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Sustained delivery of captopril from floating matrix tablets

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ABSTRACT

The development of a controlled release formulation of captopril has been a challenge for some time. In this work, the in vitro sustained release of captopril from Metolose SH 4000 SR/sodium bicarbonate floating tablets has been studied, varying the proportions of Metolose and bicarbonate. This was studied at two different compaction pressures. Other studied variables include the kinetics of the hydration volume, the matrices floating time and the matrix density. The results show that matrices compacted at 55 MPa float in the dissolution medium for more than 8 h while those compacted at 165 MPa float only when sodium bicarbonate is included in the formulation. The increase of the matrix polymer proportion increases the maximal hydration volume as well as the time to attain this maximum. The matrices hydration volume increases with the inclusion of sodium bicarbonate in the formulation. The matrix density is lower when compacted at 55 MPa. The drug release constant (k) decreases and the exponent indicative of the release mechanism (n) increases with increasing polymer contents. The drug released with time is lesser when sodium bicarbonate is included in the formulation. Carbon dioxide bubbles obstruct the diffusion path and decrease the matrix coherence. The effect of compaction pressure to reduce the drug release rate has to be made clear in further studies.

1. Introduction

Floating drug delivery systems were first described by Davis in 1968. These systems were used to prolong the gastric residence time of drug delivery systems. They remain buoyant in the stomach for prolonged period of time without affecting the gastric emptying rate of other contents. A floating dosage form is useful for those drugs that act locally in the proximal gastrointestinal tract (GIT), 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 that may cause gastric lesions. Also, the drug substances that are unstable in the strong acidic environment of the stomach are not suitable candidates to be incorporated in such systems (Talukder and Fassihi, 2004).

Compressed hydrophilic matrices are commonly used as oral drug delivery systems because of their good compatibility. 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 overall drug release process is influenced not only by drug solubility but also by the physical and mechanical properties of the gel barrier that forms around the tablet. The extent of matrix swelling, erosion, and diffusion of drug determines the kinetics as well as the mechanism of drug release (Sriamornsak et al., 2007).

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 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 effect can be varying with time according to the

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rates of production and dissipation of gas bubbles. The formation of gas bubbles starts with the beginning of the hydration process. Although the reduction of the diffusion path reduces the surface area available for drug transport, the continuing development of carbon dioxide bubbles contributes also to expand the matrix volume and to decrease the coherence of Methocel matrices. This second effect of carbon dioxide bubbles overrules in a second part of the release process, facilitating drug transport and increasing the cumulative drug released over that showed by pure Methocel matrices (Gutiérrez-Sánchez et al., 2008).

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 haemodynamic effect is observed after 45–90 min (Liebau, 1982). The drug is freely water soluble and has elimination half-life after an oral dose of 1.7 h. It is stable at pH 1.2, and as the pH increase, the drug becomes unstable and undergoes a degradation reaction (Nur and Zhang, 2000a; Cheng et al., 2008). Captopril has been a drug of choice in hypertension management. However, 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). The development of oral controlled release formulations 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, 2000b).

It is evident the importance of swelling behaviour on drug release and the necessity of sodium bicarbonate to produce buoyancy in floating tablets. In this sense, the aim of this work is the evaluation of the effect of sodium bicarbonate and the ratio of captopril to matrix polymer content, on the floating and hydration behaviour and on the release profile of the drug from Metolose SH 4000 SR matrices.

2. Materials and methods

2.1. Materials

The pharmaceutical excipient Metolose 90 SH 4000 SR, a brand of hydroxypropyl methylcellulose, batch 303574, obtained from Nutrer Farma, 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.

2.2. Methods

2.2.1. Matrix preparation

As a previous step of the matrix preparation, sodium bicarbonate was size reduced in a mortar for 20 min. The drug and the polymer 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 11 mm punch and die set at pressures of 55 MPa and 165 MPa during 10 s. No lubricant was used in the tablets. Matrix tablets were produced by using 50 mg/tablet of the drug and different quantities of Metolose: 150, 200, 250, 300, 350 and 400 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.

2.2.2. 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.

2.2.3. 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 determined weight and volume were used to calculate the tablet density over the dissolution study. The results for each time point of three repetitions are registered as an average.

2.2.4. 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 for each experiment were obtained. Captopril solubility in water at 25 °C is 160 mg/ml (Sigma–Aldrich, February/01/2008). Therefore, dissolution of 50 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 formula.

2.2.5. Significance test

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. The applied test was a two-tailed *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.

3. Results and discussion

3.1. Floating behaviour of matrix tablets

Captopril/Metolose formulations compacted at 55 MPa float more than 8 h while matrices compacted at 165 MPa do not float, with exception of those matrices containing 200 mg and 250 mg polymer per tablet that float only the first 40 min sinking thereafter (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 and display a density not allowing the matrices

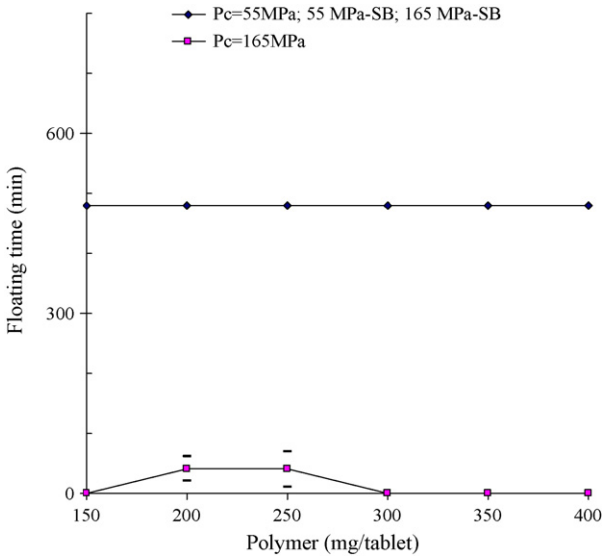

Fig. 1. Floating time of matrices containing 50 mg captopril and variable proportions of Metolose, with and without 15% sodium bicarbonate, obtained at two compaction pressures 55 MPa and 165 MPa. Experimental points and standard deviation.

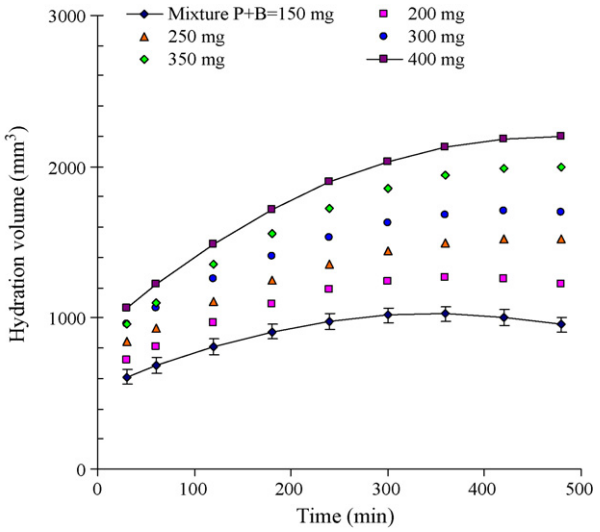

Fig. 3. Hydration kinetics of matrices containing 50 mg Captopril and a variable proportion of a mixture of Metolose (P) with 15% sodium bicarbonate (B), compacted at 55 MPa. Calculated values after regression and the standard error of the curve corresponding to 150 mg/tablet of the mixture.

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.

3.2. Hydration behaviour of matrix tablets

The matrices hydration volume increases at the beginning, attains a maximum and then declines. As can be seen in Fig. 2, matrices compacted at 55 MPa show greater hydration volumes than matrices compacted at 165 MPa. The curves of hydration volume of matrices containing the drug and polymer show distinct intercepts ($P = 0.011$) in the same manner than matrices containing bicarbonate ($P < 0.0001$). However, after 7–8 h dissolution the hydration volumes are practically the same, independently of compaction pressure. 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 decreases slowly because of polymer dissolution. Polymeric matrices experience simultaneously swelling and polymer dissolution and diffusion.

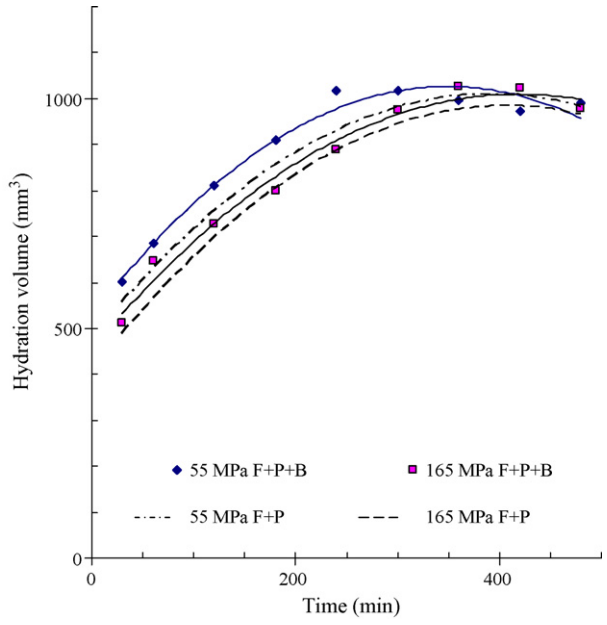

Fig. 2. Hydration kinetics of matrices containing 50 mg captopril (F) and 150 mg Metolose (P) or 122.5 Metolose and 22.5 mg sodium bicarbonate (B) obtained at compaction pressures of 55 MPa and 165 MPa.

Fig. 3 shows the effect of polymer content on matrices hydration profiles. As expected, matrices containing increasing polymer proportions show increasing hydration volumes. In this case the matrices contain 50 mg captopril and a variable quantity of a mixture composed of Metolose with 15% sodium bicarbonate. As the matrix polymer proportion increases the hydration volume increases as well as the time necessary to attain its maximum.

Fig. 4 summarizes the effect of compaction pressure and polymer proportion, with and without sodium bicarbonate, on the maximal hydration volume attained by captopril matrices. Although individual hydration profiles (Fig. 2) show a different hydration volume during the first 5 h, for matrices obtained at different compaction pressures, the compaction pressure do not show a clear effect on the maximal hydration volume (Fig. 4). Data corrected after regression show consistently greater maximal hydration volumes for drug/polymer/bicarbonate matrices compacted at lower pressure (55 MPa), in line with the observation of individual hydration profiles (Fig. 2). The slopes of the curves are distinct ($P = 0.0057$). However, the regression parameters do not show clear differences between matrices without sodium bicarbonate, compacted at different pressures. The slopes are not different ($P = 0.135$) as well as the intercepts ($P = 0.103$).

In contrast, the effect of sodium bicarbonate on hydration volume is clear. Matrices containing sodium bicarbonate show greater and faster growing hydration volumes. The curves corresponding to matrices with and without sodium bicarbonate are distinct. Although the intercepts obtained for matrices compacted

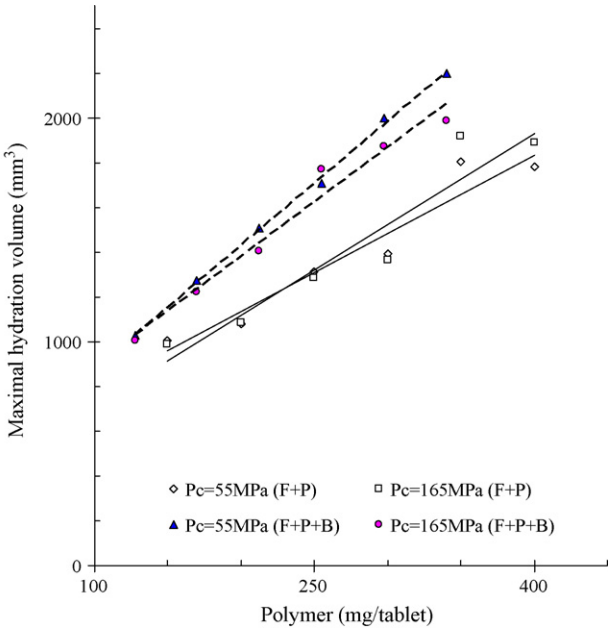

Fig. 4. Effect of the polymer (P) proportion, with and without sodium bicarbonate (B), on the maximal hydration volume reached by captopril (F) matrices compacted at 55 MPa and 165 MPa.

at 55 MPa, without and with sodium bicarbonate are considered not different ($P = 0.099$), the slopes are distinct ($P = 0.0001$). The same occurs with matrices compacted at 165 MPa, showing not different intercepts ($P = 0.2794$) and distinct slopes ($P = 0.0463$). The differences in hydration volume are attributed to a matrix volume expansion due to carbon dioxide evolution after sodium bicarbonate reaction with the acidic dissolution medium.

The time necessary to reach the maximal volume seems to be independent of the sodium bicarbonate content; it is apparently dependent only on the polymer content. The time to reach the maximal hydration volume increases gradually as the matrix polymer content increases (Fig. 5). Higher polymer contents increase the tortuosity and the length of matrices delaying its entire hydration.

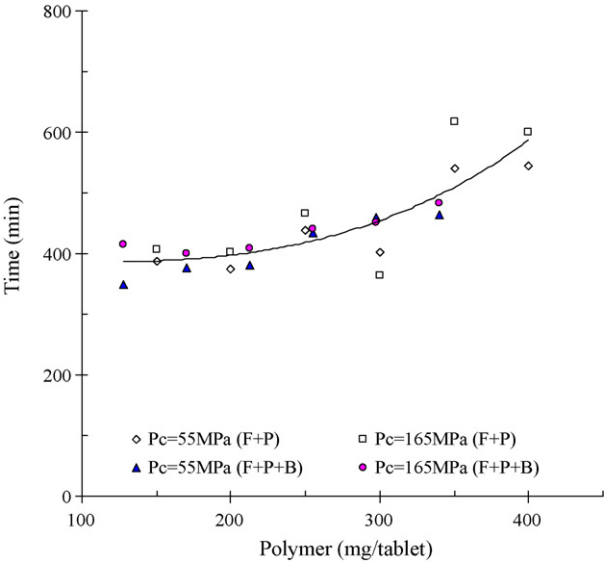

Fig. 5. Effect of polymer (P) content, with and without 15% sodium bicarbonate (B), on the time necessary to reach the maximal hydration volume of captopril (F) matrices compacted at 55 and 165 MPa.

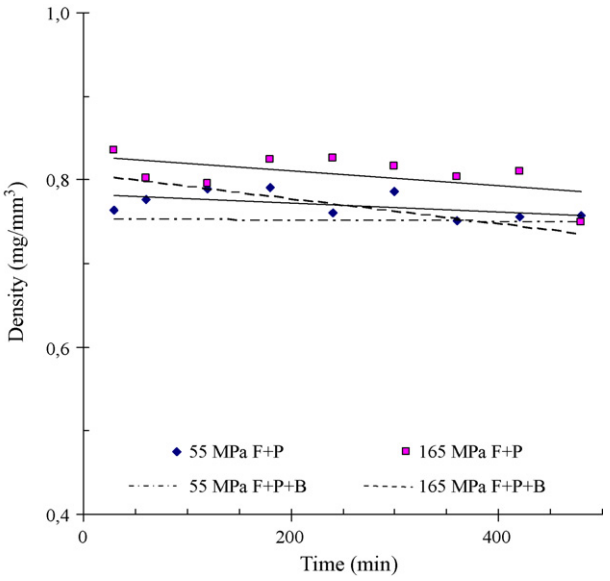

Fig. 6. Density of matrices containing 50 mg captopril and 300 mg Metolose or 255 mg Metolose and 45 mg sodium bicarbonate, compacted at 55 MPa and 165 MPa. Systematic error of the density giving values about 0.2 mg/mm^3 lower.

However, matrices containing the drug, polymer and bicarbonate and compacted at higher pressure (165 MPa) require consistently some extra time to reach the maximal hydration volume (Fig. 5). A linear regression of the data show that the lines corresponding to matrices compacted at different pressures have distinct intercepts ($P < 0.0001$) as well as distinct slopes ($P = 0.0009$). This is in line with the smaller hydration volumes observed in Fig. 2 with matrices compacted at 165 MPa. It is also in accordance with the observation of something smaller maximal hydration volumes observed in Fig. 4, for matrices containing the drug, polymer and sodium bicarbonate and compacted at 165 MPa. The higher time to reach the maximal hydration volume can by ascribed to smaller porosity of matrices compacted at higher pressures (165 MPa) that reduce the water transport through the matrix.

In the case of matrices without sodium bicarbonate, linear regressions of the data in Fig. 5, corresponding to matrices compacted at 55 MPa and 165 MPa, show that the intercepts and slopes are not different. This is attributed to a greater variance of matrices without sodium bicarbonate. While by matrices with sodium bicarbonate the average standard error of the intercept and slope are, respectively, 19.1 and 0.0782, the same values for matrices without sodium bicarbonate are 83.7 and 0.291, respectively. The greater variance of matrices without sodium bicarbonate seems to hide the effect of compaction pressure on the time necessary to reach the matrices maximal hydration volume.

3.3. Density of the matrix tablets

The matrix density exhibits a general trend to decrease with time, most probably because of a decreasing content of solids as the drug dissolves (Fig. 6). Matrices obtained at 165 MPa show a greater density as compared to those obtained at 55 MPa. 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

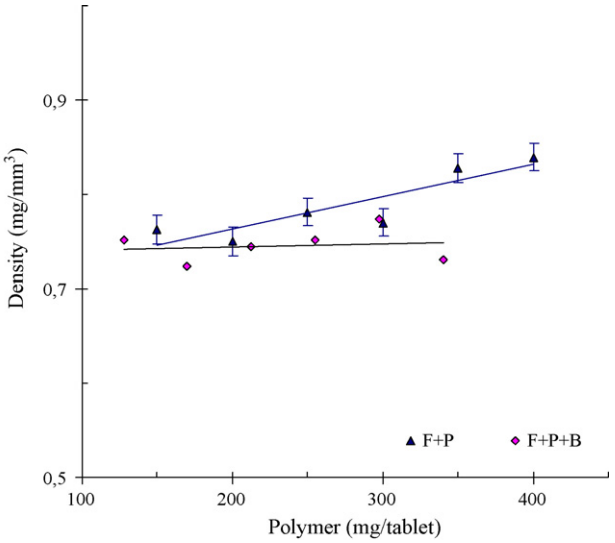

Fig. 7. Effect of polymer (P) content of matrices, with and without sodium bicarbonate (B), on the average density of captopril (F) matrices throughout 8 h dissolution. Pc = 55 MPa. Systematic error of the density giving values about 0.2 mg/mm^3 lower.

floating behaviour of these matrices the error should be of about 0.2 mg/mm^3.

As explained in methods, the volume is determined through 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 effect, and not corresponding with the actual physical volume of matrices.

The average density of matrices throughout 8 h dissolution increases with an increasing polymeric content. This occurs with matrices without sodium bicarbonate. The presence of sodium bicarbonate hides the effect of the increasing polymer content. This is attributed to carbon dioxide evolution that expands the matrices. Matrices containing lesser polymer quantities display lower resistance to carbon dioxide expansion than matrices containing higher polymer quantities. However, greater polymer quantities produce greater hydration volumes. The polymer content and the carbon dioxide bubbles counteract, maintaining constant the hydration volume (Fig. 7). All matrices containing sodium bicarbonate display densities that allow their floating.

3.4. Drug release from the matrix tablets

All dissolution profiles were described with the exponential expression attributed to Korsmayer and Peppas (Escudero et al., 2008; Hilton and Deasy, 1992; Cárdenas, 2003). 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 Fig. 8, lay in a range between 0.994 and 0.998. In this circumstance, the experimental points used to calculate the regressions included the dissolution time up to 6 h.

As expected, increasing polymer contents produce decreasing drug release rates. The effect of polymer content is attributed to an increasing tortuosity and length of the diffusion path through the matrix as the polymer content increases. This can be seen in Fig. 8, for matrices containing different quantities of polymer and a fixed captopril quantity of 50 mg/tablet. Matrices compacted at 55 MPa show percentages of captopril dissolved after 6 h with an average of 70.0%, and a span from 55.0% to 91.7%. Matrices compacted at 165 MPa show an average of captopril dissolved after 6 h of 69.2%, with a span of 51.9–91.9%. This suggests no effect of compaction pressure on the release profile of captopril/Metolose matrices. Considering a linear regression, the relationship between the dissolution parameters (k) and (n) against the polymer proportion of matrices from Fig. 8 do not differ from the regression lines of matrices compacted at 165 MPa. In example, the relationships of the release constant (k) against the polymer content show not different intercepts ($P = 0.115$) as well as not different slopes ($P = 0.184$).

In case of matrices containing sodium bicarbonate the effect of compaction pressure on the regression parameters of the release profiles is, in part, also considered not significant. A linear relationship between the release constants (k) and the polymer content, obtained at compaction pressure of 55 MPa, do not differ from that of matrices compacted at 165 MPa; neither the intercepts ($P = 0.584$) nor the slopes ($P = 0.080$) of the regression lines are considered different. However, linear relationships of the exponent (n) values against the polymer content of matrices compacted at 55 MPa and 165 MPa show that their intercepts ($P = 0.041$) as well as their slopes ($P = 0.0008$) are distinct.

This apparent lack of effect of compaction pressure seems to be the reflection of the small differences in the maximal hydration volumes and in the time necessary to attain them. A lack of effect of compaction pressure on dissolution profiles has been acknowledged before by other authors (Nur and Zhang, 2000a). Given this circumstance, the regression parameters of release profiles, (n) and (k), are registered in Fig. 9 as the average of results of both compaction pressures as a function of the polymer content.

Increasing polymer proportions decrease the values of the release constant (k) while increase the values of the exponent indicative of the release mechanism (n). 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 as the drug release rate is restricted. This has been attributed to greater extension or exercise of hydration and dissolution of the polymeric matrix as the drug release is subject to limitation (Martínez-González and Villafuerte-Robles, 2003). The increasing release restriction given by increasing

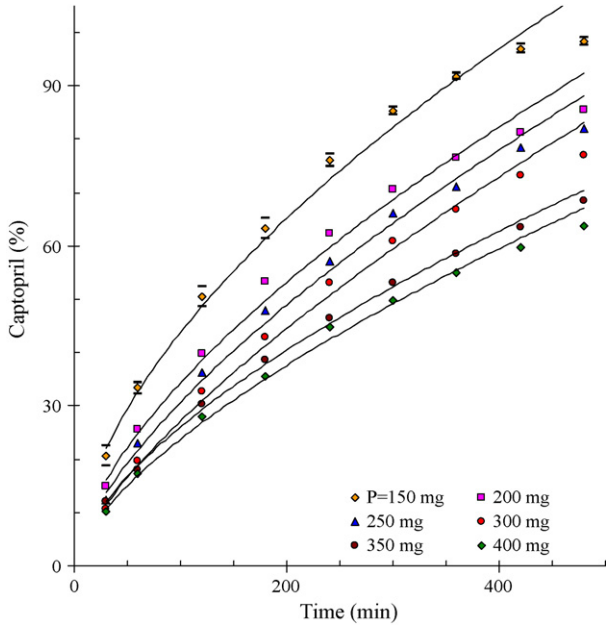

Fig. 8. Effect of polymer (P) content on the release profile of 50 mg captopril matrices compacted at 55 MPa. Experimental points and standard deviation.

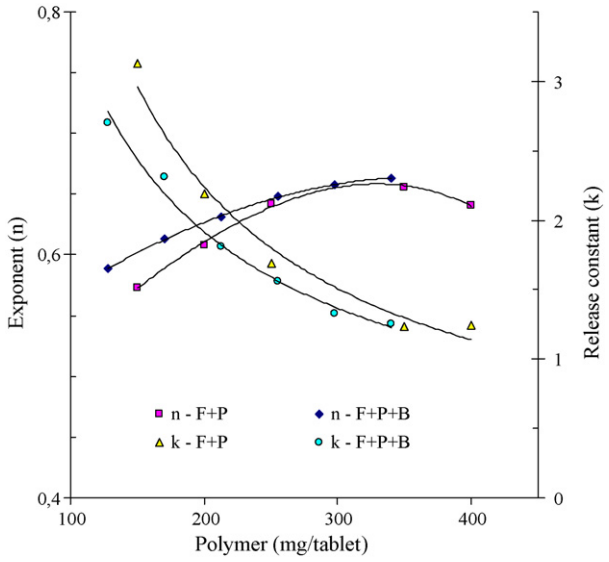

Fig. 9. Effect of polymer proportion, with and without sodium bicarbonate, on the exponent indicative of the release mechanism (n) and the release constant (k) of captopril/Metolose matrices. F: drug, P: polymer, B: sodium bicarbonate.

Metolose proportions 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 dissolution medium to release a given quantity of the drug. Consequently, every release restriction in the captopril/Metolose 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. Moreover, by increasing water content the diffusion coefficient of the drug increases substantially (Siepmann et al., 2002).

The presence of carbon dioxide bubbles, produced after reaction of sodium bicarbonate with the acidic dissolution medium, decrease the drug release rate. This is observed in Fig. 9 as smaller values of the release constant (k) and is attributed to an obstruction of the diffusion path by the gas bubbles that reduce water and drug transport through the matrix. The effect is more noticeable at low polymer proportions; increasing polymer proportions reduce gradually the effect of sodium bicarbonate. After a polymer proportion of 300 mg/tablet, there is practically no difference in the release constant values of matrices with and without sodium bicarbonate.

The effect of polymer proportion on the exponent indicative of the release mechanism of matrices containing sodium bicarbonate is similar to that observed before by matrices without it. However, the values of the exponent (n) are greater for matrices containing sodium bicarbonate (Fig. 9). The carbon dioxide bubbles moving from the matrix inside to its periphery decrease the matrix coherence and, in this way, facilitate the matrix relaxation. This loss of matrix coherence allows more matrix relaxation evidenced by greater (n) values. In the same way as with the release constant, the differences are more noticeable at low polymer proportions, disappearing with increasing polymer proportions. The effect of gas bubbles to decrease the matrix coherence become less important as the matrix consistency increases because of greater polymer proportions.

The release mechanism showed by both types of matrices with and without sodium bicarbonate is predominantly controlled by diffusion. However, the addition of sodium bicarbonate produces a shift toward higher values of the exponent indicative of the release mechanism (n). Matrices added with sodium bicarbonate indicate a little more contribution of relaxation and erosion to release mechanism.

The general reduction of captopril release rate after addition of sodium bicarbonate goes with an expansion of Metolose matrices (Figs. 2 and 4). In this way, the reduction of captopril released can be attributed to a partial obstruction of the diffusion path by the gas bubbles that also produce the above mentioned matrix expansion. This effect is maintained through the dissolution process, although with greater emphasis in matrices containing lower polymer proportions. The partial obstruction of the diffusion path produce lower quantities of captopril released after 6 h (Fig. 10).

A similar effect has been observed by metronidazole release from Methocel matrices (Gutiérrez-Sánchez et al., 2008). The average release constant values are higher by pure Methocel matrices (5.292) than by matrices of Methocel with sodium bicarbonate (3.249). However, metronidazole matrices containing sodium bicarbonate show exponent (n) values that allow the attainment of higher quantities of metronidazole released after 8 h dissolution. Beginning with lower quantities of drug released, given by the lower release constant values of matrices containing sodium bicarbonate, the drug released growths faster because of the greater exponent (n) values. The exponent (n) values correspond with the slope of the release profile. Matrices without sodium bicarbonate showed greater release constant values, however, their lower values of the exponent (n) produce a slower growth of the metronidazole released with time. Finally, matrices without sodium bicarbonate showed lesser quantities of metronidazole released after 8 h dissolution.

In case of captopril matrices containing sodium bicarbonate, their exponent (n) values, although higher, do not allow the overcoming of the initial greater drug release showed by matrices without sodium bicarbonate (Fig. 10). This can be attributed to greater polymer proportions in matrices containing 50 mg captopril compared to matrices containing 200 mg metronidazole. Nevertheless, the increase of the matrix polymer content shows a trend to equalize the regression parameters and the captopril released after 6 h from both types of matrices with and without sodium bicarbonate (Figs. 9 and 10).

Fig. 11 show the calculated response surface depicting the possibilities to formulate a matrix with a given dissolution profile of

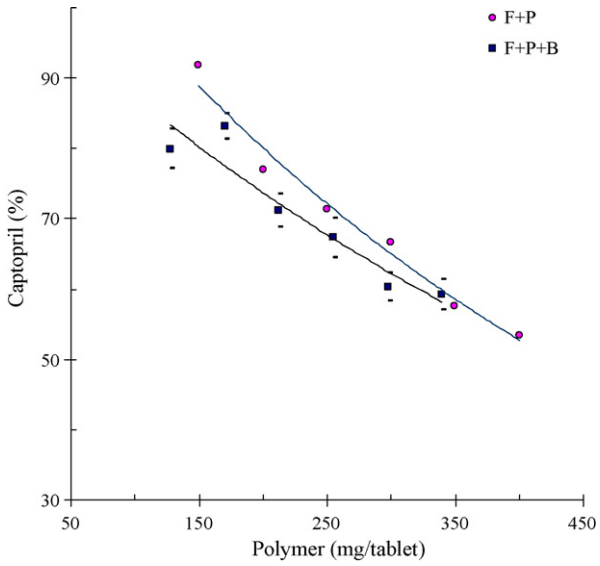

Fig. 10. Effect of polymer proportion, with and without sodium bicarbonate, on captopril released after 6 h from Metolose matrices, average of two compaction pressures and standard deviation.

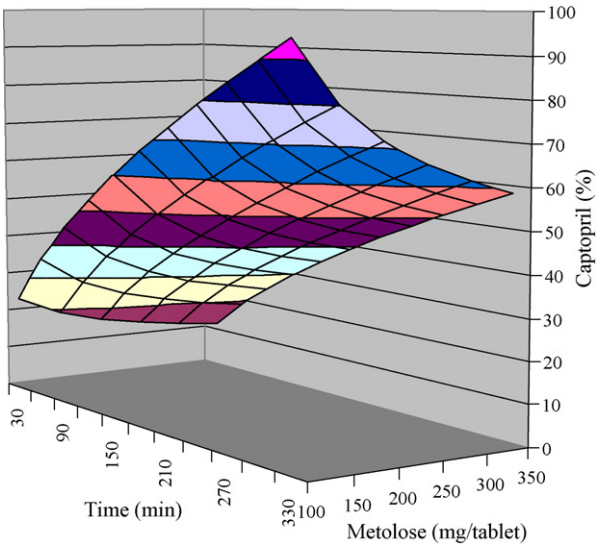

Fig. 11. Calculated response surface for dissolution of 50 mg captopril from Metolose/sodium bicarbonate floating matrices, calculated from matrices compacted at 55 MPa and 165 MPa.

captopril from Metolose/sodium bicarbonate floating matrices. The response surface was calculated with the average of regression parameters corresponding to both compaction pressures, 55 MPa and 165 MPa. The experimental area studied cover dissolution profiles with captopril dissolved after 6 h from about 60% to almost 100%. Due to the lack of in vivo data concerned with these systems, it is unfair to justify their suitability and efficiency for delivering captopril in a sustained release dosage form. However, knowing the variables controlling the release rate is possible to adjust the components and the size of a matrix tablet to satisfy a desire release profile.

4. Conclusion

The floatability of Metolose matrices depends on the porosity obtained after compaction at a given pressure; matrices with insufficient porosity can be made float increasing their porosity with carbon dioxide bubbles obtained from the reaction of sodium bicarbonate with the acidic dissolution medium. An increasing proportion of the swelling polymer in the matrix increases the maximal hydration volume as well as the time necessary to attain it. Matrices containing sodium bicarbonate show greater hydration volumes because of matrix expansion produced by the evolution of carbon dioxide bubbles. This matrix expansion is associated to less consistent or more vulnerable to erosion matrices. The matrix density was found to decrease by reducing the compaction pressure and by addition of sodium bicarbonate. According to floating behaviour, density measurements obtained by the method described here display values lower than those of the actual matrix densities. This is attributed to miscalculation of the volume; obtaining values about 20% higher than the actual matrix volumes.

The release profiles of captopril from Metolose matrices display greater percentages of drug released compared to similar matrices containing sodium bicarbonate. This is attributed to an obstruction effect of the diffusion path by carbon dioxide bubbles. This restriction effect on drug dissolution is in part overcome by a greater slope of the release profile, produced by lower matrix coherence. Increasing polymer contents increase the exponent (n) and reduce the release constant (k). This is attributed to an increasing restriction of drug release produced by increasing polymer proportions. This increasing restriction makes the matrices accessible for longer time to the action of the dissolution medium before a given quantity of the drug is released; producing a greater hydration and polymer dissolution that shift the release mechanism toward relaxation and erosion. No concluding evidence was found indicating significant greater release profiles of matrices compacted at 55 MPa, compared to those compacted at 165 MPa.

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