ABSTRACT The stability of captopril in a controlled release formulation has been a challenge for some time. In this work, the sustained release of captopril from floating matrices has been studied varying the antioxidant load, the sodium bicarbonate proportion and the compaction pressure. Other studied variables include the matrix hydration kinetics, the matrices floating time and the matrix density. The results show that matrices compacted at 55 MPa have smaller density and float in the dissolution medium for more than 8 h while those compacted at 165 MPa float only when sodium bicarbonate is included. The increase of compaction pressure reduces the hydration volume and increases the time necessary to attain its maximum and corresponds with greater values of the exponent (n) and smaller values of the release constant (k). These changes are attributed to lower matrix porosity and to the consequent diminution of water and drug transport. Increasing antioxidant proportions increase the matrix hydration volume and the drug released. A partial substitution of polymer (15%) with sodium bicarbonate along with substitution of ascorbic acid with sodium ascorbate reduces the matrix hydration volume, shortens the matrix hydration process and increases the drug released. Moreover, the release constant (k) of captopril release profiles increases and the exponent (n) decreases. This phenomenon is attributed to carbon dioxide bubbles that decrease the matrix coherence and expand the matrix volume, facilitating the drug dissolution and allowing only a limited further matrix expansion due to polymer hydration.

KEY WORDS: Hydroxypropyl methylcellulose; captopril floating tablets; antioxidants; hydration kinetics; compaction pressure.
INTRODUCTION

Captopril is an angiotensine-converting enzyme inhibitor that has been widely used for the treatment of hypertension and congestive heart failure. Captopril acts orally and the dosage used for the treatment of congestive heart failure ranges from 50 to 150 mg daily. After oral ingestion of a single dose the maximum hemodynamic effect is observed after 45-90 min (Liebau, 1982). The drug is freely water soluble and has an elimination half-life after an oral dose of 1.7 h. After single oral dosing of the drug, the antihypertensive action is only effective for 6-8 h. Development of a controlled delivery system for captopril would bring many advantages for patients (Khan et al., 2000). However, the development of an oral controlled release formulation for captopril is difficult because of in vivo and in vitro instability. The drug also undergoes from dose dumping and burst phenomenon (being freely water soluble) when formulated as controlled or sustained release formulation (Nur and Zhang, 2000a).

Captopril is stable at pH 1.2, and as the pH increases, the drug becomes unstable and undergoes a degradation reaction (Nur and Zhang, 2000b; Cheng et al., 2007). The unique chemical structure of these ACE inhibitors has been reported to reveal certain types of degradation, such as cyclization, hydrolysis, and/or oxidation. Captopril is the first generated ACE inhibitor and possesses three unique functionalities; a mercapto, amide and carbonyl moiety in structure (Cheng et al., 2007). Captopril in aqueous solution undergoes an oxygen facilitated, first order, free radical oxidation at its thiol to yield captopril disulfide. Oxidation was delayed by adjustment to lower pH, addition of chelating agents, increasing captopril concentration and incorporation of antioxidants (Kadin, 1982). The oxidative rate of degradation of captopril shows maximum stability below pH 4.0. The oxidation reaction is the predominant route of degradation over the pH range of 2-4 (Timmins et al., 2007).

Captopril was found to be dramatically unstable in presence of food. The addition of ascorbic acid to the system improved its stability. The stabilization effect of ascorbic acid on captopril in dog food supernatant was determined after incubation for 3 hours. The half-life periods obtained were 1.3 h without ascorbic acid and 2.3 h with ascorbic acid. It is presumed that ascorbic acid inhibits the binding of the SH group of captopril to the SH groups present in food component (Seta et al., 1988).

A floating dosage form is useful for those drugs that act locally in the proximal gastrointestinal tract (GIT) (Rajinikanth and Mishra, 2008), are unstable in lower parts of GIT, or are poorly absorbed in the intestine (Srivastava et al., 2005). This type of formulation has been also used for drugs absorbed only in the initial part of the small intestine, in the same way as ranitidine. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability (Dave et al., 2004). Higher bioavailability from floating dosage forms of furosemide has been attributed to the fact that the upper gastrointestinal tract is the primary site of absorption for the drug. Gastroretentive delivery systems, however, are not suitable for drugs unstable in the environment of the stomach (Talukder and Fassihi, 2004).

Drug release from hydrophilic matrix tablets is controlled by formation of a hydrated viscous layer around the tablet which acts as a barrier to drug release by opposing
penetration of water into tablet and also movement of dissolved solutes out of the matrix tablets. The extent of matrix swelling, erosion, and diffusion of drug determines the kinetics as well as mechanism of drug release. (Sriamornsak et al., 2007a).

Methocel matrices hydrate rapidly only at the surface, retaining their original air bubbles and extending floatation beyond 8 h. Further addition of sodium bicarbonate (8-24%) maintains also their floatability longer than 8 h. The addition of sodium bicarbonate to Methocel matrices expands their volume due to the gas bubbles formed after reaction with an acidic dissolution medium, increasing their hydration volume (Cedillo-Ramírez et al., 2006). Although the expansion of hydrated matrices contributes to increase the 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 be varying with time according to the rate of production and the rate of dissipation of the gas bubbles. Although carbon dioxide bubbles obstruct the drug release path at the beginning of the dissolution process, its continuing development contributes also to expand the volume and to decrease the coherence of Methocel matrices. This second effect overrules in a second part of the release process, facilitating drug transport and increasing the cumulative drug released after 8 h over that showed by pure Methocel matrices (Gutiérrez-Sánchez et al., 2008).

It is evident that the goodness of a hydrophilic floating matrix depends on the stability of the drug in the stomach. In this sense, the aim of this work is the evaluation of the effect of sodium bicarbonate and the load of an antioxidant (ascorbic acid or sodium ascorbate), on the floating and hydration behavior of captopril matrices and their influence on the release profile. The antioxidant is added to maintain the drug protected against oxidation while releasing in the stomach. The results contribute to the understanding of the formulation of this type of drug delivery systems.

MATERIALS AND METHODS

Materials

The pharmaceutical excipient Metolose 90 SH 4000 SR, a brand of hydroxypropyl methylcellulose, batch 303574, obtained from Nutrer Farma; ascorbic acid batch SB97020871, obtained from HELM de México; sodium ascorbate, batch DY02208, obtained from Astroquim and the drug captopril, batch 1001934001, obtained from Química Alkano, 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, sodium bicarbonate and sodium ascorbate were size reduced in a mortar for 20 min. The drug, the polymer and other components corresponding to 10 tablets of each different formulation were mixed for 30 min in a mortar. The tablets were compressed in a hydraulic press fitted with flat faced 12.8 mm punch and die set at pressures of 55 MPa and 165 MPa during 10 seconds. No lubricant was used in the tablets. Matrix tablets were produced by using 50 mg of the drug, 400 mg Metolose and different quantities of ascorbic acid: 150, 200, 250 and 275 mg/tablet. In a
second series of matrix tablets 15% of the polymer content was substituted by sodium bicarbonate, keeping the quantity of the polymer/bicarbonate mixture in the formulation in the same magnitude as the original polymer content. Each tablet contained 50 mg captopril, 340 mg Metolose, 60 mg sodium bicarbonate and different quantities of sodium ascorbate: 150, 200, 250, 275 mg/tablet.

**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 the dissolution studies. At various time intervals the tablets were removed from dissolution medium and measured in their height and wide using a microscope with 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 are registered as an average.

The floating time was determined by observation of the floating behaviour throughout the dissolution studies and was registered as the average of 3 repetitions.

**Matrix tablets density**

The weight and volume reached by the matrix tablets over time was determined by withdrawing the tablets at various time intervals. The tablets were weighed on an analytical balance after slight blotting with tissue paper to remove the excess test liquid. The volume of the tablets was obtained by measuring the height and wide, considering a right circular cylinder form. The weight and volume obtained in this manner were used to calculate the tablet density. The results for each time point of three repetitions are registered as an average.

**Drug release**

Dissolution studies were performed in 900 ml of HCl 0.1N using the paddle method (USP 26), at 50 rpm and 37 °C (JT R09, TEMSA, Mexico). The amount of captopril released over time was determined by withdrawing samples at various time intervals. The concentration of captopril was obtained by measuring the absorbance at 343 nm, of the reaction product of captopril with 2, 2’ dithiodipyridine, in a Beckman DU-650 ultraviolet spectrophotometer (Grassetti and Murray, 1967). Three replicates were made for each experiment. Captopril solubility in water at 25 °C is 160 mg/ml (Kadin, 1982; Sigma-Aldrich, 2008). Ascorbic acid and sodium ascorbate show higher solubilities in water, 1 in 3.5 and 1 in 1.6 respectively. Therefore, dissolution of 50 mg captopril and 275 mg ascorbic acid or sodium ascorbate in 900 ml at 37 °C is considered under sink conditions.

**Statistical analysis**
This test was applied to compare two regression curves through the calculated intercepts and slopes, using the square of the standard error as the variance of regression parameters. When nothing else is mentioned in the text, the applied test was a two-tailed or two-sided t-test, considering the samples with unequal variances and at a level of 0.05. The values of P were calculated from the obtained t-values and the corresponding degrees of freedom.

RESULTS AND DISCUSSION

Floating behaviour of matrix tablets

Captopril/Metolose formulations containing ascorbic acid and compacted at 55 MPa float more than 8 h while matrices compacted at 165 MPa do not float (Fig. 1). Tablets compacted at a lower pressure keep more entrapped air, decreasing the agglomerate density and allowing the tablets floating. On the other hand, tablets compacted at higher pressure are less porous, displaying a density not allowing the matrices floatation. The presence of sodium bicarbonate in matrix tablets compacted at 55 MPa assured their floatability while in matrices compacted at 165 MPa made possible their floatability. All matrices containing sodium bicarbonate floated more than 8 h.

Hydration behaviour of matrix tablets

Generally speaking, the matrices hydration volume increases at the beginning, attains a maximum and then declines. However, not all matrices show this complete profile in the interval of 8 h dissolution; some of them do not reach the maximal hydration volume within this interval. This behaviour has been observed previously by matrices made of different polymers such as pectin (Sriamornsak et al., 2007b), alginate (Sriamornsak et al., 2007a) and Hydroxypropyl methylcellulose and Carbopol (Gutiérrez-Sánchez et al., 2008).

The matrices behaviour can be ascribed to a natural hydration process. Hydrophilic matrices in contact with water swell and increase their volume due to water diffusion through the matrix. The polymer chains continue the hydration process and the matrix gain more water. The increasing water content dilutes the matrix until a disentanglement concentration is attained. At this point, the polymer molecules are released from the matrix, diffusing to the bulk of the dissolution medium. Then, the matrix volume slowly decreases because of polymer dissolution. Polymeric matrices experience simultaneously swelling, dissolution/erosion and diffusion of dissolved polymer.

As can be seen in Fig. 2, captopril/Metolose matrices containing different quantities of ascorbic acid and compacted at 165 MPa show minor differences in hydration kinetics. These results differ of previous studies with Methocel matrices containing fixed quantities of metronidazole and sodium bicarbonate and variable quantities of Pharmatose DCL 11 where the trend is clear to a matrix volume reduction as the polymer proportion decreases or the Pharmatose content increases (Cedillo-Ramírez et al., 2006). This can be attributed to a smaller proportion of Methocel in metronidazole matrices that increases from 18% to the double (36%). This makes easier to quantify the effect of the polymer proportion. In the case of captopril/Metolose matrices the polymer proportion is greater (55%) and increases only about 20% of the initial polymer proportion (up to 67%).
Given this not so clear effect of ascorbic acid on the hydration volume, all hydration profiles were taken as whole, making an average hydration profile corresponding to different antioxidants and compaction pressures. Fig. 3 shows to what degree the matrices hydration profile changes as the antioxidant and the compaction pressure change. It is clear an increase of hydration volume of matrices containing ascorbic acid as the compaction pressure decreases. Considering the regression parameters of the data fitting in a quadratic relationship, the intercepts of matrices containing ascorbic acid and compacted at 55 MPa and 165 MPa are not different (P = 0.218) while the coefficients of \( x \) (P < 0.0001) and \( x^2 \) (P = 0.0002) are distinct. Similar results are observed when comparing the curves of matrices containing bicarbonate and sodium ascorbate, compacted at 55 MPa and 165 MPa (Fig.3). Considering a quadratic regression, the intercepts are not different (P = 0.912) and the slopes are different, \( x \) (P < 0.0001) and \( x^2 \) (P = 0.0001). Compared to matrices compacted at 165 MPa, matrices compacted at 55 MPa contain more pores and are less coherent, both facts allowing a faster hydration of the dry matrix and an increased hydration volume. As above mentioned, the hydration behaviour of matrices with and without sodium bicarbonate is similar with respect to compaction pressure; however, both types of formulations show a different pattern of hydration profile (Fig. 3).

Matrices compacted at the same pressure show a different hydration profile of formulations containing sodium bicarbonate, compared to formulations without it. The presence of sodium bicarbonate abbreviates the hydration sequence. The evolution of carbon dioxide, after reaction of sodium bicarbonate with the hydrochloric acid of the dissolution medium, decreases the matrix coherence facilitating the hydration process. The complete hydration process occurs in a shorter time. This has been observed before with metronidazole/Methocel matrices where the gas bubbles were considered to have an effect similar to that observed with solid particles included in a hydrophilic matrix (Gutiérrez-Sánchez et al., 2008). 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; Jamzad et al., 2005).

Matrices containing sodium bicarbonate attain the maximal hydration volume within 8 h dissolution. In these matrices, the stage of polymer dissolution/erosion that reduces the matrix volume is more evident within the time-span of the study. The lower hydration volumes of matrices containing sodium bicarbonate are mostly due to lower polymer content (15%). The maximal volumes of matrices containing sodium bicarbonate are about 16% lower than that of matrices without sodium bicarbonate.

The time necessary to attain the maximal hydration volume is lesser as the matrix coherence decreases. In this way, the application of a lower compaction pressure as well as the inclusion of sodium bicarbonate reduces this time. This can be observed in Fig. 4, for a given formulation a reduction of compaction pressure decreases the time to attain the maximal hydration volume. In the same way, the evolution of carbon dioxide bubbles from inside of the matrix to its periphery reduces the matrix coherence and with this, reduces also the time necessary to attain the maximal hydration volume.

Although the reduction of the maximal hydration volume of matrices containing sodium bicarbonate is almost exclusively attributed to a reduction of the polymer content (15%), the time to attain this maximum is reduced not 15% but about 30%. The reduction of time to reach the maximal hydration volume is attributed in part to lesser polymer
content and in part to lower coherence of these matrices, produced by the evolution of carbon dioxide bubbles. Reduced matrix coherence, due to lower compaction pressures and gas bubbles evolution, facilitates a faster matrix hydration, reaching the maximal hydration volume in a shorter time.

A two-tailed paired t-test at a level of 0.05 shows that the time necessary to attain the maximal hydration volume of matrices without bicarbonate (captopril/Metolose/ascorbic acid) is greater than that of matrices containing bicarbonate. This occurs in matrices compacted at 55 MPa (P = 0.00035) as well as in matrices compacted at 165 MPa (P = 0.00303). The same test applied to matrices containing sodium ascorbate and bicarbonate shows that matrices compacted at 55 MPa need lesser time to reach the maximal hydration volume than those compacted at 165 MPa (P = 0.00030). The test applied to matrices without bicarbonate shows that the time necessary to reach the maximal hydration volume of matrices compacted at 55 MPa is lesser than that of matrices compacted at 165 MPa (P = 0.0339).

**Density of matrix tablets**

The density of matrices containing ascorbic acid exhibits a trend to decrease with time, most probably because of a decreasing content of solids as they dissolve (Fig. 5). Matrices obtained at 165 MPa show a greater density as compared to those obtained at 55 MPa. Considering a quadratic fitting of the data the regression parameters show distinct intercepts (P < 0.0001) and not different x coefficients (P = 0.2347) as well as not different $x^2$ coefficients (P = 0.3543). Although in both cases the density was registered as inferior to 1.0 mg/mm$^3$, only matrices compacted at 55 MPa float while those compacted at 165 MPa do not float. It means that the actual density of matrices compacted at 55 MPa has to be lesser than 1.0 mg/mm$^3$ while those compacted at 165 MPa has to be greater. A systematic error comes about while determining the matrix density, most probably due to miscalculation of the matrix volume. Given the floating behaviour of these matrices their volumes have been determined as greater than they really are.

As explained in methods, the volume is determined by measurement of the axial and radial expansion of matrix tablets following exposure to dissolution medium and considering the matrix as a right circular cylinder. Obviously, the measurement of the volume is to be considered as an operative measurement, just useful to determine trends of the variables effects, and not corresponding with the actual physical volume of matrices.

The average density of the matrices containing the mixture of sodium bicarbonate / sodium ascorbate is practically maintained during the dissolution process, decreasing slightly throughout 8 h dissolution. The presence of sodium bicarbonate hides the effect of the solids being dissolved. This is attributed to carbon dioxide evolution that expands the matrices, decreasing the matrix density almost to a constant value. All matrices containing sodium bicarbonate display densities that allow their floating (Fig. 1).

**Drug release from matrix tablets**

All dissolution profiles were described with the exponential expression attributed to Korsmayer and Peppas (Escudero et al., 2008; Cárdenas, 2003; Hilton and Deasy, 1992).
Although the exponential equation is recommended to be used only for data corresponding up to 60% of drug released, the actual experimental data fit the mathematical model satisfactorily in a time interval up to 6 h. The determination coefficients of regressions, in example those of drug/Metolose/ascorbic acid matrices, lay in a range between 0.977 and 0.996. In this circumstance, the experimental points used to calculate the regressions included the dissolution time up to 6 h.

Ascorbic acid loading in the range from 150 mg/tablet to 275 mg/tablet, while keeping the drug and polymer content constant, affected the release process. As the content of ascorbic acid was increased the ability to sustain drug release decreased. The increase in the ascorbic acid content increased the amount of the captopril dissolved after 4 h dissolution (Fig. 6). Considering the captopril dissolved after 4 h from matrices compacted at 55 MPa and those of matrices compacted at 165 MPa as an average, the captopril dissolved increased from 57% to 70% (Fig. 6). The ascorbic acid enhancement of captopril dissolution is attributed to a loosening of the matrix structure through an increased porosity created after its dissolution and release and through the shortfall or loss of binding point linking polymer particles. The release of ascorbic acid would increase the porosity and decrease the tortuosity and therefore would allow a faster release rate. A similar effect has been observed with water soluble excipients such as citric acid in pelanserin/HPMC matrices (Espinoza et al., 2000) and with Pharmatose DCL 11 in metronidazole/Methocel matrices (Cedillo-Ramírez et al., 2006).

The substitution of 15% polymer with sodium bicarbonate and addition of sodium ascorbate instead of ascorbic acid produced higher release rates. However, the effect of ascorbic acid to increase the drug dissolved is not so clearly observed in matrices containing sodium ascorbate. This can be seen in Fig. 6 as percentage captopril released after 4 h for matrices containing different quantities of ascorbic acid or sodium ascorbate. Matrices containing ascorbate show average percentages of captopril dissolved after 4 h ranging from 70% to 74%.

The effect of substitution of 15% polymer with sodium bicarbonate along with the addition of sodium ascorbate instead of ascorbic acid show a less pronounced effect of the antioxidant on the captopril released. The slope of the regression line of matrices containing sodium ascorbate (0.0189) is smaller (P = 0.011) than that of matrices containing ascorbic acid (0.0977). These regressions were calculated including data of both compaction pressures, 55 MPa and 165 MPa.

Although a doubtful effect of compaction pressure is observed in the drug released after 4 h from matrices compacted at 55 MPa and 165 MPa, Fig. 7 shows a clear effect of compaction pressure on the exponent indicative of the release mechanism (n) of matrices added with ascorbic acid. The regression parameters, the intercepts (P = 0.0013) and the slopes (P = 0.0118), of curves corresponding to compaction pressures of 55 MPa and 165 MPa are distinct. These results reflect those of Fig. 3 corresponding with matrices added of ascorbic acid compacted at 55 MPa and 165 MPa. The higher n values correspond with matrices with lower hydration volumes, compacted at 165 MPa. Matrices compacted at lower pressure (55 MPa) display lower values of the exponent indicative of the release mechanism and higher hydration volumes. The lower values of the exponent (n) are attributed to a faster (Fig. 4) and higher matrix hydration (Fig. 3).
Moreover, the increase of compaction pressure decreases the values of the release constant (k) (Fig. 8). Matrices compacted at lower pressure (55 MPa) display higher values of the release constant (k) and higher hydration volumes. The higher values of the release constant (k) are in line with a faster (Fig. 4) and higher matrix hydration (Fig. 3).

As the matrices compaction pressure increases from 55 MPa to 165 MPa, the exponent (n) moves from a release mechanism predominantly controlled by diffusion toward a mechanism with a little more emphasis on relaxation, erosion and polymer dissolution while the release constant values decrease. This has been attributed to greater extension or exercise of hydration and dissolution of the polymeric matrices as the drug release is subject to limitation (Martínez-González and Villafuerte-Robles, 2003). The increase in release restriction given by the increase of compaction pressure modifies the release mechanism from diffusion toward a relaxation and erosion controlled process. Every restriction of drug release is associated with an extended time of matrix exposition to the dissolution medium to release a given quantity of the drug. Consequently, every release restriction in the captopril/Metolose/ascorbic acid system is associated to a higher degree of matrix hydration before a given quantity of the drug is released. It means a greater contribution of matrix relaxation and erosion processes to predominant release mechanism.

The effects of the antioxidant on the exponent indicative of the release mechanism (n) and the release constant (k) of matrices containing sodium bicarbonate is similar to that mentioned before by matrices without it. However, a greater variance of results of the exponent (n) values obtained from matrices added with sodium ascorbate and sodium bicarbonate does not allow the same conclusion. The values of the exponent (n) are lesser and the release constants (k) are greater for matrices containing sodium bicarbonate (Figs. 7 and 8). These results are attributed to a lower polymer proportion and to a rapid loss of the matrix coherence given by carbon dioxide bubbles produced after the reaction of bicarbonate with the hydrochloric acid of the dissolution medium. The matrix tablets expand and relax from the very beginning allowing the matrix hydration with a limited further expansion or relaxation of the structure (curves SB-SA MPa in Fig. 3).

The total effect of sodium bicarbonate on the drug dissolution kinetics seems to be dependent of the matrix polymer proportion and the overall interactions with all other excipients. The effect of sodium bicarbonate on the matrix behaviour is basically expansion of the matrix and a loss of coherence that facilitate dissolution and, on the other hand, an obstruction of water and drug transport due to reduction of the diffusion path through carbon dioxide bubbles that obstruct dissolution. The increase or reduction of the drug dissolution rate depends of what effect predominates. Actually, using polymer proportions of 55-65%, the effect of sodium bicarbonate is an increase of captopril dissolution, in the same way as bicarbonate produces an increase of metronidazole dissolution using polymer proportions of 57-80% (Gutiérrez-Sánchez et al., 2008). On the other hand, using polymer proportions of 75-89% produced a decrease of captopril dissolution (Jiménez-Martínez et al., 2008).

**CONCLUSIONS**

The results show that matrices compacted at 55 MPa have smaller density and float in the dissolution medium for more than 8 h while those compacted at 165 MPa float only
when sodium bicarbonate is included. The increase of compaction pressure reduces the hydration volume and increases the time necessary to attain its maximum, producing release profiles with greater values of the exponent (n) and smaller values of the release constant (k). The changes produced by the increase in compaction pressure are attributed to lower matrix porosity that reduces the penetration of water into tablet and also the movement of dissolved solutes out of the matrix tablets. Increasing antioxidant proportions increase the matrix hydration volume and the drug released. A partial substitution of polymer (15%) with sodium bicarbonate along with substitution of ascorbic acid with sodium ascorbate reduces the matrix hydration volume, shortens the matrix hydration process and increases the drug released. Moreover, the release constant (k) of captopril release profiles increases and the exponent indicative of the release mechanism (n) decreases. This phenomenon is attributed to carbon dioxide bubbles that decrease the matrix coherence and expand the matrix volume, facilitating the drug dissolution and allowing only a limited further matrix expansion due to polymer hydration.
REFERENCES


Figure 1. Floating time of matrices containing 50 mg captopril, the polymer and different quantities of ascorbic acid (AA) or sodium bicarbonate (SB) / sodium ascorbate (SA), compacted at 55 MPa or 165 MPa.
Figure 2. Hydration kinetics of 50 mg captopril matrices containing 400 mg polymer (P) and different proportions of ascorbic acid (AA), compacted at 55 MPa.
Figure 3. Effect of compaction pressure (55 MPa and 165 MPa) on the average hydration volume of captopril / Metolose matrices containing ascorbic acid (AA) or sodium bicarbonate (SB) / sodium ascorbate (SA).
Figure 4. Effect of compaction pressure (55 MPa, 165 MPa) on the average time necessary to attain the maximal hydration volume of captopril/Metolose matrices containing ascorbic acid or sodium ascorbate / sodium bicarbonate.
Figure 5. Effect of compaction pressure ($P_c=55$ MPa and $P_c=165$ MPa) on the density profile of captopril/Metolose matrices containing ascorbic acid (AA) or sodium bicarbonate (SB)/sodium ascorbate (SA).
Figure 6. Effect of compaction pressure (55 MPa and 165 MPa) on the calculated captopril released after 4 h from Metolose matrices containing ascorbic acid (AA) or sodium ascorbate (SA) and the substitution of 15% polymer with sodium bicarbonate.
Figure 7. Effect of an antioxidant (ascorbic acid-AA or sodium ascorbate-SA with sodium bicarbonate) on the exponent indicative of the release mechanism (n) of captopril releasing from Metolose matrices compacted at 55 MPa and 165 MPa.
Figure 8. Effect of an antioxidant (ascorbic acid-AA or sodium ascorbate-SA in mixture with sodium bicarbonate) on the release constant (k) of release profiles of captopril from Metolose matrices compacted at 55 MPa and 165 MPa.