Drug Development and Industrial Pharmacy, 32:955–965, 2006

ISSN: 0363-9045 print / 1520-5762 online
DOI: 10.1080/03639040500534127

informa
healthcare

Effect of Added Pharmatose DCL11 on the Sustained-Release of Metronidazole From Methocel K4M and Carbopol 971P NF Floating Matrices

E. Cedillo-Ramírez and L. Villafuerte-Robles
Departamento de Farmacia de la Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional de México, Carpio y Plan de Ayala s/n, Col. Santo Tomas, C. P. 11340, D. F., México

A. Hernández-León
Departamento de Sistemas Biológicos, Universidad Autónoma Metropolitana-Xochimilco, Calzada del Hueso 1100, Col. Villa Quietud, C. P. 04960, D. F., México

ABSTRACT In vitro dissolution of metronidazole from sustained release floating tablets was studied with varied proportions of sodium bicarbonate (SB) and Pharmatose DCL 11. Two polymers with different hydration characteristics, Methocel K4M and Carbopol 971P NF, were used to formulate the matrices. The variables studied include the matrices' release profile, hydration volume, and floating behavior. All Methocel matrices floated more than 8 h with SB proportions up to 24%, while Carbopol matrices floated more than 8 h with SB proportions only up to 12%. Matrices' hydration increased with time until reaching a peak and declining thereafter. Methocel matrices showed greater hydration volumes and greater drug dissolution compared to Carbopol matrices. After adding increasing quantities of Pharmatose to matrices containing 12% SB, hydration volume decreased while dissolution increased. These results were attributed to water-filled pores that formed following the Pharmatose dissolution and to reduced polymer proportions. Carbopol matrices showed greater susceptibility to the added Pharmatose, becoming more erodible and releasing higher quantities of metronidazole. The greater Carbopol susceptibility to added Pharmatose was attributed to its faster hydration. Methocel matrices hydrate rapidly only at the surface, delaying hydration and Pharmatose dissolution.

KEYWORDS Matrices hydration, Gastric retention, Sodium bicarbonate, Sustained-release parameters, Matrix erosion

Address correspondence to L. Villafuerte-Robles, Departamento de Farmacia de la Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional de México, Carpio y Plan de Ayala s/n, Col. Santo Tomas, C. P. 11340, D. F., México; Fax: +(52) 57296000-46211; E-mail: lvillaro@encb.ipn.mx

INTRODUCTION

Oral sustained-release formulations can be disadvantageous in that certain classes of active ingredients are poorly absorbed during passage through the gastrointestinal tract. This is due to the formulations' physicochemical properties and/or to favorable sites of absorption. Medicaments that are not retained in a given part of the gastrointestinal tract, for instance the stomach, could not

be considered open to conventional sustained-release formulations (Sheth & Tossounian, 1979).

Helicobacter pylori infection is one of the two most common causes of peptic ulcer disease. Consequently, H. pylori eradication is now recognized to be the correct approach along with conventional therapies in the treatment of the disease. For effective H. pylori eradication a targeted drug delivery within the stomach environment is required. A successful therapy not only includes the selection of the right drugs but also the timing and frequency as well as the formulation of the delivery system (Yang et al., 1999).

Amoxicillin and metronidazole, which are effective in treating *H. pylori* under in vitro conditions, score poorly when used to treat infections in vivo. The failure of these antibiotics has been attributed to subeffective bactericidal concentrations at the site following oral administration (Risbud et al., 2000). To overcome some deficiencies of metronidazole, a matrix tablet along with gastroretentive delivery strategies have been proposed (Wu & Fassihi, 2005).

Intragastric floating systems have been used pharmaceutically to deliver active compounds for sustained release and targeting. Low-density additives (e.g. fatty acids, fatty alcohols) and gas-generating agents (such as bicarbonate) are suitable for this purpose (Xu & Groves, 2001).

Floating delivery systems seem to offer a greater safety for clinical uses than some other approaches (Li et al., 2002). Gastric floating drug delivery systems are able to prolong the stomach retention time of a dosage form, thereby improving the local activity of the drug (Li et al., 2001).

The buoyant delivery systems can be of an effervescent type consisting of a polymeric matrix containing effervescent components such as sodium bicarbonate. The matrices are fabricated so that upon arrival in the stomach, carbon dioxide is liberated by the acidity of the gastric contents and is entrapped in the gellified hydrocolloid. This produces an upward motion of the dosage form and maintains its buoyancy (Singh & Kim, 2000).

The use of hydrophilic polymers is the most common method for controlling the release of drugs in the formulation of oral pharmaceutical dosage forms. Hydroxypropyl methylcellulose (HPMC) is a polymer frequently used in the formulation of controlled-release dosage forms. The mechanisms by which it retards drug release include its ability to form rapidly a gel layer at the matrix periphery exposed to aqueous fluids (Mandal, 1995). The drug is released from the matrix mainly by diffusion through water-filled pores. Consequently, the release rate is associated with porosity and the tortuosity of the channels network. The porosity and tortuosity of a swellable matrix are primarily attributed to polymer swellability (Efentakis et al., 1997).

Carbopol 971P NF is one of the polymers of the carbomer series. These polymers readily hydrate, absorb water, and swell quickly. Their hydrophilic nature and highly crosslinked structure renders them suitable for use in controlled-release drug delivery systems (Khan & Zhu, 1999). Carbopol 971P NF has a semienteric behavior, providing slow release in the stomach but quickly releasing the drug as the pH rises in intestinal tract. Carbopols feature extremely rapid and efficient gelation characteristics (Chikhalikar & Moorkath, 2002).

Changing several formulation factors, such as type of excipients and manufacture processes can modify drug release from matrix tablets. Adding nonpolymeric excipients to a polymer matrix has been claimed to bring about marked increases in the release rates of hydrosoluble active principles if the excipients are soluble (such as lactose). Less marked increases have been claimed for insoluble excipients like tricalcium phosphate. The effect of nonpolymeric excipients is also concentration-dependent. Low concentrations of insoluble excipients decrease release rates while high concentrations produce an increase (Lapidus & Lordi, 1968; Holgado et al., 1995; Espinoza & Villafuerte, 1999; Martínez-González & Villafuerte-Robles, 2003b, 2004).

The objective of this study is to examine the effect of sodium bicarbonate and Pharmatose DCL 11 load on the floating, hydration behavior, and release profile of metronidazole from matrices made of polymers with different hydration characteristics, Carbopol 971P NF and Methocel K4M. The results will increase our understanding of the tablet's floatability and the release control from this type of matrix.

MATERIALS AND METHODS

Materials

The pharmaceutical excipients Carbopol 971P NF, a brand of a synthetic high molecular weight polymer of acrylic acid from B. F. Goodrich Co., obtained

from Noveon-Mexico; Methocel K4M, hydroxypropyl methylcellulose supplied by the Dow Chemical company; Pharmatose DCL11 obtained from Helm de México; and the drug metronidazole obtained from Química Alkano Mexico, were used as received. The sodium bicarbonate was analytical grade from J. T. Baker-Mexico.

Matrix Preparation

As a previous step of the matrix preparation, the drug was pulverized 1 min. using an analytical mill at 20,000 rpm (Tekmar A-10, Janke and Kunkel GmbH, Germany). The sodium bicarbonate was size-reduced in a mortar for 10 min.

In a first series, matrix tablets were produced with a basic matrix formed by 400 mg polymer and 150 mg metronidazole. Part of the polymer was replaced with proportions of sodium bicarbonate (8, 12, and 24% of the polymer mass), keeping a total matrix weight of 550 mg. A second series of matrix tablets contained 12% sodium bicarbonate and different quantities of Pharmatose DCL 11: 50, 100, 150, 200, and 250 mg; keeping constant the total matrix weight with corresponding reductions of polymer content.

Powders corresponding to 20 tablets of each formulation were mixed for 30 min. in a mortar, blending with a spatula. The weight of powder corresponding to a tablet of each formulation was compressed in a hydraulic press at 137 MPa for 10 seconds with 12.5-mm diameter flat-faced tooling. No lubricant was used in the tablets.

Matrices Hydration and Floating Time

Swelling was ascertained by measuring the axial and radial expansion of matrix tablets following exposure to dissolution medium. The dimensions of each matrix were measured using a dial caliper (General Tools, New York) prior to dissolution studies. Tablet hydration tests were performed using the same conditions described in the dissolution studies. At various time intervals the tablets were removed from the dissolution medium and their dimensions measured using a microscope with a digital camera (National Optical & Scientific Instruments, USA). The tablet volume was calculated considering a right circular cylinder form. The results for each time point of three repetitions were registered as an average.

The floating time was determined by observation of the floating behavior throughout the dissolution studies and was registered as the average of three repetitions.

Drug Release

Dissolution studies were performed in triplicate, in accordance with USP 26 apparatus II procedure (TEMSA - JT R09, Mexico) at 37°C in 900 mL HCl 0.1N. The paddle speed was 50 rpm. The amount of metronidazole released from their corresponding formulations, contained in samples taken at appropriate time intervals, was independently measured on a Beckman DU-650 spectrophotometer at 276 nm. The solubility in dissolution medium is high enough to consider the dissolution of tablets containing 150 mg metronidazole in 900 mL under sink conditions.

The results for each time point of three different dissolution curves were registered as an average in the figures. The average of each time point was used to calculate the regression parameters of each dissolution curve representing a given formulation.

RESULTS AND DISCUSSION

Floating Time of Carbopol 971P NF and Methocel K4M Matrix Tablets

Matrices made of pure Carbopol show practically no floating behavior, submerging in the dissolution medium immediately or after some minutes. The addition of 8% and 12% of sodium bicarbonate to Carbopol matrices containing 150 mg metronidazole allowed floating times of more than 8 h. A higher sodium bicarbonate load (24%) reduced floating time to less than 8 h (228 min.).

On the other hand, pure Methocel matrices float more than 8 h; as do matrices containing 150 mg metronidazole. The addition of sodium bicarbonate (8–24%) does not reduce the floating time; all these matrices float longer than 8 h.

The behavior of Carbopol matrices is attributed to a relatively rapid and complete hydration, causing them to sink. The CO_2 bubbles formed after the reaction of sodium bicarbonate improve the matrices floating, in spite of their rapid and total hydration. However,

the CO_2 bubbles disappear as the matrix hydration progresses. Bubble distribution concentrated at the center and decreased toward the matrix periphery. The addition of sodium bicarbonate (tapped density = 1.369 g/cm^3, true density = 2.173 g/cm^3 [Kibbe, 2000]) not only produces gas bubbles but also increases the matrix density (tapped density of Carbopol = 0.260 g/cm^3, specific gravity = 1.41 [Kibbe, 2000]), pushing the matrices downward. At low bicarbonate concentrations the bubble effect is enough to float the matrices in spite of an increased tablet density. However, at a proportion of 24% sodium bicarbonate the effect of increased tablet density overcomes the bubble effect as bubbles begin to disappear through the hydrated gel layer. Floating behavior persists less than 4 h.

Pure Methocel matrices, which hydrate rapidly only at the surface, retain their porosity or original air bubbles for longer time, extending floatation beyond 8 h. Methocel matrices added of 150 mg metronidazole as well as matrices with a further addition of sodium bicarbonate (8–24%) maintain also their floatability longer than 8 h.

Fig. 1 shows the floating time of matrices loaded with 150 mg metronidazole, 12% sodium bicarbonate, and different quantities of Pharmatose DCL11 for a total matrix weight of 550 mg. In spite of the addition of increasing quantities of Pharmatose DCL11, Methocel matrices maintain the floating state longer than 8 h. On the other hand, the addition of Pharmatose DCL11 (50–250 mg) to Carbopol matrices decreases floating times from more than 8 h to zero. Greater proportions of Pharmatose DCL11 increase the Carbopol tablet density in such a way that floating time decreases proportionally to the added Pharmatose DCL11. When the speed of bubble-formation is insufficient to counterweigh bubble-dissipation through the gel layer, the matrix sinks.

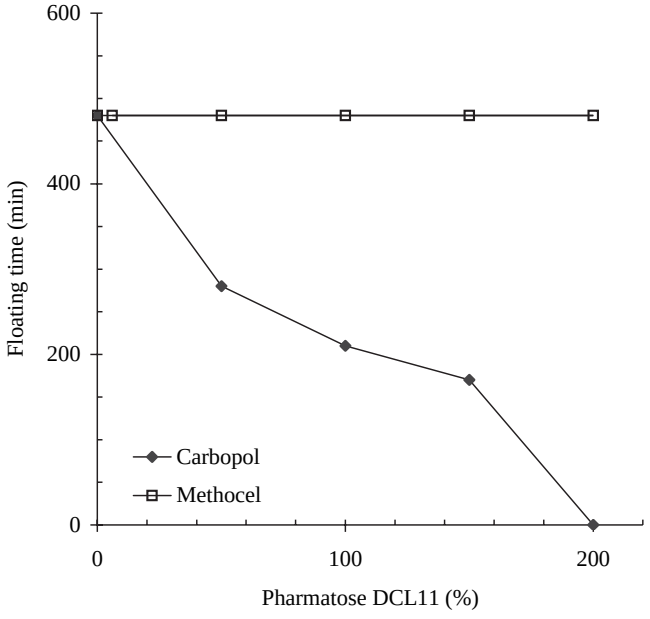

FIGURE 1 **Floating Time of Matrices of Carbopol 971P NF and Methocel K4M Containing 150 mg Metronidazole, 48 mg Sodium Bicarbonate and Variable Quantities of Pharmatose DCL11. Matrix Total Weight of 550 mg.**

Hydration Behavior of the Matrix Tablets

Hydrophilic matrices immersed in water swell and eventually dissolve. When they are placed in water, swelling starts and the tablet thickness increases. Initially, water diffuses through the polymeric matrix. As the polymer chains become more hydrated, and the gel becomes more diluted, the disentanglement concentration may be reached, that is, the critical polymer concentration below which the polymer chains disentangle and detach from a gellified matrix. Thus, there is a slow diminution of the matrix thickness due to polymer dissolution. The polymer in the matrix undergoes simultaneous swelling, dissolution, and diffusion into the bulk medium, resulting in erosion of the polymer (Shott, 1992; Katzhendler et al., 1997; Kavanagh & Corrigan, 2004).

The matrix hydration volume increases rapidly at the beginning, reaches a maximum, and then declines. While polymer swelling progresses in the direction of higher volumes, polymer dissolution produces the opposite effect.

Matrices of Methocel with 8% sodium bicarbonate show an increase in hydration volume that reaches a maximum of 2034 mm^3, declining thereafter. The addition of sodium bicarbonate to Methocel matrices expands their volume due to the gas bubbles formed after reaction with the acidic dissolution medium, increasing their hydration volume. This occurs in spite of a reduction of the polymer mass that was substituted in a quantity equivalent to the added sodium bicarbonate. However, this matrix expansion leads also to a decreased matrix consistency, facilitating its

erosion. An increased erosion of the gel layer of hydrophilic matrices has been attributed to the presence of solid particles in the gel that reduce its resistance to erosion, making the matrices more erodible (Bettini et al., 2001). Gas bubbles can be considered to produce a similar result.

The addition of 12% sodium bicarbonate further increases the hydration volume of the Methocel matrix to a maximal volume of 2853 mm^3; however, the addition of 24% sodium bicarbonate shows a maximum hydration volume of only 1873 mm^3, evidencing an increase of the erosion effect and emphasizing a reduction of matrix volume due to decreased matrix polymer content.

The addition of increasing proportions of sodium bicarbonate to Methocel matrices produces increasing maximal hydration volumes that peak and then decline. The same trend occurs in Carbopol matrices, although the hydration volumes differ. Carbopol matrices with added sodium bicarbonate show maximal hydration volumes of 2251, 2463 and 1786 mm^3 for matrices containing 8, 12 and 24% sodium bicarbonate.

Fig. 2 shows the change of hydration volume (reflecting swelling and erosion over time) for matrices of Methocel with sodium bicarbonate (12%) and loaded with different proportions of Pharmatose DCL11. This figure shows 3 of the 6 studied proportions of Pharmatose DCL11. There is a trend toward decreasing hydration volumes as the Pharmatose DCL11 load increases. This is attributed to a decreasing matrix consistency and erosion caused by Pharmatose DCL11 dissolution. Moreover, the decreasing hydration volumes are attributed also to decreasing polymer proportions the added quantities of Pharmatose DCL11 increased.

After addition of Pharmatose DCL11, matrices of Carbopol do not change hydration volume in an important manner. It seems that hydration volume, after the addition of Pharmatose DCL11, remains at a minimum as a consequence of a greater consistency and a partial separation of particles of hydrated Carbopol matrices. Although there are some changes in the slope of hydration curves, the volume of Carbopol matrices stays in a narrower range compared to Methocel matrices (Fig. 3).

Metronidazole Release from Matrices

Release data from swellable systems can be analyzed according to the power law expression shown in the following equation. The kinetics and mechanism of drug release for each system was investigated by

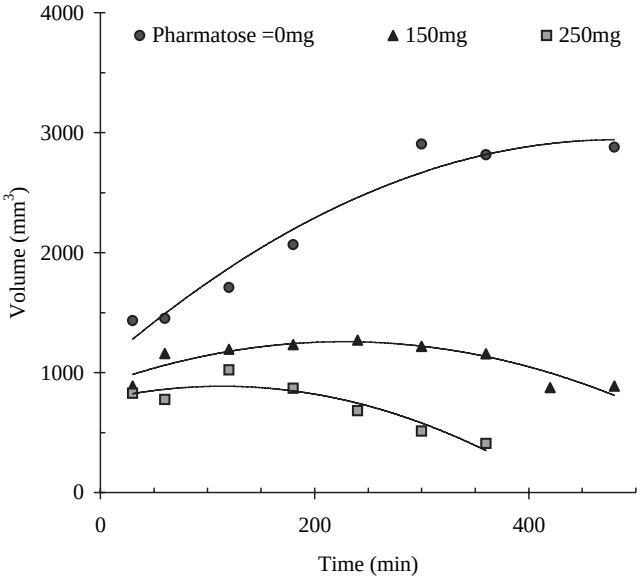

FIGURE 2 **Effect of Addition of Pharmatose DCL11 on the Hydration Volume of Methocel K4M Matrices Containing Fixed Quantities of Metronidazole (150 mg) and Sodium Bicarbonate (48 mg). Total Matrix Weight of 550 mg.**

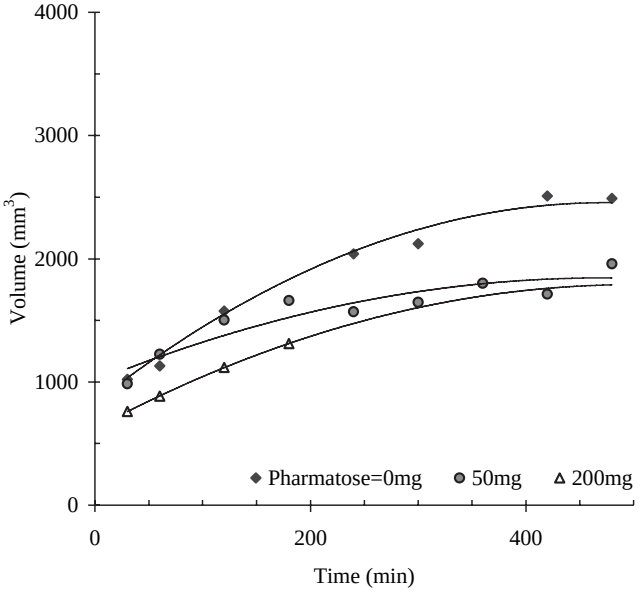

FIGURE 3 **Effect of Added Pharmatose DCL11 on the Hydration Volume of Carbopol 971P NF Matrices Containing Fixed Quantities of Metronidazole (150 mg) and Sodium Bicarbonate (48 mg). Total Matrix Weight of 150 mg.**

fitting the release data into this equation (Mandal, 1995; Vigoreaux & Ghaly, 1994; Rinaki et al., 2003):

$$M_t/M_{inf} = k * t^n \quad \text{or} \quad \ln(M_t/M_{inf}) = n * \ln(t) + \ln(k) \quad (1)$$

The terms in this equation are as follows: M_t, the amount of drug released at time t; M_{inf}, the total drug released over a long time period; k, the kinetics constant; and n, the mechanism of drug release. The value of n ranges from 0.5 ($t^{1/2}$ dependence, generally referred to as Fickian release) to 1 (representing the case II transport which is purely relaxation-controlled). The values in between indicate an anomalous behavior corresponding to coupled diffusion/relaxation. When the value of n is greater than that of the case-II transport (n >1.0), the release is said to be Super case-II transport (Brazel & Peppas, 2000; Ranga Rao et al., 1988). In the case of a matrix with cylinder form, n is said to be 0.45 instead of 0.5 and 0.89 instead of 1.0 (Kim & Fassihi, 1997).

Release profiles of metronidazole from Carbopol 971P NF and Methocel K4M matrices containing different sodium bicarbonate loads produced straight lines for data corresponding to drug release up to 8 h. Although the differences in release profile are small, it is clear that Methocel matrices release higher quantities of metronidazole than Carbopol matrices do. Methocel matrices containing 8, 12 and 24% sodium bicarbonate released respectively, after 5 h, metronidazole proportions of 46, 55 and 49%. For the same sodium bicarbonate proportions Carbopol matrices released after 5 h metronidazole proportions of 43, 50 and 48% respectively. The complete data characterizing the formulations containing different sodium bicarbonate proportions are registered in Table 1.

TABLE 1 **Floating Time, Maximal Hydration Volume and Regression Parameters of Metronidazole Release Profiles of Methocel K4M and Carbopol 971P NF Matrices Containing Different Proportions of Sodium Bicarbonate**

$NaHCO_3$ (%)	n	k	r^2	Vmax (mm^3)	Floating t. (min)
Methocel					
8	0.6014	1.4511	0.984	2034	480
12	0.4764	3.563	0.993	2853	480
24	0.736	0.7284	0.999	1873	480
Carbopol					
8	0.8364	0.3654	0.996	2251	480
12	0.5693	1.965	0.99	2463	480
24	0.7184	0.8051	0.985	1786	228

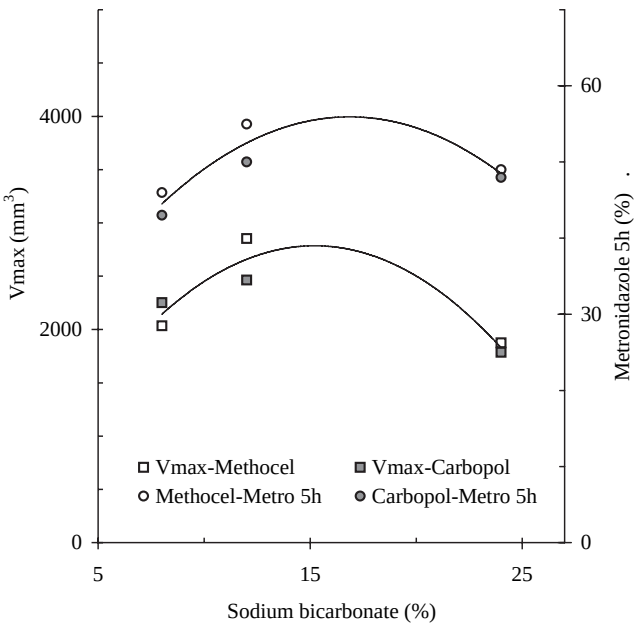

FIGURE 4 **Effect of Added Sodium Bicarbonate on the Maximal Hydration Volume (Vmax) and the Metronidazole Released After 5 h in Matrices of Methocel K4M and Carbopol 971P NF.**

As can be seen in Fig. 4, the metronidazole release data show the same trend as those data corresponding to the maximal hydration volume (Vmax) reached by these formulations. Although the metronidazole released after 5 h and the Vmax do not show a simple relationship, it is clear that the changes in drug release are reflecting the changes in Vmax produced after addition of different proportions of sodium bicarbonate to the matrix tablets. Matrices of both polymers containing 12% sodium bicarbonate release higher metronidazole quantities than matrices containing 8% and 24% sodium bicarbonate. This behavior seems to be due in part to the matrices' hydration volumes mentioned above. According to results not yet published, another factor contributing to the peak and subsequent decrease in drug release after 5 h is the presence of CO_2 bubbles. These bubbles reduce the surface area available for water and drug transport through the gelled matrix.

The changes in the regression parameters of metronidazole release profiles produced by the substitution of sodium bicarbonate for a portion of the polymer content also correlate with Vmax, in the same way that drug release after 5 h does. The higher release constant value (k) corresponds with the higher value of Vmax. Although not related in a simple manner, this means that the increase in hydration volume corresponds to a higher release constant value. It can be assumed that a greater matrix expansion facilitates the water and drug transport.

As in other cases (Martínez-González & Villafuerte-Robles, 2003a), faster matrix hydrations correspond with lower values of the exponent indicative of the release mechanism (*n*). The higher hydration volume reached by matrices containing 12% sodium bicarbonate allows a faster drug release rate and reduces the impact of relaxation and erosion effects on metronidazole release.

The effect of the addition of different proportions of Pharmatose DCL11 on the release profile of Methocel matrices containing 12% sodium bicarbonate is depicted in Fig. 5. Increasing proportions of Pharmatose DCL11 produce an increasing dissolution of metronidazole. This agrees with a previous report about pelanserin dissolution from HPMC/lactose matrices (Espinoza & Villafuerte, 1999). The complete data characterizing the effect of Pharmatose DCL11 on Methocel K4M matrices are registered in Table 2.

The increased metronidazole dissolution that accompanies the addition of Pharmatose DCL11 is the result of the increased porosity and reduced consistency of the matrix tablets. These changes are attributed to the additional room of water-filled pores following Pharmatose dissolution and to the obstruction of polymer particle binding. This circumstance

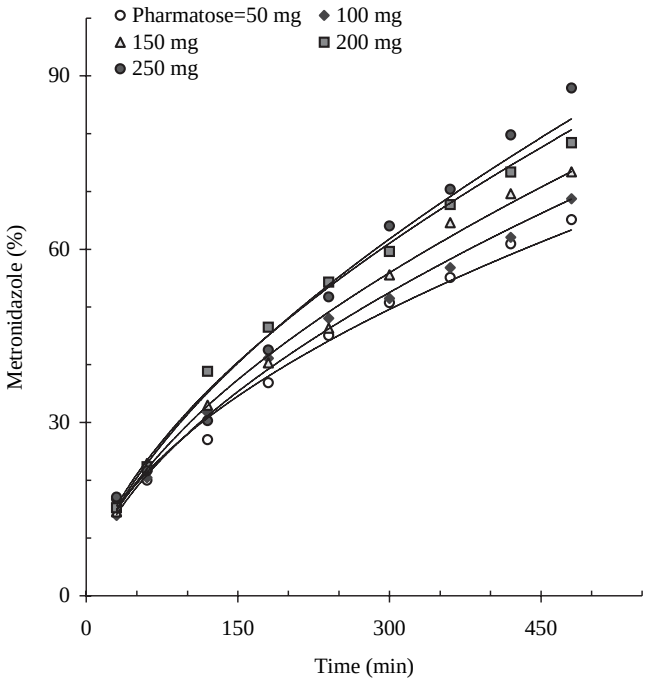

FIGURE 5 **Effect of Added Pharmatose DCL11 on the Release Profile of Metronidazole (150 mg) from Methocel K4M Matrices Containing 48 mg Sodium Bicarbonate. Matrix Total Weight of 550 mg.**

TABLE 2 **Floating Time, Maximal Hydration Volume, and Regression Parameters of Metronidazole Release Profiles of Methocel K4M Matrices Containing Sodium Bicarbonate (12%) and Different Proportions of Pharmatose DCL11**

Pharmatose (%)	n	k	r^2	Vmax (mm^3)	Floating t. (min)
0	0.4764	5.2806	0.9933	2941	480
50	0.5213	3.9589	0.9806	1775	480
100	0.5716	3.1276	0.9973	1783	480
150	0.5805	3.3362	0.9964	1257	480
200	0.5939	3.3459	0.9944	1073	480
250	0.6168	3.0078	0.9796	886	480

causes the increased permeability and decreased consistency of the matrix that facilitates relaxation and erosion. While a double effect was expected after the addition of sodium bicarbonate to the polymeric matrices, matrix expansion and matrix relaxation/erosion, when Pharmatose DCL11 was added produced no direct matrix expansion. Matrix permeability did increase, due to increased porosity and matrix relaxation/erosion. The result of these effects is a progressive reduction of the matrix hydration volume and a reduced restriction of drug dissolution. The consequence is an increasing dissolution of metronidazole.

The effect of the Pharmatose DCL11 addition on the maximal matrix hydration volume and on the exponent indicative of the release mechanism (*n*) of the metronidazole release profiles is depicted in Fig. 6. Increasing additions of Pharmatose DCL11 reduce exponentially the maximal hydration volumes reached by the matrices. The matrices increase progressively their porosity due to dissolution of increasing Pharmatose DCL11 quantities, reducing their consistency as a result of the porosity changes, reduced polymer proportion, and the obstruction of polymer particle binding. The lowered matrix consistency allows an increasing matrix relaxation/erosion, evidenced by increasing values of the exponent indicative of the release mechanism (*n*).

The release constant (*k*) of equation 1 is also modified (Fig. 7). Decreasing values of this constant correspond with increasing additions of Pharmatose DCL11, in the same manner that increasing Pharmatose DCL11 additions correspond with decreasing values of the maximal hydration volume (Vmax) reached by the matrices.

The decreasing values of Vmax showed by increasing Pharmatose DCL11 proportions in Methocel

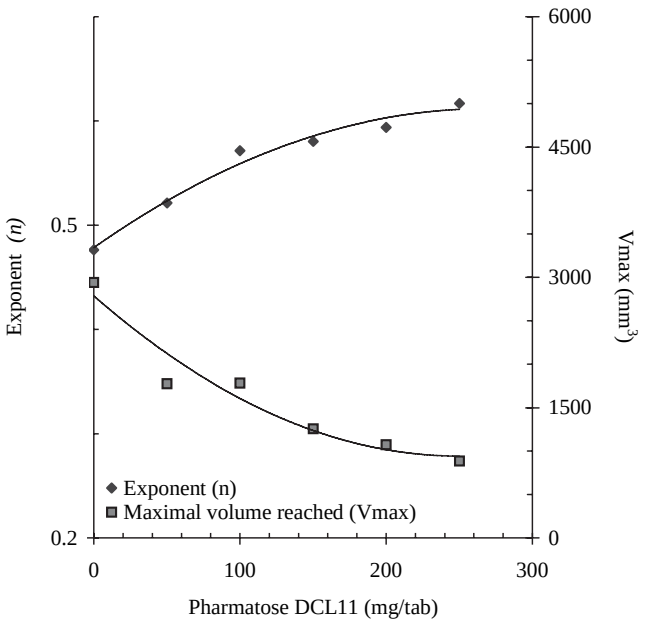

FIGURE 6 **Effect of Added Pharmatose DCL11 on the Exponent Indicative of the Metronidazole Release Mechanism (*n*) and the Maximal Hydration Volume of Methocel K4M Matrices Containing 12% Sodium Bicarbonate.**

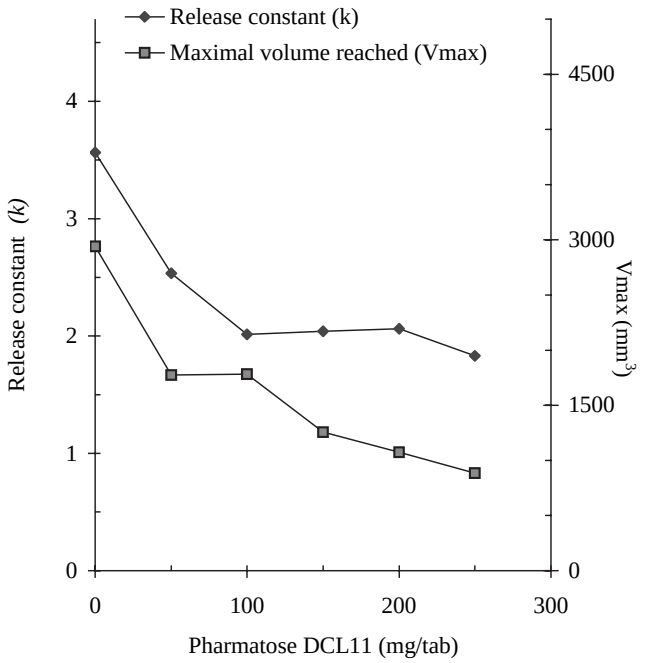

FIGURE 7 **Effect of Added Pharmatose DCL11 on the Release Constant (*k*) of Metronidazole Dissolution Curves and the Maximal Hydration Volume of Methocel K4M Matrices Containing 12% Sodium Bicarbonate.**

matrices can be ascribed to a lesser polymer content, which corresponds to a lower matrix swelling capacity. However, it can also be ascribed to a lower availability of water for the swelling process caused by competition between the swelling polymer and the dissolving Pharmatose DCL11, particularly at high Pharmatose DCL11 proportions.

This expectation arises from the fact that the quantity of water penetrating the tablet is limited. The soluble excipient will consume some of the available water, leaving only a portion of the total water penetrating the tablet for the deployment of the polymer swelling capacity. The result of this competition for water is a mutual inhibition of the polymer swelling process and the dissolution of the water soluble excipient; this competition for the available water decreases the drug dissolution improvement activities of the swelling polymer and in the water dissolving excipient. This competition for the available water strengthens as the polymer avidity for water increases (López-Solis & Villafuerte-Robles, 2001).

As a consequence of these facts, drug release can be limited. In this way, the release constant (*k*) decreases with increasing Pharmatose DCL11 additions. It seems that the porosity and consistency of the matrices are the main variables affecting the release rate. However, the competition between the swelling polymer and the dissolving Pharmatose DCL11 for the available water inside the tablet also affects the drug release rate.

The release profiles of Carbopol 971P NF matrices containing 12% sodium bicarbonate, 150 mg metronidazole, and variable quantities of Pharmatose DCL11 are depicted in Fig. 8. The corresponding regression parameters, the floating time, and the maximal hydration volumes reached by the different Carbopol matrix formulations are registered in Table 3.

The results are similar to those obtained with Methocel matrices. Increasing proportions of Pharmatose DCL11 produce Carbopol matrices with increasing drug release rates. However, the Carbopol hydration behavior does not allow the preservation of the matrix integrity at high Pharmatose DCL11 proportions. Matrices containing 200 mg and 250 mg Pharmatose DCL11 per tablet begin to lose their tablet form after 4 h and 1 h respectively.

This partial disintegration of Carbopol matrices can be ascribed to the above mentioned competition for the available water between the swelling polymer and the dissolution of the water-soluble excipient. The water used in the dissolution of Pharmatose DCL11 does not permit sufficient polymer hydration to develop adhesive forces capable of maintaining the

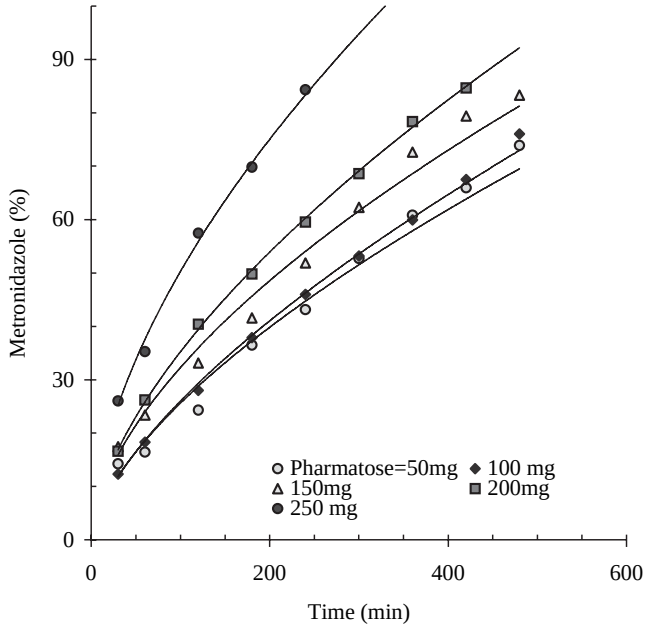

FIGURE 8 **Effect of Added Pharmatose DCL11 on the Release Profile of Metronidazole (150 mg) From Carbopol 971P NF/ $NaHCO_3$ Matrices With a Total Weight of 550 mg.**

TABLE 3 **Floating Time, Maximal Hydration Volume, and Regression Parameters of Metronidazole Release Profiles From Carbopol 971P NF Matrices Containing Sodium Bicarbonate (12%) and Different Proportions of Pharmatose DCL11**

Pharmatose (%)	n	k	r^2	Vmax (mm^3)	Floating t. (min)
0	0.5693	1.9655	0.9902	2454	480
50	0.6363	1.3681	0.9715	1845	280
100	0.6569	1.2637	0.9979	2434	210
150	0.5879	2.1564	0.9868	3000	170
200	0.6052	2.1696	0.9986	1782	0
250	0.57656	3.5539	0.9937	——	0

integrity of Carbopol matrices. The increased competition for water can be attributed to the higher avidity for water of Carbopol. The hygroscopicity of Carbopol (8–10% w/w), at a relative humidity of 50%, is much higher than that of hydroxypropyl methylcellulose (desorption 1.3%- sorption 4.5%) (Kibbe, 2000). This explains the more drastic effect of Pharmatose DCL11 on Carbopol than on Methocel matrices.

The addition of Pharmatose DCL11 more drastically reduces the consistency of Carbopol matrices than Methocel matrices. It produces an inversion of the behavior observed before in matrices containing the polymer and sodium bicarbonate. Methocel/ sodium bicarbonate matrices released metronidazole faster than matrices made of Carbopol/sodium bicarbonate because of a greater Methocel matrix expansion. However, the reduced consistency following the addition of Pharmatose DCL11 (owing to the increased porosity and competition for water that erodes Carbopol matrices) decreased their ability to restrict drug transport. This behavior can be related to the differing hygroscopicity and hydration characteristics of the polymers. While Carbopol hydration is strongly affected by the addition of Pharmatose DCL11, Methocel matrices hydrate rapidly only at the surface, delaying the hydration process and reducing the effects of Pharmatose DCL11. As a consequence, Carbopol matrices containing Pharmatose DCL11 release the drug faster than formulations containing Methocel.

Although the effect of particle separation from Carbopol matrices is more evident at higher proportions of Pharmatose DCL11 (200–250 mg/tab), Fig. 9 shows that effects begin at lower Pharmatose DCL11 proportions (100–150 mg/tab). Fig. 9 depicts the effect of the Pharmatose DCL11 proportion on the exponent indicative of the metronidazole release mechanism (*n*) from Carbopol and Methocel matrices. Carbopol and Methocel matrices show a similar trend to increasing exponent (*n*) values as Pharmatose DCL11 proportions

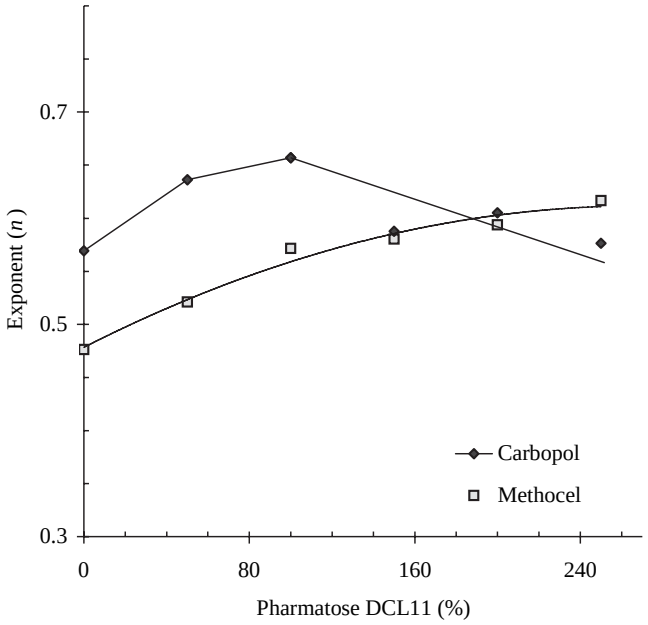

FIGURE 9 **Effect of Added Pharmatose DCL11 on the Exponent Indicative of the Metronidazole Release Mechanism (*n*) from Carbopol 971P NF and Methocel K4M Matrices Containing 12% Sodium Bicarbonate.**

increase. However, Carbopol matrices show at a Pharmatose proportion of 100 mg/tab a deviation that becomes more evident with Pharmatose proportions ≥150 mg/tab. The exponent (*n*) values decrease as Pharmatose DCL11 proportions increase.

The faster hydration and gel formation of Carbopol matrices is evidenced by higher values of the exponent (*n*) and lower values of the release constant (*k*) (Tables 1, 2, and 3). However, the partial separation of particles from Carbopol matrices not only reduces the exponent (*n*) values but also increases the release constant values (*k*), given the higher surface area available for drug dissolution (Fig. 10). The effect can be seen at Pharmatose DCL11 proportions ≥ 150 mg/tab.

Fig. 11 shows that the metronidazole released after 8 h is always greater for Carbopol matrices, with exception of those matrices containing only the polymer and sodium bicarbonate.

Carbopol matrices hydrate rapidly, allowing Pharmatose dissolution. As water-filled pores replace the Pharmatose particles, matrix consistency decreases, allowing greater permeability and an increased transport of drug.

In the case of Methocel matrices, Pharmatose is supposed to dissolve at lower rates than in Carbopol matrices. Pharmatose solid particles, persisting longer

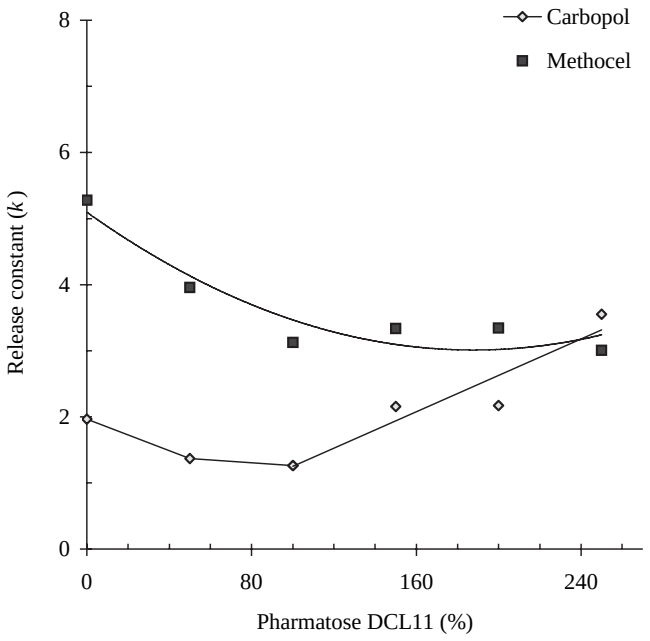

FIGURE 10 **Effect of Added Pharmatose DCL11 on the Release Constant (*k*) of Metronidazole From Carbopol 971P NF and Methocel K4M Matrices Containing 12% Sodium Bicarbonate.**

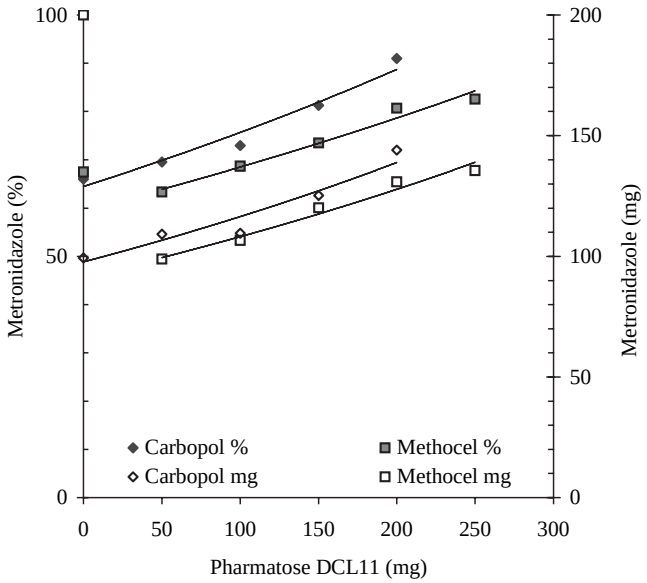

FIGURE 11 **Effect of Added Pharmatose DCL11 on the Metronidazole (150 mg) Released After 8 h From Carbopol 971P NF and Methocel K4M Matrices Containing 48 mg Sodium Bicarbonate. Matrix Total Weight of 550 mg.**

in Methocel matrices, decrease and delay the release rate of metronidazole. This is observed as a diminution of the metronidazole released after 8 h from Methocel matrices containing 50 mg Pharmatose (compared to matrices without Pharmatose). Increasing concentrations of Pharmatose DCL11 in Methocel matrices produce similar effects, as mentioned above for Carbopol matrices.

CONCLUSIONS

The floating behavior of hydrophilic matrices depends primarily on the intrinsic properties of polymers, properties that can be modified by the addition of excipients. The rapid gelling characteristics of Carbopol allow the formation of a gelled matrix and the production of CO_2 from sodium bicarbonate particles, making matrix floatation possible. However, the rapid swelling of Carbopol also allows the relatively rapid displacement of the CO_2 bubbles, increasing density to the critical value at which the matrix sinks. On the other hand, the ability of Methocel to form rapidly a gel layer at the matrix periphery preserves the sodium bicarbonate gas bubbles that keep the matrix afloat. While the rapid swelling of Carbopol matrices results in a small matrix expansion, the rapid hydration of the periphery of Methocel matrices delays total hydration, allowing a greater expansion of the matrix

due to gas bubbles. These circumstances are reflected in the drug-release behavior. The more expanded Methocel matrices release the drug faster than the less expanded Carbopol matrices do.

The addition of a water soluble excipient such as Pharmatose DCL11 increases the porosity and decreases the Carbopol matrix consistency, facilitating the matrix relaxation and some separation of particles. These processes occur more quickly in Carbopol matrices due to their faster hydration and faster dissolution of the water-soluble excipient; matrices containing high Pharmatose proportions show high levels of erosion. The same occurs in a delayed manner in Methocel matrices, where relaxation and erosion effects decrease to a degree that no particle separation can be observed. These circumstances are reflected in the dissolution behavior; Carbopol matrices containing Pharmatose DCL11 release the drug faster than the corresponding Methocel formulations.

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