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Effect of Sodium Bicarbonate on the Properties of Metronidazole Floating Matrix Tablets

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The effect of sodium bicarbonate (SB) on the swelling behavior and the sustained release of floating systems was studied with varied proportions of this excipient and metronidazole. Two polymers with different hydration characteristics, Methocel K4M and Carbopol 971P NF, were used to formulate the matrices. Under in vitro dissolution conditions, the addition of SB to metronidazole sustained-release tablets modifies the matrix hydration volume, increasing at the beginning, reaching a maximum, and then declining. Pure Carbopol matrices show a rapid hydration with a limited further effect of the SB and metronidazole loads. Methocel show a significant increase of the apparent hydration volume due to SB addition with no further notable change due to metronidazole load. Increasing the metronidazole load reduces the floating time of Carbopol matrices while no effect on Methocel matrices could be observed within 8 hours dissolution. Matrices show increasing release constant values (*k*) as the metronidazole load increases. Methocel matrices release the drug 10% to 15% faster than Carbopol matrices. SB increases the cumulative amount of drug released from Methocel but not that releasing from Carbopol. These results are attributed to the intrinsic polymer properties, the barrier effect of CO_2 bubbles, and the matrix volume expansion produced after addition of SB.

Keywords polymer hydration; sustained release; metronidazole; Carbopol 971P NF; Methocel K4M; floating tablets

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INTRODUCTION

Swellable controlled-release systems are widely used for controlled drug administration, particularly in the form of tablets. These systems are attractive approaches from an economic as well as process development point of view. The hydrophilic gel-forming matrix tablets are extensively used for oral extended-release dosage forms due to their simplicity, cost-effectiveness, and reduction of the risk of systemic toxicity due to dose dumping (Huang et al., 2004). However, some medicaments are not open to conventional sustained-release formulations if they are not retained in a given part of the gastrointestinal tract, for instance the stomach (Sheth & Tossounian, 1979).

Various approaches have been used to prepare dosage forms for gastric retention; one of them is the effervescent floating system. Matrices are prepared so that upon arrival to the stomach, carbon dioxide is liberated by the acidity of the gastric content and is entrapped in the gellified hydrocolloid. This produces an upward motion of the dosage form and maintains its buoyancy (Singh & Kim, 2000). Intragastric floating systems have been used pharmaceutically to deliver active compounds for sustained release and targeting (Xu & Groves, 2001). 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, Lin, Chien, Daggy, & Mirchandani, 2001). Although some other attempts have been made to provide a dosage form with a longer gastrointestinal transit time, floating delivery systems seem to offer a greater safety for clinical uses than some other approaches (Li, Lin, Daggy, Marchandani, & Chien, 2002).

A successful therapy not only includes selection of the right drugs but also the right timing and frequency as well as the formulation of the right delivery system (Yang, Eshraghi, &

Fassihi, 1999). Amoxicillin and metronidazole, which are effective in treating *H. pylori* under in vitro conditions, show a limited activity when used to treat infections in an in vivo situation. It has been proposed that the failure of these antibiotics is an outcome of sub-effective bactericidal concentrations available at the site following oral administration (Risbud, Hardikar, Bhat, & Bhonde, 2000). To overcome some deficiencies of metronidazole, as a part of the therapy, a matrix tablet along with gastroretentive delivery strategies has been proposed (Wu & Fassihi, 2005).

Hydrophilic matrices consist of a drug dispersed in a hydrophilic polymer. Hydrophilic solid polymers and polymer gels immersed in water or aqueous solutions swell and eventually dissolve. The relative importance of swelling and polymer dissolution on the hydration behavior of polymeric matrices and the drug release rate is determined by the characteristics of the polymer (Katzhendler, Hoffman, Goldberger, & Friedman, 1997). Swellable compressed matrices exhibit drug release rates directly proportional to the matrix's external surface area. The drugs are released at a given rate per exposed area (Colombo, Castellani, Peppas, Maggi, & Conte, 1992).

The drug release from a hydrophilic polymeric matrix is attributed to drug diffusion through and attrition of the gel sheath formed around the tablet. However, drug release can also be affected by addition of other formulation components such as soluble and insoluble polymers and non-polymeric substances. The observed effects have been explained by differences in solubility of the excipients and their subsequent effects on the gelled matrix tortuosity (Espinoza & Villafuerte, 1999; Holgado et al., 1995; Lapidus & Lordi, 1968; Martínez-González & Villafuerte-Robles, 2003, 2004).

Among different substances that affect the release of drugs from swelling matrices, the entrapped air within the matrix tablets works as a transport barrier. Vanishing of the entrapped air in the matrix after 1.4 to 4.0 hours was observed as an increase in release rate (Korsmeyer, Gurny, Doelker, Buri, & Peppas 1983).

Hydroxypropylmethylcellulose (HPMC) is a hydrophilic polymer used in the preparation of sustained-release formulations. The drug release is considered to be controlled by the extent and nature of the swelling process of HPMC (Papadimitriou, Buckton, & Efentakis, 1993). The mechanisms by which it retards drug release include its ability to form a gel layer rapidly 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 tortuosity of the pores and channels network (Efentakis, Vlachou, & Choulis, 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 cross-linked structure renders them suitable for use in controlled-release drug delivery systems (Khan & Zhu 1999). Carbomer formulations demonstrated sustained release under both simulated gastric and intestinal fluids (Singla, Chawla, & Singh, 2000). Carbopol 971P NF has a semi-enteric behavior, providing slow release in the stomach but releasing the drug faster as the pH rises in intestinal tract. This behavior could be particularly beneficial in formulations targeted to the intestine (Singla et al., 2000). Carbopols feature extremely rapid efficient gelation characteristics (Chikhalikar & Moorkath, 2002).

In spite of the above-mentioned properties of Carbopol, Carbopol/HPMC matrices with phenoporlamine hydrochloride have been reported to release the drug faster in an acidic medium than in distilled water (Xu, Sun, Zhi, & Hu, 2006). However, this formulation contained 25% sodium bicarbonate (SB), which reacts rapidly in an acidic medium evolving CO_2, but not in water. Further, SB can raise the pH of water (the pH of a 0.1 M aqueous solution is 8.3), transforming the hydrochloride ($pK_a = 7.47$) in a less soluble base. In this sense, the faster drug dissolution in an acidic medium than in water could be ascribed to SB instead to Carbopol.

Although there are some articles that deal with oral floating systems, the information about the effect of the floating element (SB—CO_2) on the drug dissolution profile and the matrix hydration behavior is limited. It is evident the importance of the swelling behavior on drug release and the necessity of SB to produce buoyancy. Because of this, the aim of this work is the evaluation of the effect of SB and the load of a model drug, metronidazole, on the floating and hydration behavior and on the release profile of the drug from Carbopol 971P NF and Methocel K4M matrices. The floating feature is incorporated for possible prolongation of the gastric retention time of the delivery system, thus increasing localized concentration and effects of the drug.

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; and the drug metronidazole, obtained from Química Alkano Mexico, were used as received. The SB was analytical grade from J. T. Baker-Mexico.

Matrix Preparation

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

Initially, matrix tablets were produced using 200 mg of pure polymers. In a second series of matrix tablets, different quantities of the polymer content were substituted with SB, maintaining the matrix total weight of 200 mg. These matrices contained 3%, 5%, 8%, 12%, 16%, 20%, and 24% SB.

A third series of matrix tablets contained 200 mg of polymer and different quantities of metronidazole: 50, 100, and 150 mg. In a fourth series, 24 mg of polymer content were substituted by SB, leaving 176 mg of the original polymer content. Different quantities of metronidazole were added to these matrices: 50, 75, 100, 125, and 150 mg.

All components corresponding to 20 tablets of each different formulation were mixed for 30 minutes in a mortar, blending with a spatula. The tablets were compressed in a hydraulic press fitted with a flat-faced 8 mm punch and die set at a pressure of 22 MPa for 10 seconds. No lubricant was used in the tablets.

Matrices Hydration and Floating Time

Apparent 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 dissolution studies. At various time intervals the tablets were removed from the dissolution medium and measured using a microscope with a digital camera (National Optical & Scientific Instruments, United States). The tablet volume was calculated considering a right circular cylinder form. The results are registered as an average of three repetitions.

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 apparatus II procedure (JT R09, TEMSA, Mexico) at 37 °C in 900 ml of HCl 0.1 N. The paddle speed was 50 rpm. The amount of metronidazole released over time was determined by withdrawing samples at various time intervals. The concentration of metronidazole was obtained by measuring its absorbance at 276 nm in a Beckman DU-650 ultraviolet spectrophotometer. Metronidazole solubility in water at 20° C is 10 mg/ml. Therefore, dissolution of 150 mg in 900 ml at 37° C is considered under sink conditions.

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

RESULTS AND DISCUSSION

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

Matrices made of pure Carbopol float only a few minutes showing practically no floating behavior. The addition of SB to Carbopol matrices produces floating times greater than 8 hours. However, after different times ranging from 200 minutes to 360 minutes the matrices begin an up and down movement, attributed to rapid changes in CO_2 production and with this to changes in matrix density. After 20 to 30 minutes of this behavior, the matrix tablets recovered stable buoyancy.

The poor floating functioning of pure Carbopol matrices is attributed to their rapid entire hydration that facilitates the disappearance of the original air bubbles remaining from tablet porosity and with this, their fall.

Figures 1 and 1a show the comparative hydration characteristics of matrices made of pure polymers as well as their air bubble distribution; in this case with 50-mg matrices to facilitate the process of producing the images.

The CO_2 bubbles obtained after addition of SB to Carbopol matrices improve their floating behavior, in spite of their rapid entire hydration. The CO_2 bubbles disappear progressively with time, as the matrix hydration progresses.

On the other hand, pure Methocel matrices float for more than 8 hours. Methocel matrices, which hydrate rapidly only at the surface (Figure 1a), keep their original air bubbles for a longer time. The addition of SB reinforces the floating behavior. Certainly, this reinforcement of the floating behavior due to gas evolution produced gas explosions at times ranging from 10 minutes to 60 minutes. This abrupt gas evolution produced an effect similar to a tablet lamination that divided the tablet into two joined parts. Although each part was surrounded by a gellified layer, they were maintained together.

After addition of metronidazole to pure Carbopol matrices, no further effect was observed on their non-floating behavior. As

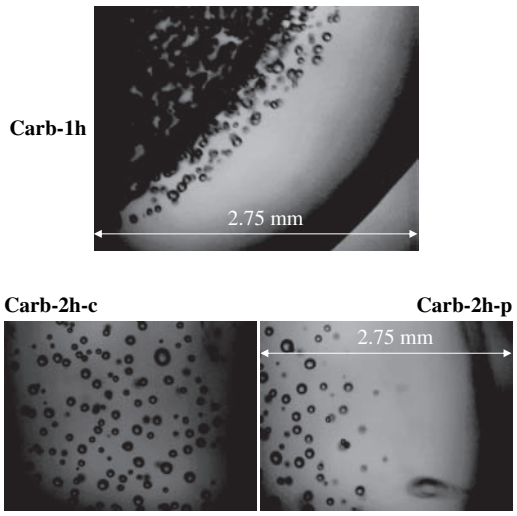

FIGURE 1. Hydration characteristics of pure Carbopol 971P NF matrices, after 1 hour hydration (Carb-1h) and after 2 hours hydration: (Carb-2h-c) central part and (Carb-2h-p) periphery of the matrix.

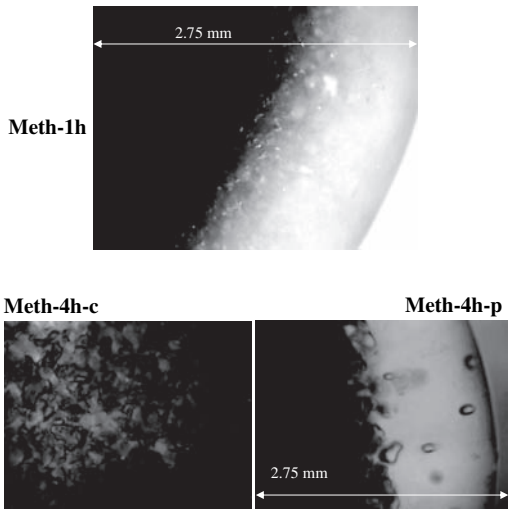

FIGURE 1a. Hydration characteristics of pure Methocel K4M matrices after 1 hour hydration (Meth-1h) and after 4 hours hydration: (Meth-4h-c) central part of the matrix and (Meth-4h-p) its periphery.

mentioned above, addition of 12% SB to pure Carbopol matrices produced floating times longer than 8 hours. Metronidazole loading of these matrices shows that this quantity of SB is enough to maintain the floating condition up to a drug load of 100 mg per tablet, equivalent to 33% of the total matrix weight. Higher metronidazole loads produced floating times under 8 hours (Figure 2).

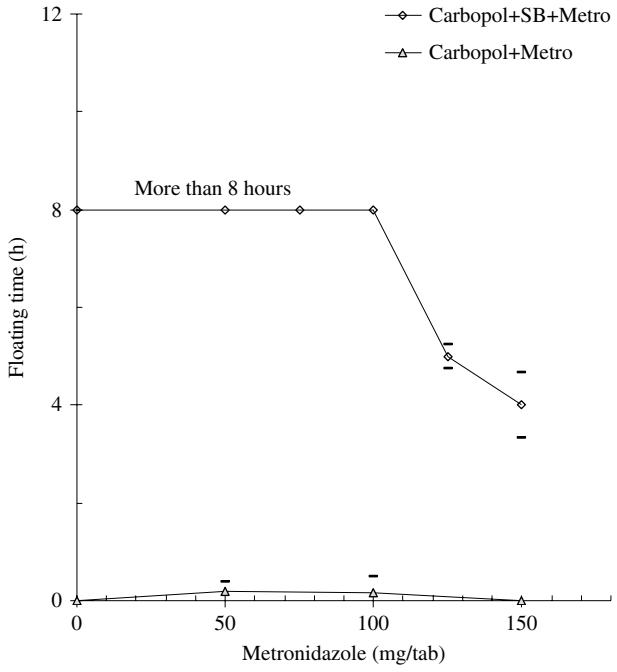

FIGURE 2. Effect of added metronidazole on the floating behavior of Carbopol 971P NF matrices with and without 12% sodium bicarbonate, under dissolution conditions. $M \pm 95\%$ C.I.

As mentioned above, the behavior of the Carbopol matrices is attributed to a relative rapid entire hydration. The rapid entire hydration allows a faster movement of the original air bubbles as well as the CO_2 bubbles obtained after addition of SB. After some time, the distribution of the gas bubbles concentrates at the middle of the matrix, decreasing its concentration in the path to the matrix periphery. The increase in matrix density, due to an increasing drug load, causes the fall of matrices loaded with more than 100 mg metronidazole per tablet. The sinking of the matrices occurs after a certain proportion of the gas bubbles disappear.

Pure Methocel matrices float more than 8 hours, independently of the metronidazole loaded. The addition of 12% SB increases their apparent hydration volume, producing an important elongation but no rupturing. The floating time of Methocel matrices containing SB was still longer than 8 hours after addition of metronidazole.

Hydration Behavior of Carbopol 971P NF and Methocel K4M Matrix Tablets

Hydrophilic matrices immersed in water swell and eventually dissolve. When they are placed in water, swelling starts and the tablet thickness increases. The polymer dissolves because of the chain disentanglement. As the polymer chains become more hydrated and the gel becomes more diluted, the disentanglement concentration may be reached and the polymer chains 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 simultaneously swelling, dissolution, and diffusion into the bulk medium, resulting in a reduction of strength and erosion of the matrix (Katzhendler et al., 1997; Kavanagh & Corrigan, 2004; Jamzad, Tutunji, & Fassihi, 2005; Schott, 1992).

Figure 3 shows the change in the tablets' volume with time for matrices of pure Methocel and Methocel with 5% SB. The matrix hydration volume increases rapidly at the beginning, reaches a maximum, and then declines. The hydration volume is described by two processes occurring at the same time but with opposite consequences. While polymer swelling progresses in the direction of higher volumes, polymer dissolution produces the contrary. The addition of 5% SB generates an expansion of the hydration volume of Methocel matrices, producing an important elongation. This occurs in spite of a lesser polymer mass, due to substitution of 5% polymer with SB. The increase in hydration volume is attributed to an inclusion in the matrix of a certain quantity of CO_2 bubbles, formed after reaction of SB with hydrochloric acid.

The addition of SB reduces the matrix coherence, producing a strong axial elongation of HPMC matrices. The predominantly axial swelling of hydroxypropyl methylcellulose, rather than the radial dimension, has been observed previously. This type of behavior is not exhibited by certain other hydrogel systems (Papadimitriou et al., 1993).

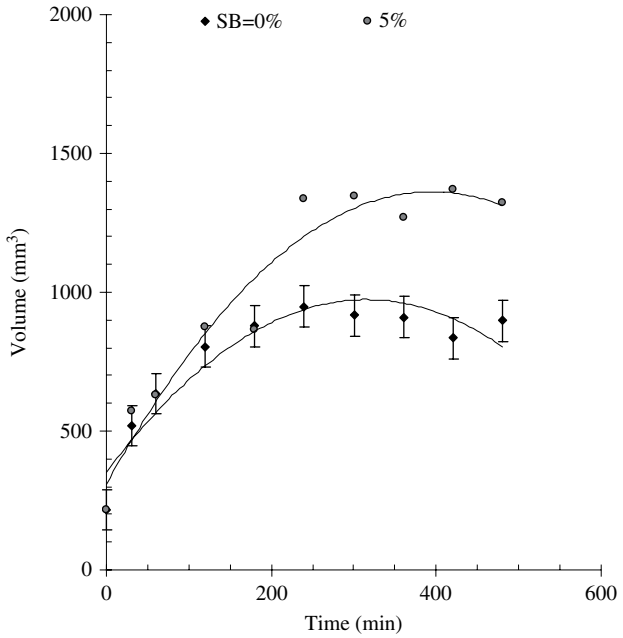

FIGURE 3. Hydration volumes of Methocel K4M matrices with and without sodium bicarbonate (SB). Vertical lines denote the standard error of the mean ($n = 3$).

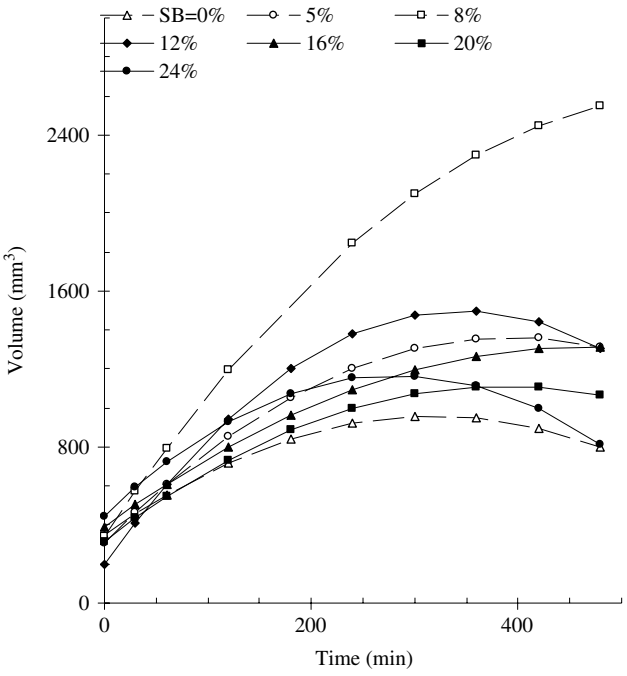

FIGURE 4. Effect of the sodium bicarbonate proportion on the hydration volume of Methocel K4M matrices, in HCl 0.1N at 37ºC and padle stirring at 50 rpm. Calculated regressions.

Figure 4 depicts the calculated regressions of hydration curves of HPMC matrices containing different proportions of SB. The effect of increasing SB proportions up to 8% is an increasing apparent hydration volume. Thereafter, higher bicarbonate proportions produce decreasing apparent matrix hydration volumes. The changes are explained as a combination of polymer swelling and dissolution/erosion and a matrix expansion due to CO_2 bubbles. The progressive reduction of the polymer content, after substitution with SB, also contributes to the observed changes in the apparent hydration volumes.

An increased erosion of the gel layer of hydrophilic matrices has been attributed to inclusion of solid particles in the gel that reduce its resistance to erosion (Bettini et al., 2001). Increased erosion has been also reported by matrices containing about 30% of spray-dried lactose or calcium phosphate dihydrate (Jamzad et al., 2005). Therefore, an increasing reduction of gel consistency can be expected after addition of increasing proportions of SB; this reduction of gel consistency increases the matrix's propensity for erosion. Moreover, the produced gas bubbles are expected to contribute to the same effect, as foreign matter in the matrix and because of their tendency to leave the matrix.

Increasing proportions of SB, and with this an increasing evolution of carbon dioxide, generate an increasing expansion of the matrix. However, the concomitant reduction of the polymer mass, after its partial substitution by increasing SB quantities, produces the opposite, a reduction of the hydration volume.

Compared with Methocel matrices, matrices of Carbopol show a limited change in hydration volume after addition of SB (Figure 5). The exceptions are the higher SB concentrations, namely 20% and 24%, that show an appreciable decrease in hydration volume. These changes in hydration volume are primarily attributed to the polymer mass reduction produced

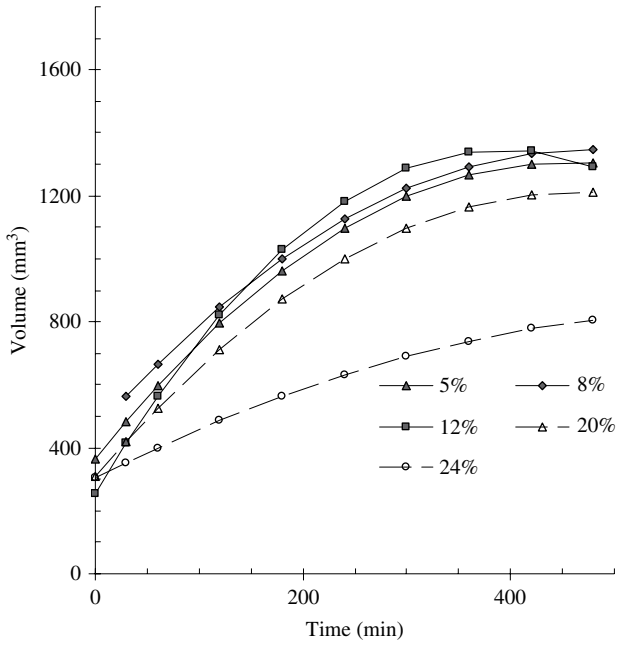

FIGURE 5. Effect of the sodium bicarbonate (SB) proportion on the hydration volume of Carbopol 974P NF matrices, in HCl 0.1N at 37ºC and with paddle stirring at 50 rpm. Calculated regressions.

after its partial substitution with different quantities of SB. Furthermore, it seems that the expected increase in volume after addition of SB is inhibited by a greater consistency of Carbopol matrices and a faster disappearance of the CO_2 bubbles. This behavior is attributed to Carbopol's faster entire hydration, which facilitates an earlier formation and dissipation of the gas bubbles. Carbopol matrices do not show a strong axial elongation like Methocel matrices do.

In order to increase the confidence of the hydration results the average of the last three measurements (hours 6, 7, and 8) was used to examine the changes produced by the formulation variables. As can be seen in Figure 6, Carbopol matrices show a limited change in hydration volume after addition of different proportions of SB. As mentioned above, the exceptions are the higher SB proportions, 20% and 24%, which show an appreciable decrease in hydration volume.

Methocel matrices show greater changes in hydration volume due to addition of different proportions of SB. This greater susceptibility is attributed to a comparatively lower coherence of Methocel matrices due in part to delayed hydration.

The apparent hydration volume (average after 6, 7, and 8 hours) of Methocel matrices containing 12% SB is kept in a range of comparable values after addition of different proportions of metronidazole. However, there is a clear trend toward increasing hydration volumes as the metronidazole load increases in matrices without SB. The average hydration volume observed by matrices of pure Methocel is 1,105 mm^3 while formulations containing SB show an average of 1,592 mm^3.

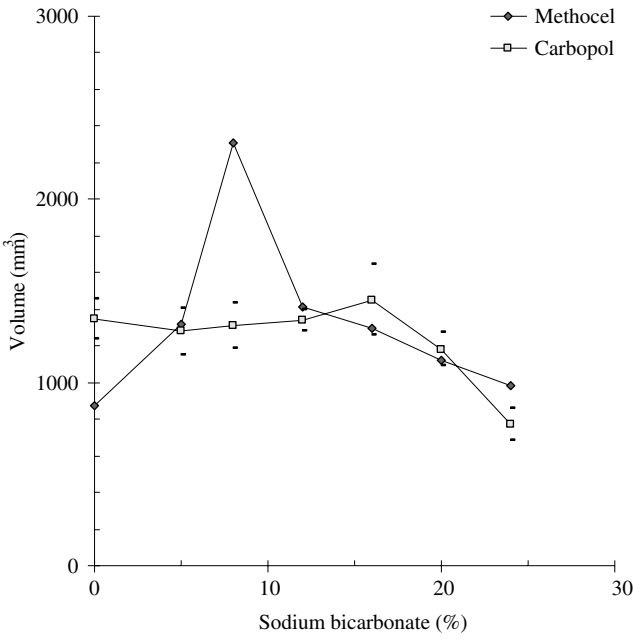

FIGURE 6. Effect of the sodium bicarbonate proportion on hydration volume of Carbopol 71P NF and Methocel K4M matrices, average of the volumes after 6, 7 and 8 hours. $M \pm 95\%$ C.I.

The matrix expansion produced by SB hides from view the effects of loading different proportions of metronidazole.

Matrices of Carbopol containing different metronidazole loads show an average apparent matrix hydration volume of 1,350 mm^3, while matrices with the same formulations but containing SB show an average volume of 1,342 mm^3. It seems that an increased hydration volume due to CO_2 bubbles is compensated by reduced polymer mass and increased polymer dissolution.

Carbopol matrices show a less pronounced curvature of hydration curves. Some curves do not show a maximum in hydration volume. After 8 hours of hydration, all Carbopol matrices, with and without SB, show an average hydration volume of about 1,346 mm^3 that is in between the average hydration volume of Methocel matrices without (1,031 mm^3) and with SB (1,549 mm^3).

Metronidazole Release from Carbopol 971P NF and Methocel K4M Matrices

Release data from swellable systems can be analyzed according to the power law expression shown in equation 1. The kinetics and mechanism of drug release for each system were investigated by fitting the release data into this equation (Mandal, 1995; Rinaki, Valsami, & Macheras, 2003; Vigoreaux & Ghaly, 1994):

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

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 1.0 (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, Padmalatha Devi, & Buri, 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).

The release profile is determined by the constant terms of the equation, namely the release constant k and the exponent indicative of the release mechanism n. The release constant determines the height of the curve—higher k values meaning higher quantities of drug released. The n values are the slope of the curve, meaning the rapidness of increase of the drug released with time. In this sense, a process with a lower value of the release constant and a higher value of the exponent n can reach higher quantities of drug released after some time because of its higher speed to increase the quantity of drug released, in spite of an initial lower quantity of the drug dissolved. The quantity of drug released after some time, for instance after 8 hours, depends on both the height of the curve and the rapidness to increase the drug released with time.

Release profiles of metronidazole from Carbopol 971P NF and Methocel K4M matrices containing different drug loads, fitting dissolution data into equation 1, produced straight lines for data corresponding to drug release up to 8 hours. Although the original expression of equation 1 was described to apply to drug release up to 60%, in this case and given the determination coefficients of nearly all regression curves greater than 0.990 it was applied to release data up to about 90%.

Although most of the matrix tablets studied float, they are totally enclosed by water. They are at the water surface but inside the water volume (Xu et al., 2006). In this way the effects of water on the matrix structure are similar to those of non-floating matrix tablets. As a consequence, it was considered that variations in the release profiles can be analyzed according to the power law expression shown in equation 1.

The effect of the relative amount of polymer to drug content was expected to confirm earlier findings that the percentage drug released from polymeric matrices decreases with an increase in polymer content (Baveja, Ranga Rao, & Padmalatha Devi, 1988; Tapia-Albarran & Villfuerte-Robles, 2004; Troz de Ilarduya et al., 1997). However, this is not the case for metronidazole releasing from Carbopol 971P NF matrices. An increasing metronidazole content (50, 75, 100, 125, and 150 mg/tab) while maintaining constant the matrix polymer (176 mg) and SB (24 mg/tab) content showed only a minor change in the percentage drug released. The same circumstance is observed by metronidazole releasing from Methocel K4M matrices. The average percentage drug released from Methocel K4M matrices after 8 hours (91.3% ± 7.0%) is greater than that released from Carbopol 971P NF matrices (79.4% ± 3.4%).

In spite of a lack of correlation between the drug load and the percentage drug released with time, the cumulative mass of metronidazole released increases clearly as the drug load increases. Figure 7 shows the calculated response surface for metronidazole dissolution from Methocel matrices. Similar results were observed by Carbopol matrices (Figure 8).

The effect of SB on individual release profiles of metronidazole from Methocel matrices is shown in Figure 9. The addition of SB, with the resulting reduction of the polymer load, produces an increase in the metronidazole released after 8 hours. Matrices containing SB release after 8 hours an average of 94.4 mg while matrices without SB release an average of 83.4 mg. These results go with an increase in the apparent hydration volume of Methocel matrices without SB from 1,105 mm^3 to 1,592 mm^3 after addition of this excipient. In this way, the increase of metronidazole dissolution can be attributed to an increase in the matrix surface area available for dissolution and a decrease in matrix consistency, obtained after addition of SB.

The initial higher quantities of metronidazol released from matrices without SB, corresponding with higher values of the release constant, are overcome by matrices containing SB at the end of 8 hours dissolution because of their higher values of the exponent *n*.

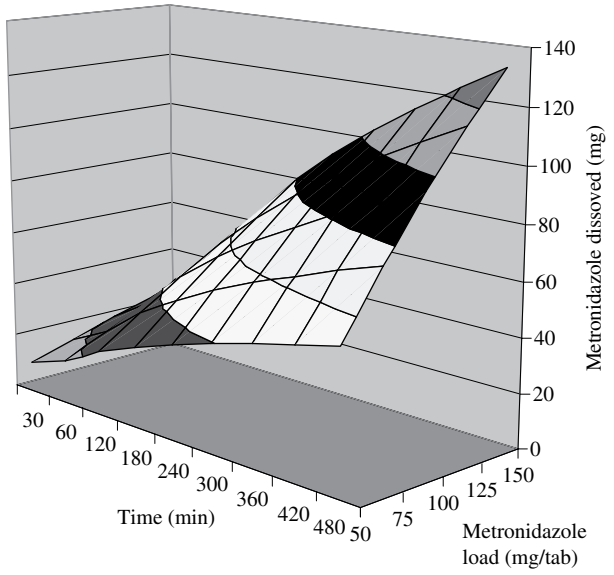

FIGURE 7. Calculated response surface for metronidazole dissolution from Methocel K4M (176 mg/tab) matrices containing sodium bicarbonate (24 mg/tab).

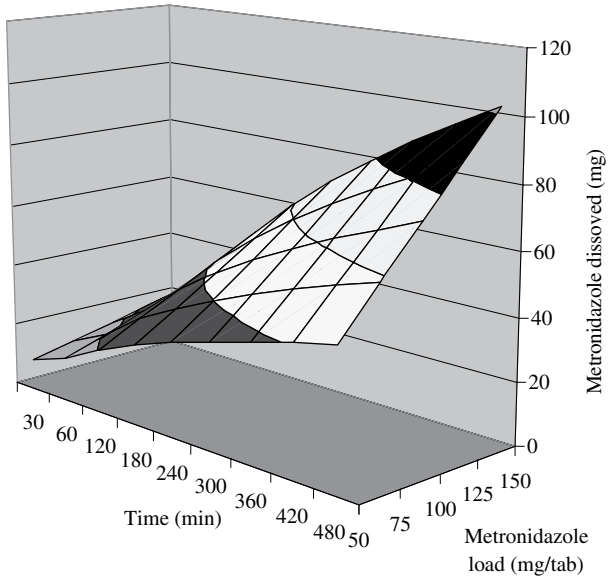

FIGURE 8. Calculated response surface for metronidazole dissolution from Carbopol 971P NF (176 mg/tab) matrices containing sodium bicarbonate (24 mg/tab).

Carbopol matrices show the same effect of SB, although not as clearly defined (Figure 10). Carbopol matrices containing SB release after 8 hours an average of 79.2 mg while matrices without SB release an average of 78.2 mg. The substitution of 24 mg of the total polymer content with the same quantity of SB shows practically no change on the metronidazole dissolved after 8 hours. These results are in line with a minor

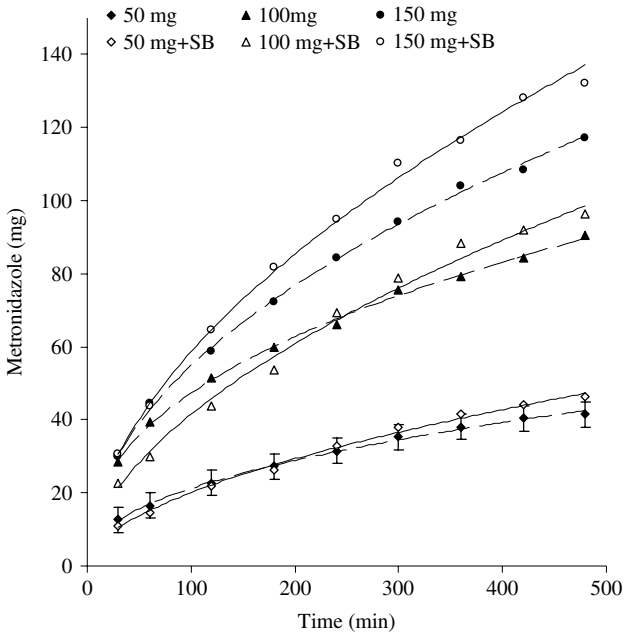

FIGURE 9. Effect of sodium bicarbonate on the release profile of metronidazole from Methocel K4M matrices loaded with different quantities of the drug. Vertical lines denote the standard error of the mean (n = 3).

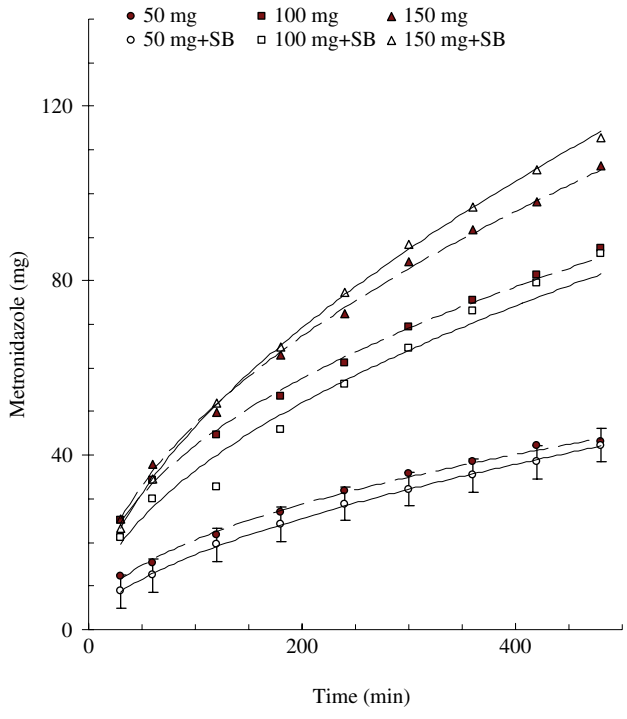

FIGURE 10. Effect of sodium bicarbonate on the release profile of metronidazole from Carbopol 974P NF matrices loaded with different quantities of the drug. Vertical lines denote the standard error of the mean (n = 3).

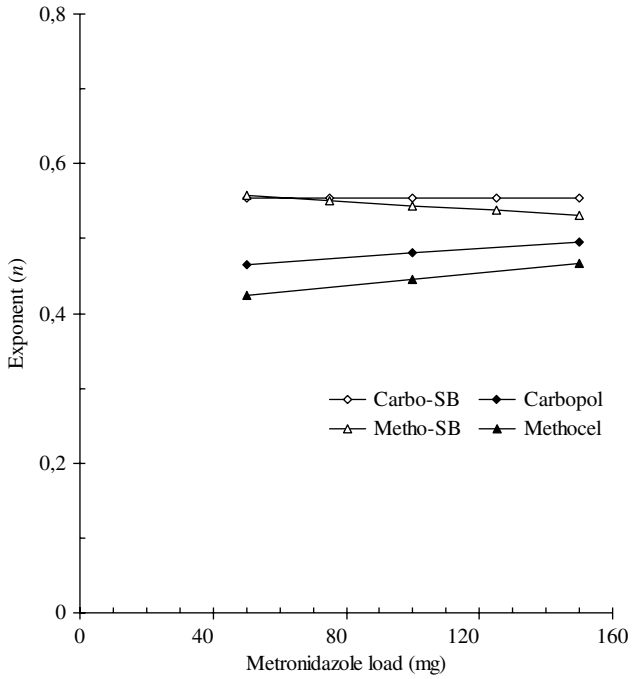

FIGURE 11. Effect of the metronidazole load on the exponent indicative of the release mechanism (n) of release profiles from Carbopol 974P NF and Methocel K4M matrices with and without sodium bicarbonate. Calculated regressions.

change in the apparent hydration volume observed before (1,350 mm^3) and after (1,342 mm^3) addition of SB.

The release mechanism showed by both types of matrices with and without SB is predominantly controlled by diffusion (Figure 11). However, the substitution of 24 mg of polymer content with SB produces a shift toward higher values of the exponent indicative of the release mechanism. Matrices added with SB show a little more contribution of relaxation and erosion to the release mechanism. Methocel matrices show a change of the exponent indicative of the release mechanism (n) from an average of 0.446 to 0.546, for before and after addition of SB, respectively. Carbopol matrices show similar results, changing the average of the exponent (n) from 0.481 to 0.552.

Figure 12 shows a linear trend of increasing release constant values (k) with an increasing matrix metronidazole load. This is in line with an increasing drug surface area in contact with the dissolution medium as the drug load increases.

Compared with Carbopol matrices, Methocel matrices show higher release constant values that increase faster as the drug load increases. This is attributed to the faster entire hydration of Carbopol matrices, which generates a greater coherence and lesser capability to expand after addition of SB. Methocel matrices show slower hydration, lower coherence, and greater capability to matrix expansion.

The functioning of the matrix is related to its inherent polymer properties. The particular rate of swelling of a given

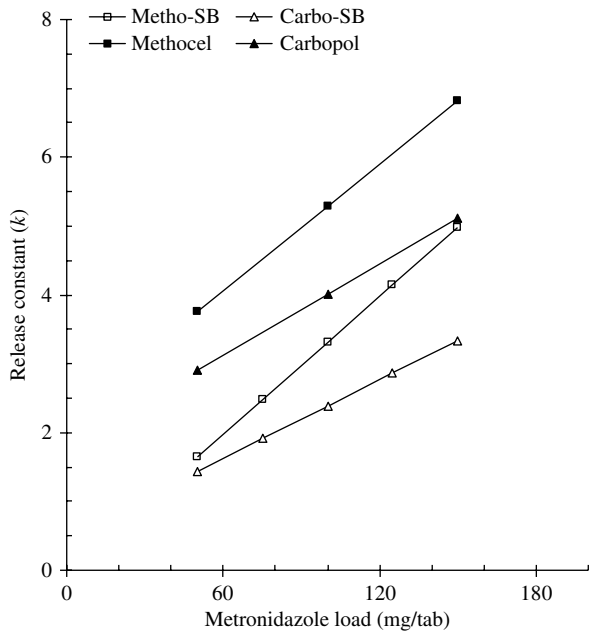

FIGURE 12. Effect of the metronidazole load on the release constant (k) of release profiles from Methocel K4M and Carbopol 971P NF matrices with and without sodium bicarbonate. Calculated regressions.

polymer is determined by the intrinsic properties and is assumed to be directly proportional to the percent swelling capacity still available at a given time, and to the total internal specific boundary area enclosing those sites capable of swelling that have not yet become hydrated and swollen at that time (Schott, 1992).

The effect of the substitution of 24 mg of the polymer content with SB is a lessening of the release constant values. The average of the release constant values is higher by pure Methocel matrices (5.292) than by matrices of Methocel with SB (3.249). Pure Carbopol matrices show an average release constant values of 4.018 while the average of matrices containing SB is 2.674. Although the trend is similar to that showed by Methocel matrices, the release constant values of Carbopol matrices are smaller and the differences between matrices with and without SB are also smaller.

Although the expansion of hydrated matrices contributes to the increase in matrix surface area available for dissolution, the presence of gas bubbles obstructs the diffusion path, decreasing the release constant values. Each one of these effects can vary with time according to the rate of production and the rate of dissipation of the gas bubbles.

Mechanistically, the behavior of Methocel matrices containing SB can be attributed to a predominant obstruction of the release path by CO_2 bubbles at the beginning of the process. This circumstance reduces the surface area available for drug transport. However, the continuing development of CO_2 bubbles contributes also to expand the matrix volume and to decrease the coherence of Methocel matrices. This second effect of the CO_2 bubbles can overrule the release process as the time goes by, facilitating the drug transport and increasing the cumulative drug released over that showed by pure Methocel matrices.

The results obtained by Methocel matrices were expected to be also produced by Carbopol matrices. Although the changes in dissolution behavior of Carbopol matrices before and after addition of SB are similar to those of Methocel matrices, they are less obvious. This can be attributed to the minor effect of SB on the hydration volume of Carbopol matrices. The external surface area and the release kinetics have been found to be closely related to matrices dissolution and swelling properties (Colombo et al., 1990, 1992; Varma Singla, & Dhawan, 2004).

Generally speaking, the effect of SB on the release profile from hydrophilic matrices is a reduction of the release constant (k) and an increase of the exponent indicative of the release mechanism (n). Both effects contribute to a desired flattening of the release profile.

CONCLUSIONS

The substitution of a given quantity of the matrix polymer content with SB in a hydrophilic matrix increases the apparent matrix hydration volume and reduces the gel consistency, facilitating matrix erosion. At the beginning, an increasing concentration of SB increases the matrix expansion, in spite of the concomitant polymer mass reduction. However, after a given matrix concentration of SB, the opposite occurs; the polymer mass reduction and the effects of the matrix erosion progressively reduce the apparent hydration volume. These effects are attributed to expansion of the matrix due to carbon dioxide evolution and to concomitant reduction of the swelling polymer mass.

The poor floating behavior of Carbopol matrices is improved substantially by the addition of SB. However, this improvement is not enough to maintain the floating condition for 8 hours of matrices loaded with elevated drug proportions (> 33%). The floatability of Methocel matrices is sufficient to maintain the floating condition for more than 8 hours. This floatability is reinforced by addition of SB and is maintained after addition of proven drug loads up to 43% of the total weight of the matrix.

The metronidazole release from Methocel K4M and Carbopol 971P NF matrices is explained as a function of the inherent polymers' hydration behavior, which determines the permeability and the matrix surface area available for drug transport. The effect of SB on the matrix release profile is explained as a result of alterations produced on the drug transport and on the apparent matrix hydration volume. The evolution of carbon dioxide produces gas bubbles that obstruct the diffusion path and drug transport. However, the carbon dioxide evolution expands progressively the swelling matrices, reducing their strength, and increasing the external surface area available for drug transport. The increase in surface area and in the apparent hydration volume predominates with time over

the obstruction effect on the drug diffusion path, improving drug transport.

Methocel matrices show slower hydration and lesser coherence than Carbopol matrices; because of that, they are more susceptible to changes after addition of SB.

REFERENCES

Baveja, S. K., Ranga Rao, K. V., & Padmalatha Devi, K. (1988). Relationship between gum content and half-life of soluble β blockers from hydrophilic matrix tablets. *Int. J. Pharm.*, *47*, 133–139.

Bettini, R., Castellani, P. L., Santi, P., Massimo, G., Peppas, N. A., & Colombo, P. (2001). Translocation of drug particles in HPMC matrix gel layer: Effect of drug solubility and influence on release rate. *J. Control. Release, 70*, 383–391.

Brazel, C. S., & Peppas, N. A. (2000). Modeling of drug release from swellable polymers. *Eur. J. Pharm. Biopharm, 49*, 47–58.

Chikhalikar, K., & Moorkath, S. (2002). Carbopol polymers: A versatile range of polymers for pharmaceutical applications. Retrieved Dec. 17, 2007, from http://www.PHARMABIZ.com.

Colombo, P., Conte, U., Gazzaniga, A., Maggi, L., Sangelli, M. S., Peppas, N. A., & LaManna, A. (1990). Drug release modulation by physical restrictions of matrix swelling. *Int. J. Pharm., 63,* 43–48.

Colombo, P., Castellani, P. L., Peppas, N. A., Maggi, L., & Conte, U. (1992). Swelling characteristics of hydrophilic matrices for controlled release: New dimensionless number to describe the swelling and release behavior. *Int. J. Pharm., 88*, 99–109.

Efentakis, M., Vlachou, M., & Choulis N. H. (1997). Effects of excipients on swelling and drug release from compressed matrices. *Drug Dev. Ind. Pharm., 23*, 107–112.

Espinoza, R., & Villafuerte, L. (1999). Influence of admixed lactose on pelanserin hydrochloride release from hydroxypropyl methylcellulose matrix tablets. *Pharm. Acta Helv., 74*, 65–71.

Holgado, M. A., Caraballo, I., Alvarez-Fuentes, J., Fernández-Hervás, M. J., Fernández-Arevalo, M., & Rabasco, A. M. (1995). Influence of diluents and manufacturing method on the in vitro dissolution of carteolol hydrochloride matrix tablets. *Int. J. Pharm., 118*, 151–160.

Huang, Y., Tsai, Y., Yang, W., Chang, J., Wu, P., & Takayama, K. (2004). Once-daily propanolol extended-release tablet dosage form: Formulation design and in vitro/in vivo investigation. *Eur. J. Pharm. Biopharm., 58*, 607–614.

Jamzad, S., Tutunji, L., & Fassihi, R. (2005). Analysis of macromolecular changes and drug release from hydrophilic matrix systems. *Int. J. Pharm., 292*, 75–85.

Katzhendler, I., Hoffman, A., Goldberger, A., & Friedman, M. (1997). Modeling of drug release from erodible tablets. *J. Pharm. Sci., 86*, 110–115.

Kavanagh, N., & Corrigan, O. I. (2004). Swelling and erosion properties of hydroxypropylmethylcellulose (Hypromellose) matrices: Influence of agitation and dissolution medium composition. *Int. J. Pharm*., *279*(1–2), 141–152.

Khan, G. M., & Zhu, J. B. (1999). Studies on drug release kinetics from ibuprofen-carbomer hydrophilic matrix tablets: Influence of co-excipients on release rate of the drug. *J. Control. Release 57*, 197–203

Kim, H., & Fassihi, R. (1997). Application of binary polymer system in drug release rate modulation: 2. Influence of formulation variables and hydrodynamic conditions on release kinetics. *J. Pharm. Sci., 86*, 323–328.

Korsmeyer, R. W., Gurny, R., Doelker, E., Buri, P., & Peppas, N. A. (1983). Mechanisms of potassium chloride release from compressed, hydrophilic, polymeric matrices: Effect of entrapped air. *J. Pharm. Sci., 72*, 1189–1191.

Lapidus, H., & Lordi, N. J. (1968). Drug release from compressed hydrophilic matrices. *J. Pharm. Sci., 57*, 1292–1301.

Li, S., Lin, S., Chien, Y. W., Daggy, B. P., & Mirchandani, H. L. (2001). Statistical optimization of gastric floating system for oral controlled delivery of calcium. *AAPS PharmSciTech*, *2*(1), article 1.

Li, S., Lin, S., Daggy, B. P., Marchandani, H. L., & Chien, Y. W. (2002). Effect of formulation variables on the floating properties of gastric floating drug delivery system. *Drug Dev. Ind. Pharm., 28*, 783–793.

Mandal, T. K. (1995). The influence of binding solvents on drug release from hydroxypropyl methylcellulose tablets. *Drug Dev. Ind. Pharm., 21*, 1389–1397.

Martínez-González, I., & Villafuerte-Robles, L. (2003). Influence of enteric citric acid on the release profile of 4-aminopyridine from HPMC matrix tablets. *Int. J. Pharm*., *251*(1–2), 183–193.

Martínez-González, I., & Villafuerte-Robles, L. (2004). Influence of enteric lactose on the release profile of 4-aminopyridine from HPMC matrix tablets. *Pharm. Dev. Tech., 9*, 145–153.

Papadimitriou, E., Buckton, G., & Efentakis, M. (1993). Probing the mechanism of swelling of hydroxypropylmethylcellulose matrices. *Int. J. Pharm., 98*, 57–62.

Ranga Rao, K. V., Padmalatha Devi, K., & Buri P. (1988). Cellulose matrices for zero-order release of soluble drugs. *Drug Dev. Ind. Pharm., 14*(15–17), 2299–2320.

Rinaki, E., Valsami, G., & Macheras P. (2003). The power law can describe the "entire" drug release curve from HPMC-based matrix tablets: A hypothesis. Int. *J. Pharm., 255*, 199–207.

Risbud, M. V., Hardikar, A. A., Bhat, S. V., & Bhonde, R. R. (2000). pH-sensitive freeze dried chitosan-polyvinyl pyrrolidone hydrogels as controlled release system for antibiotic delivery. *J. Control. Release, 68*, 23–30.

Schott, H. (1992). Kinetics of swelling of polymers and their gels. *J. Pharm. Sci., 81*, 467–470.

Singh, B. N., & Kim, K. H. (2000). Floating drug delivery systems: An approach to oral controlled drug delivery via gastric retention. *J. Control. Release, 63*, 235–259.

Singla, A., Chawla, M., & Singh, A. (2000). Potential applications of carbomer in oral mucoadhesive controlled drug delivery systems: A review. *Drug Dev. Ind. Pharm., 26*, 913–924.

Sheth, P. R., & Tossounian, J. L. (1979). Sustained release formulations. (pp. 1–2). United States patent 4, 140, 755.

Tapia-Albarran, M., & Villafuerte-Robles, L. (2004). Assay of amoxicillin sustained release from matrix tablets containing different proportions of Carbopol 971P NF. *Int. J. Pharm., 273*, 121–127.

Troz de Ilarduya, M. C., Martin, C., Goñi, M. M., Martínez-Ohárris, M. C., (1997). Oxazepem dissolution rate from hydroxypropylmethylcellulose matrices. *Drug Dev. Ind. Pharm. 23,* 393–396.

Varma, M., Singla, A. K., & Dhawan, S. (2004). Release of diltiazem hydrochloride from hydrophilic matrices of polyethylene oxide and carbopol. *Drug Dev. Ind. Pharm., 30*, 545–553.

Vigoreaux, V., & Ghaly, E. S. (1994). Fickian and relaxational contribution quantification of drug release in a swellable hydrophilic polymer matrix. *Drug Dev. Ind. Pharm., 20*, 2519–2526.

Wu, Y., & Fassihi, R. (2005). Stability of metronidazole, tetracycline HCl and famotidine alone and in combination. *Int. J. Pharm., 290*, 1–13.

Xu, G., & Groves, M. J. (2001). Effect of FITC-dextran molecular weight on its release from floating cetyl alcohol and HPMC tablets. *J. Pharm. Pharmacol., 53*, 49–55.

Xu, X., Sun, M., Zhi, F., & Hu, Y. 2006. Floating matrix dosage form for phenoporlamine hydrochloride based on gas forming agent: In vitro and in vivo evaluation in healthy volunteers. *Int. J. Pharm., 310*, 139–145.

Yang, L., Eshraghi, J., & Fassihi, R. (1999). A new intragastric delivery system for the treatment of *Helicobacter pylori* associated gastric ulcer: In vitro evaluation. *J. Control. Release 57*, 215–222.