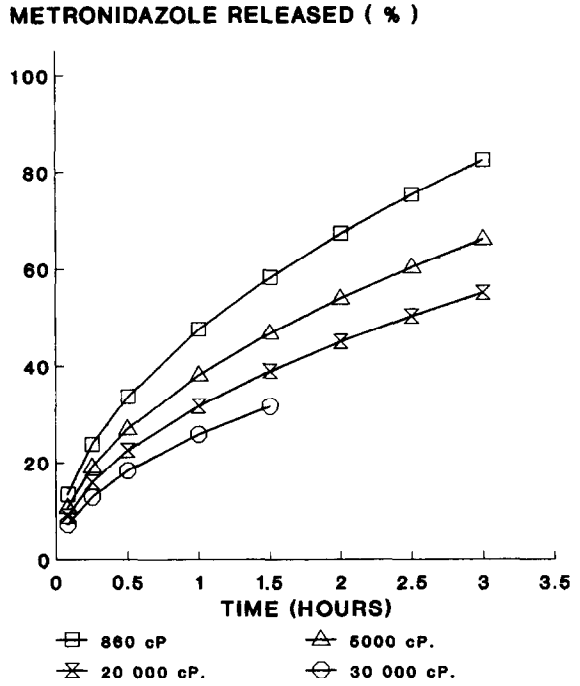

Fig. 3. Effect of viscosity grade of HPMC on the release profile of metronidazole from matrix tablets. Calculated curves for the release after burst effect.

The effect of the viscosity grade on the dissolution rate seems to disappear at higher concentrations of HPMC (20 and 30%). Apparently, the maximum effect of HPMC in decreasing the dissolution rate is achieved at an HPMC ratio of 10%, when the polymer has a viscosity grade of 30 000 cP or when higher concentrations ($\geq 20\%$) of polymer are used, irrespective of the viscosity grade studied (860, 5000 and 20 000 cP), with a limit dissolution rate of $25.6 \pm 1.8\%/h^{1/2}$.

Increasing HPMC ratios will increase the tortuosity and at the same time will increase the possibility of interaction between metronidazole and the swollen HPMC particles. Thus, HPMC ratios of 20% and more, for the given substance and particle size of the components, transform the porosity in a less important factor for the metronidazole release. This makes the release more dependent on the release restriction produced by the metronidazole–HPMC interaction leading to a constant or limit.

These results agree in part with those published by Ford et al. [10,11], for the promethazine. HCl, aminophylline and propanolol. HCl release from matrix tablets. Matrices with HPMC K100 produced consistently higher release rates at constant HPMC:drug ratios, compared with HPMC matrices of the types K4M, K15M and K100M, which showed similar release rates despite the variation in their molecular size, as stated by Ford et al. However, it is noteworthy that the release rates of these three substances show a clear

effect of the viscosity grade, when HPMC K100M is excluded, this effect being more important at low HPMC ratios. The dissolution rates showed a tendency to a limit. This limit, as explained before, can theoretically be reached by increasing the viscosity grade, the HPMC ratio or both of them. The exclusion of matrices of HPMC K100M would be justified due to some disintegration effects. Thus, this debilitated gel structure will show greater dissolution rates instead of smaller, when compared with HPMC K15M, as shown by nearly all release rates obtained by Ford et al, [10]. with the above-mentioned substances.

3.2. Effect of particle size of HPMC

The effect of the HPMC particle size on the release rate of metronidazole matrix tablets, using a HPMC ratio of 10%, is depicted in Fig. 5. The curve corresponding to a matrix made of particles of 335 μm includes the calculated standard deviation of the experimental points.

The calculated regression parameters and the corresponding determination coefficients of the Higuchi type plots of this part of the study are given in Table 2.

The slope of the curves or Higuchi type release rate (n), in matrices with 10% HPMC, increased with increasing particle size (d) of HPMC (Fig. 6), according to Eq. (3):

$$n = 34.40 + 10.79 \times 10^{-8} \times d^3 \qquad r^2 = 0.79 \qquad (3)$$

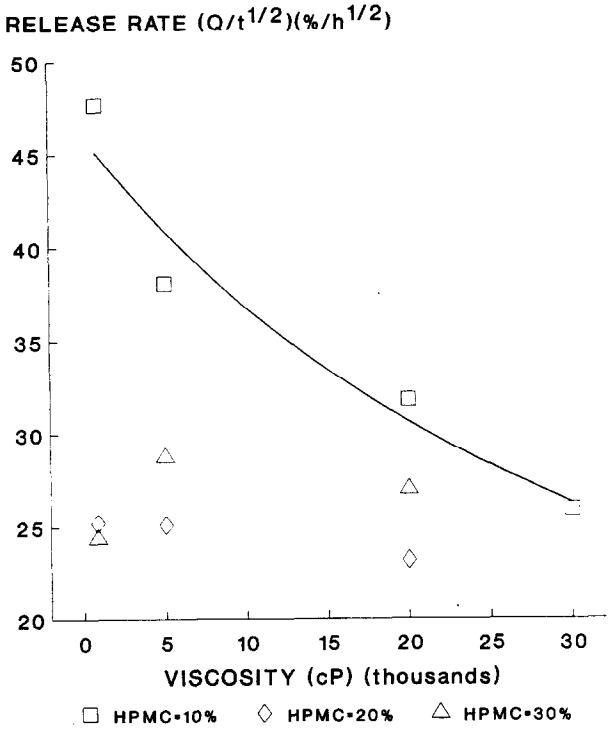

Fig. 4. Effect of viscosity grade of HPMC on the release rate of metronidazole from matrix tablets.

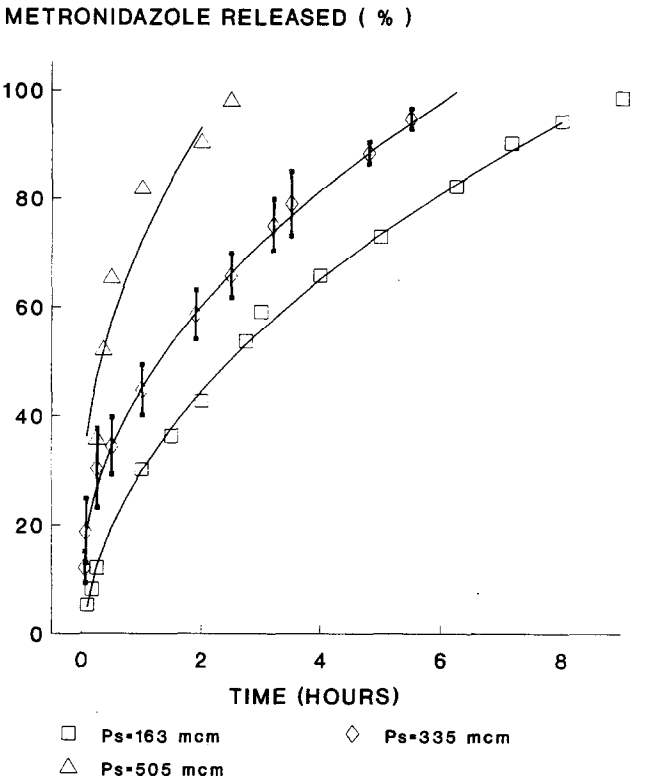

Fig. 5. Effect of particle size of HPMC on the release profile of metronidazole from matrix tablets containing 10% HPMC.

This effect can be explained assuming that particles of increasing size require increasing time for water penetration in order to swell, as a previous step before the particles bind together and form a stable gel barrier. This barrier presents a greater pore size with increasing particle size of HPMC.

In the case of a HPMC ratio of 10%, the diffusion retardation created by the gel barrier is small enough to

Table 2
Regression parameters of the metronidazole release curves for tablets made with HPMC

Particle size (μm)	Slope (n = %/h$^{1/2}$)	Intercept (I = % metronidazole)	r^2
10% Hydroxypropyl methylcellulose			
163	35.27	−5.382	0.998
213	40.88	3.258	0.991
335	36.48	8.578	0.995
505	50.61	21.65	0.895
20% Hydroxypropyl methylcellulose			
163	28.05	−13.51	0.998
213	22.79	5.024	0.981
335	24.57	7.041	0.992
30% Hydroxypropyl methylcellulose			
163	19.71	3.317	0.992
213	19.79	4.458	0.994
335	21.55	4.807	0.997

$Q = n^* t^{1/2} + I$.

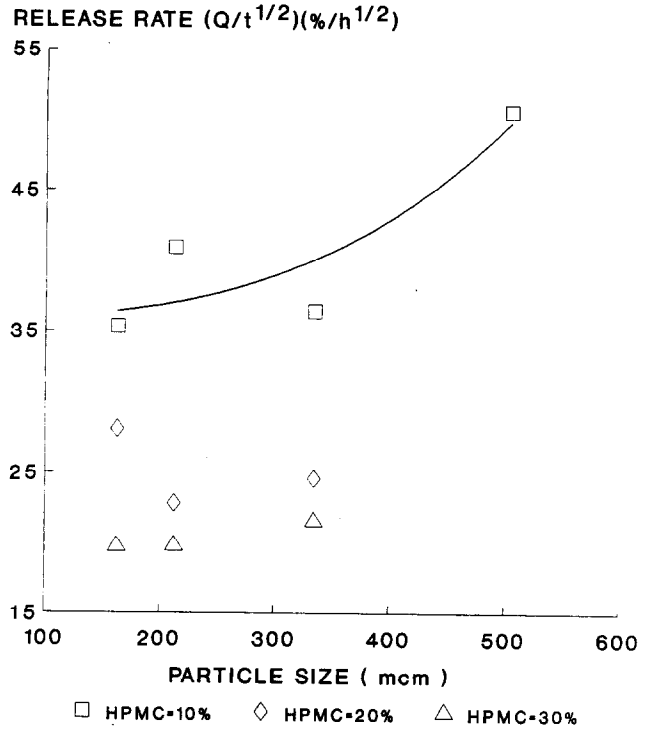

Fig. 6. Effect of particle size of HPMC on the release rate of metronidazole from matrix tablets.

allow the observation of the particle size effect. Higher concentrations of HPMC produce a diffusion retardation big enough to hide the effect of the particle size. However, there is still an effect of the HPMC ratio on the metronidazole dissolution rate (Table 2).

As can be predicted from the explanation given above for the effect of the viscosity grade on the lag time or burst effect, an increasing particle size of HPMC allowed the free dissolution of metronidazole at higher proportions before the gel barrier was established. Decreasing particle sizes caused smaller burst effects and induced lag times (Table 2). It may be because of a faster swelling of smaller particles that allow a rapid establishment of the gel barrier. This effect was less important with increasing HPMC ratios; at a HPMC ratio of 30% it is quiet small (Table 2).

The results allow us to conclude that the release rate and the initial burst or lag time effect are dependent: (i) on the HPMC capacity to form a dissolving, disintegrating or a stable matrix in the dissolution medium; and (ii) on the time necessary to establish a gel barrier with certain permeation properties. Increasing viscosity grades led to decreasing release rates and higher burst effects, before the disintegration effects appear. Gel barriers formed with increasing particle sizes led to increasing release rates and increasing burst effects. This could be better observed at low HPMC ratios (10%). Greater HPMC ratios (20 and 30%) hid the effect of particle size on release rate and the influence on the burst effect was also smaller.

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