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Matrices containing NaCMC and HPMC 2. Swelling and release mechanism study

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Abstract

The aim of the present study is an investigation of the swelling behaviour of matrix systems containing a mixture of hydroxypropylmethylcellulose (HPMC) and sodium carboxymethylcellulose (NaCMC) with a model soluble drug to find the correlation between the morphological behaviour and the drug release performance. The swelling study was conducted on tablets containing only the drug and the two polymers mixture (MB) and on reference tablets containing each polymer and the same drug, at three different pHs. MB matrices show a similar swelling trend at pH 4.5 and 6.8, while they have different behaviour in acidic fluid. At pH 1 the gel layer formed by NaCMC is characterized by a rigid structure of a partially chemically crosslinked hydrogel while HPMC and MB matrices form a physical not crosslinked gel. At pH 4.5 and 6.8, all the systems show the typical morphological behaviour of a swellable matrix in which the macromolecular chains in the gel network are held together by weak bondings (physical gel). In these buffers, MB systems maintain a constant drug release rate coupling diffusion and erosion mechanism: the gel and infiltrated layers thicknesses are maintained constant and a zero-order release kinetics can be achieved.

Keywords: Hydrophilic matrices; Swelling study; Release kinetics; Controlled drug release

1. Introduction

Hydrophilic matrix sustained release dosage forms are drug delivery systems in which a therapeutic agent is dispersed in a compressed matrix made of water swellable polymers. When exposed to aqueous medium, the surface of the polymer hydrates to form a viscous-gel layer (Melia, 1991).

The gel layer is a diffusional barrier that retards further water uptake and the release of the dissolved drug. Water soluble drugs are released primarily by diffusion of dissolved drug molecules across the gel layer, while poor water soluble drugs are released predominantly by an erosion mechanism. The contribution of each mechanism to the overall drug release process is influenced both by drug solubility and also by the physical and mechanical properties of the gel barrier formed around the tablet (Alderman, 1984).

Although outwardly simple, drug release from hydrophilic matrices is a complex phenomenon resulting from the interplay of many different physical processes. In particular, the formation and physical properties of the hydrated surface barrier are important determinants of subsequent behaviour and drug release performance. This gel layer formation and its stability, which defines the kinetics of drug delivery from matrix systems, are controlled by the concentration, viscosity and chemical structure of the polymer(s) (Varma et al., 2004).

At the molecular level, drug release is determined by water penetration, polymer swelling, drug dissolution, drug diffusion and matrix erosion. These phenomena depend upon the interaction among water, polymer, matrix content and the drug. Water has to penetrate the polymer matrix, leading to polymer swelling and drug dissolution, before the drug can diffuse out of the system. In effect, water decreases the glass transition temperature of the polymer to the experimental temperature resulting in a transformation of the glassy polymer into a rubbery phase. The enhanced mobility of the polymeric chains favours the transport of water and consequently of the dissolved drug (Jamzad et al., 2005).

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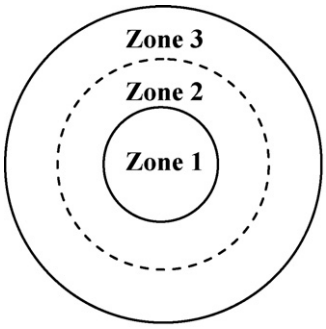

Fig. 1. Schematic illustration (cross-section view) of a swellable HPMC matrix tablet during drug release process. Three zones are well evidenced: zone 1 (glassy polymer), zone 2 (infiltrated region) and zone 3 (gel layer).

Non-ionic cellulose ethers derivates are the most used polymers in the formulation of hydrophilic matrices. Cellulose ethers represent a broad class of polymers which satisfy the key criteria for the development of controlled release oral solid dosage forms. One of the most widely employed for the development of swellable matrix is hydroxypropylmethylcellulose (HPMC) (Sinha Roy and Rohera, 2002). Various authors have investigated the phenomena involved in the swelling and drug release process for systems containing polymeric materials. They have concluded that the polymeric content, which is related to swelling behaviour, and the viscosity grade are the determining factors in predicting the drug release from hydrophilic matrices (Ranga-Rao et al., 1990; Wan et al., 1993; Katzhendler et al., 2000).

When a drug-loaded swellable high-viscosity HPMC matrix is exposed to a dissolution fluid, three distinct zones can be detected (Fig. 1) (Kiil and Dam-Johansen, 2003). The innermost, zone 1, is the region in which the polymer is still in a glassy state, while in zone 2 and 3 the material is in the rubbery phase. The HPMC present in zone 1 is in the glassy state because water has not yet penetrated and subsequently plasticized the matrix by reducing the glass transition temperature from somewhere between 154 and 184 °C to below the system temperature (37 °C) (Joshi and Wilson, 1993; McCrystal et al., 1997; Ford, 1999; McPhillips et al., 1999). In zone 1, the macromolecules mobility is very low and this leads to low diffusion rate of water in this region (of the order of 10^{-16} m/s at 37 °C) (Wesselingh, 1993). According to Fyfe and Blazek (1997), the swelling of the HPMC matrices can be mainly attributed to the disruption of hydrogen bondings among the polymeric chains. When water penetrates the solid HPMC, it inserts itself into the hydrogen bonds between adjacent polymer chains. As more water comes among the chains, the forces between the chains diminish. The macromolecular chains initially gain rotational freedom and begin to occupy more space and this is evidenced by polymer swelling. The penetrating water fills the voids between the polymer chains and diffuses into denser regions of the polymer, forcing additional chains apart. In zone 2 and 3, the mobility of the polymer chains is markedly increased compared to the situation in zone 1 leading to higher water diffusion rates (of the order of 10^{-10} m/s at 23 °C) (Gao and Fagerness, 1995).

Hence, drug dissolution takes place at the boundary between solid (zone 2) and dissolved drug (zone 3). Therefore, dissolved drug subsequently diffuses in the radial direction towards the outermost boundary between the swollen matrix and the fluid. The HPMC matrices may undergo erosion and/or dissolution of the polymer upon prolonged contact with water. For a given HPMC matrix, in a specified dissolution medium, the relative movements of the three boundaries, which separate the three zones, are determined by polymer hydration, swelling and dissolution behaviour and, amongst other parameters, by the drug-loaded and its physical properties such as water solubility (Ju et al., 1995).

The purpose of orally administered hydrophilic matrices is generally to prolong drug delivery with a zero-order kinetics to maintain a constant in vivo plasma concentration and constant pharmacological effect (Liu and Hsu, 2005).

To achieve a constant drug release rate, a number of matrix devices have been formulated using different polymeric excipients to modulate matrix hydration rate. In practice, for controlling and programming of drug release from matrix tablets, different types of modified cellulose polymers are usually employed, either alone or in mixtures with other swellable polymers (Baveja et al., 1987; Al Naoui and Vergnaud, 2000) which may alter the release mechanism and rate (Malamataris and Ganderton, 1991).

In fact, a synchronization of the movements of both the swelling and the diffusion fronts has been seen as an essential step to achieve a constant drug delivery rate (Pham and Lee, 1994).

In our previous work, we analyzed the dissolution behaviour of hydrophilic swellable matrices containing hydroxypropylmetylcellulose and sodium carboxymethylcellulose (NaCMC) (in particular systems containing a mixture of these two polymers in ratio 1:1, and reference-matrices containing each single polymer) and a model soluble drug (Diltiazem HCl) chosen to avoid the effect of drug dissolution rate; for these systems a linearization of the drug release profile is obtained at pH 4.5 and 6.8 (Conti et al., 2007).

The present study investigates the swelling behaviour of matrix systems containing the mixture of the two polymers above mentioned (NaCMC and HPMC) to find a correlation between the morphological behaviour and the drug dissolution performance.

The swelling and the erosion characteristics of the matrices were evaluated on tablets containing NaCMC/HPMC mixture (1:1), NaCMC, HPMC and Diltiazem HCl. The morphological changes that occur to these systems during the dissolution tests, were compared to the drug release modulation efficiency and kinetics.

2. Materials and methods

2.1. Material

Diltiazem HCl was used as model drug for this investigation. This drug has been supplied by Profarmaco S.p.A. (Milan, Italy). The following materials were also used in this study: hydroxypropylmethylcellulose (Methocel K15M $\eta = 15\,000$ cP), kindly donated by Colorcon, Orpington, UK

Table 1
Percentage composition of B7, MB and M15 formulations

Formulation	Components	Percentage composition
M15	Diltiazem HCl	36.6
	HPMC (Methocel K15M)	63.4
B7	Diltiazem HCl	36.6
	NaCMC (Blanose 7H4XFPH)	63.4
MB	Diltiazem HCl	36.6
	HPMC (Methocel K15M)	31.7
	NaCMC (Blanose 7H4XFPH)	31.7

and sodium carboxymethylcellulose (Blanose 7HXFPH), gently donated by Hercules, Wilmington, DE.

All materials were used as received without further purification.

2.2. Matrices preparation

Drug and polymer powders were mixed together in Turbula apparatus (Turbula T2A, Bachofen, Basel, CH) for 10 min. Formulations, in terms of the percentage composition, are reported in Table 1. Mixtures were directly compressed in a single die tabletting machine fitted with flat-faced punches (Kilian, Koln, D) and instrumented with piezoelectric load washer (Kistler, Winterthur, CH) for compression force measurements. A compression force of 2500 ± 200 kg has been applied and recorded. The cylindrical tablets show the following characteristics: a diameter of 9.8 mm; a height of 2.7 mm; a weight of 329 mg.

2.3. Release tests

The dissolution data (Conti et al., 2007) were fitted according to the well-known exponential equation, which is often used to describe the drug release behaviour from polymeric systems (Korsmeyer et al., 1983)

$$\frac{M_t}{M_\infty} = kt^n$$

where M_t/M_∞ is the fraction of drug released at time, t, k the proportionality constant which accounts for the structural and geometrical properties of the matrix, and n is the diffusional exponent indicative of the mechanism of drug release. The results of the fitting are reported in Table 2.

Table 2
n-Values obtained for B7, MB and M15 formulations at pH 1, 4.5 and 6.8

Formulation	pH 1		pH 4.5		pH 6.8	
	n	r^2	n	r^2	n	r^2
B7	0.554	0.9963	1.062	0.9946	1.431	0.9862
MB	0.679	0.9973	0.956	0.9998	0.990	0.9925
M15	0.716	0.9956	0.608	0.9999	0.656	0.9988

2.4. Morphological studies

The morphological changes, which occur in the structure of the matrix when it comes into contact with the dissolution fluids, are studied with an image analyzer. This method combines easy of manipulation with low instrument cost and high precision. Optical technique has a lot of advantages (relative simplicity and the ability to determine various parameters such as tablet geometry, thickness of the gel layer and of the infiltrated layer).

To analyze the morphological behaviour of the systems during the release process, tablets were withdrawn from the dissolution vessels at different time intervals, were sectioned and their photographs were recorded using a digital microscope camera (SV MicroTM, Sound Vision Inc., Taunton, MA, USA), equipped with a 50 mm C-mount lens.

From the images, the dimensions of the whole tablet, of the solid phase (zone 1), the thickness of the gel layer formed at the tablet surface (zone 3) and of the infiltrated region (zone 2) can be easily measured using the software provided for the image analysis (CV9000 Ver. 5.0, FKV S.r.l., Sorisole, BG, Italy). In fact, in the images, the different morphological phases appear as well defined areas of contrast.

For this study the samples were kept in dissolution condition for the following time: 30 min, 2, 4, 7 and 16 h.

3. Results and discussion

To evaluate the effect of the addition of sodium carboxymethylcellulose on morphological behaviour of hydrophilic matrices containing HPMC, a swelling photographic study has been conducted on B7, MB and M15 samples. Three series of photos have been taken on the swollen systems at pH 1, 4.5 and 6.8 after 30 min, 2, 4, 7 and 16 h from the beginning of the dissolution test.

In hydrochloric acid at pH 1, B7 formulations, containing sodium carboxymethylcellulose, show a high hydration rate as it is possible to see from the photos taken after 30 min and 2 h (Fig. 2). After 4 h, the dimensions increase and, in the matrix structure, the presence of two concentric layers can be noticed. The external one has a consistence similar to a gel and the inner core is not solid but completely wetted. After 7 h, the tablet shows an inner phase in which the solvent molecules have totally hydrated the matrix core. At the 16th hour, the matrix is characterized by a rigid and elastic structure typical of a chemically crosslinked hydrogel in which all polymer chains are crosslinked to each other by strong bonds (probably ionic bonds), and thus, the hydrogel behaves as a consistent body. For this reason, there is no concept of molecular weight of hydrogels, and hydrogels are sometimes called infinitely large molecules or supermacromolecules. One of the unique properties of hydrogels is their ability to maintain original shape during and after swelling due to isotropic swelling; in fact, swelling changes only the size of the original hydrogel while maintaining the original shape. In the case of NaCMC systems at pH 1, ionic interactions between the drug and the polymer probably cause the maintenance of a solid and rigid structure of the matrix during the dissolution test.

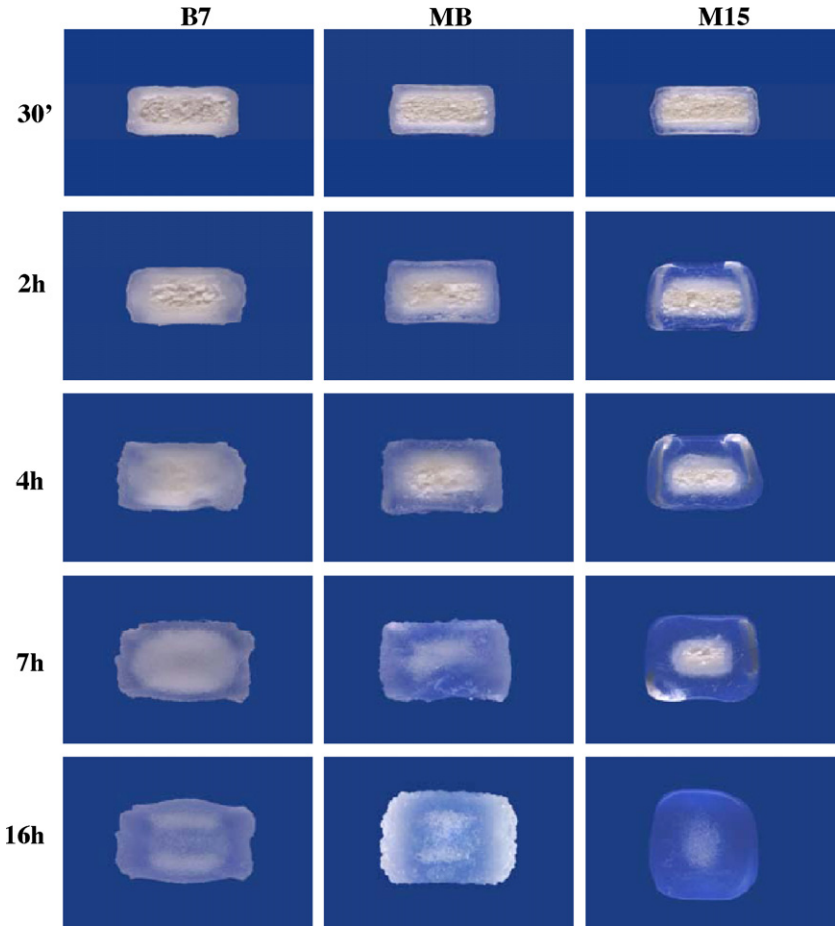

Fig. 2. Photographs taken on B7, MB and M15 systems after 30 min, 2, 4, 7 and 16 h from the beginning of the dissolution test (in hydrochloric acid at pH 1).

M15 systems, containing HPMC and the model drug, show the typical morphological behaviour of a swellable matrix in which the macromolecular changes in gel network formed at tablet surface are held together by weak bondings. In fact, upon contact with the dissolution fluid, the system hydrates slowly and swells giving rise to a thick gel layer. The gel thickness increases progressively moving inwards as a function of hydration and contemporary, the dimensions of the solid core decrease. After 16 h, the matrix appears completely hydrated and gelled (it is not possible to see the presence of any glassy core). The swelling of HPMC matrix tablets takes place mainly in axial direction; in fact, the increase in height of these systems is clearly higher and more evident than the increase in diameter.

At pH 1, MB matrices, containing both hydroxypropylmethylcellulose and sodium carboxymethylcellulose, behave in an intermediate way: during the first phases of the test, they swell and form a firm gel layer preserving a inner solid core; while after about 4 h in the dissolution medium, their morphological behaviour is more similar to that of NaCMC sample. In fact, the core is wetted by the dissolution medium and the gel layer is characterized by a rigid and compact structure of a partially chemically crosslinked hydrogel. During the performance of the whole dissolution test, the tablets maintain their original form with an increase of their overall dimensions.

Fig. 3 shows volume percent variation of the three formulations during the test conducted at pH 1. No significant differences can be evidenced among the three matrices swelling behaviours despite the different types of gel formed. M15, MB and B7's volumes increase four-fold after the seventh hour. The swelling process takes place rapidly just soon after the first period of contact with the dissolution medium. After only 30 min from

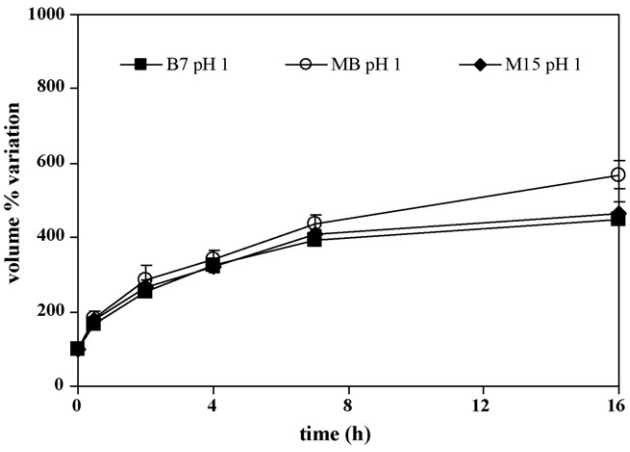

Fig. 3. B7, MB and M15 normalized volume dimensions during the swelling study conducted in hydrochloric acid at pH 1.

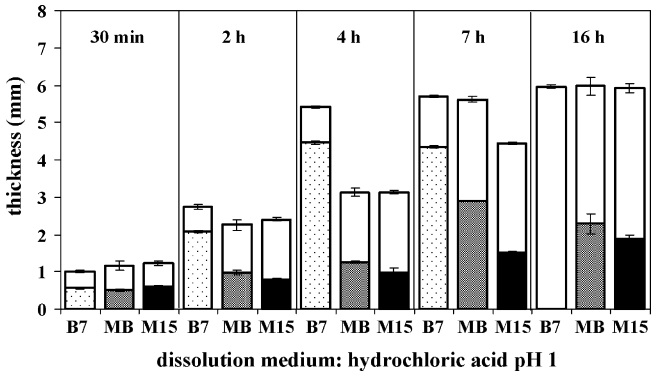

Fig. 4. B7, MB and M15 infiltrated layer (inferior bar) and gel layer (superior bar) thicknesses during the swelling study conducted in hydrochloric acid at pH 1.

the beginning of the test, tablet volume duplicates for each formulation. After 16 h, all the sample volumes reach 400–500% of the dry tablet volume although the shapes are different.

The bar graph in Fig. 4 reports the thickness (mm) of the infiltrated layer (inferior bar) and of the gel layer (superior bar) for each matrix after 30 min, 2, 4, 7 and 16 h from the beginning of the test. B7 matrices show a rapid increase of the infiltrated region thickness in the first 7 h of contact with the dissolution medium. After this time, the tablet becomes completely gelled. On the other hand, M15 samples show a slower increase of the infiltrated and gel layers up to the 16th hour when an infiltrated region is still present and it is wetted but not gelled yet. This is linked to the penetration rate of the solvent which is faster at the beginning because the fluid is in direct contact with the solid polymer. Then, when a gel layer is formed on tablet surface, it acts as a barrier to solvent penetration, preventing disintegration of the tablet and reducing the rate of diffusion of the fluid into the matrix structure. MB gel layer increases progressively during the test; moreover, MB infiltrated region shows a maximum value of dimensional extension at the seventh hour and, after this time, a reduction of its dimensions can be seen.

The results of this morphological analysis have been correlated to the results of the dissolution test with focus on the mechanisms of drug release analyzed in our previous work (Conti et al., 2007).

At pH 1 although the release rate is similar for the three formulations, the release mechanisms seem different. B7 matrix release profile has an n-value equal to 0.554 indicating a pure diffusive mechanism (Table 2). This can be associated to the structure of the tablet: as the volume of the tablet increases until the seventh hour and then it remains nearly constant, the drug diffusional path length increases with time and hence the drug release rate decreases with time (square root dependence). M15 matrices release the drug with an anomalous non-Fickian mech-

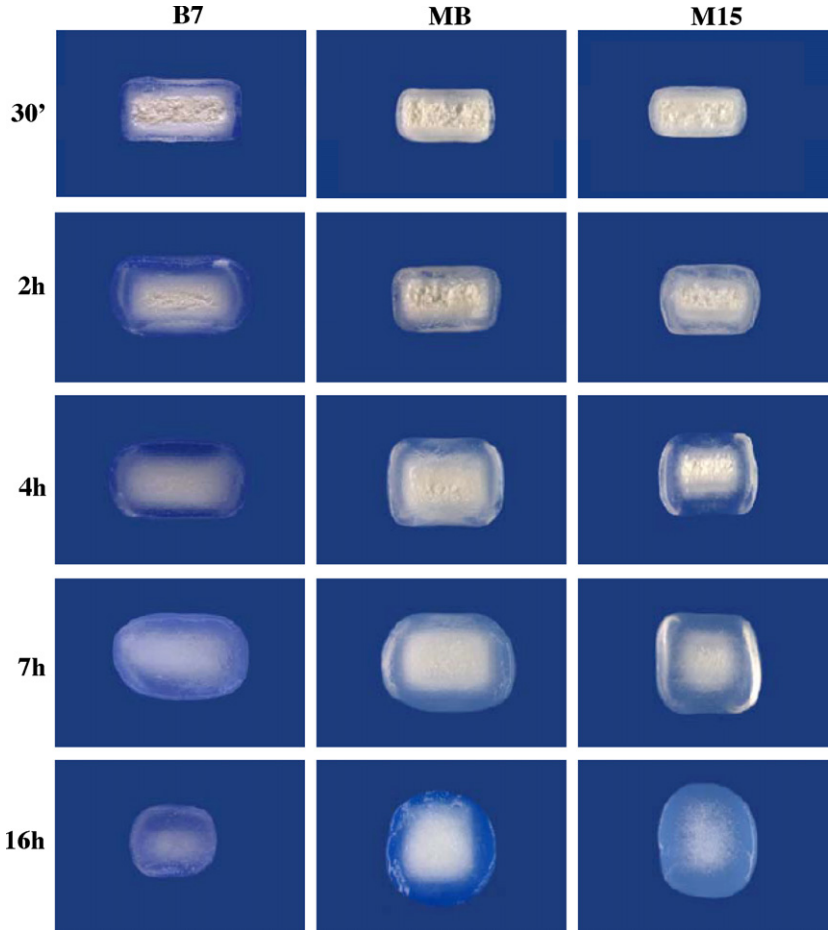

Fig. 5. Photographs taken on B7, MB and M15 systems after 30 min, 2, 4, 7 and 16 h from the beginning of the dissolution test (in acetate buffer at pH 4.5).

anism influenced both by drug diffusion through the gel layer and by macromolecular relaxation ($n = 0.716$). In this case the gel thicknesses are maintained more constant and the dissolution trend is more linear. MB samples show an intermediate n-value ($n = 0.679$) which is reflected in an intermediate behaviour well expressed by the gel and diffusion layer thickness values at the seventh hour.

The study conducted at pH 4.5 reveals similar morphological behaviours for B7 and M15 matrices, which increase their dimensions as a consequence of the swelling process (Fig. 5). The increase in volume dimensions is higher for MB matrices than for M15 matrices. For B7 matrices the erosion mechanism prevails after the fourth hour: the gel at the surface of the tablet loses consistence and the dissolution of the polymer takes place. The volume dimensions of the system undergo a drastic reduction. M15 systems show the typical morphological trend of hydrophilic swelling matrices. The solvent molecules penetrate into the system among the polymeric chains and cause their relaxation and matrix swelling. After 30 min, a thin gel layer is notable at the surface of the tablet. This layer increases in dimension and after 16 h the matrix is completely gelled. At the seventh hour, it is possible to note the presence of an inner core not yet gelled but infiltrated by the solvent. MB systems show a morphological behaviour very similar to that of B7 matrix till the seventh hour. Then no erosion process takes place, but an increase of the gel thickness and the maintenance of a core infiltrated by the solvent are evident.

Volume percent variation summarizes the data derived from diameter and height percent variations (Fig. 6). B7 samples show their maximum swelling at the fourth hour, after this time the macromolecular chains, entangled in the gel network, start to dissolve and, as a result, tablet dimensions decrease. M15 sample reaches its maximum swelling degree at the 7th hour and it maintains these dimensions till the 16th hour. The degree of swelling of MB sample at the 7th hour is similar to that of B7 matrices (at the 4th hour); they swell rapidly and they increase six-fold the volume of the tablet but these dimensions are maintained from the 7th hour to the 16th hour with a slower increase.

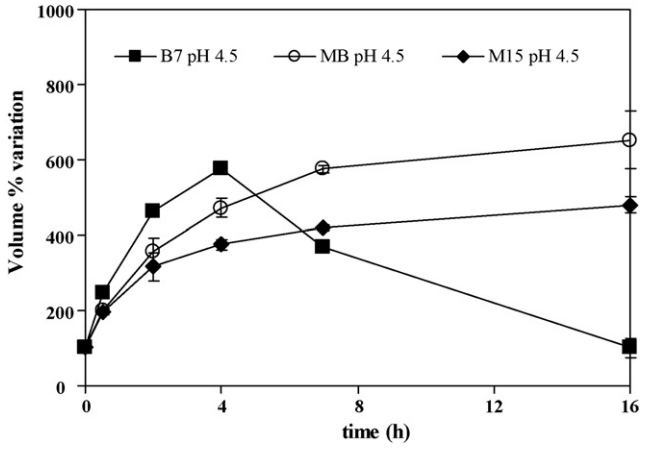

Fig. 6. B7, MB and M15 normalized volume dimensions during the swelling study conducted in acetate buffer at pH 4.5.

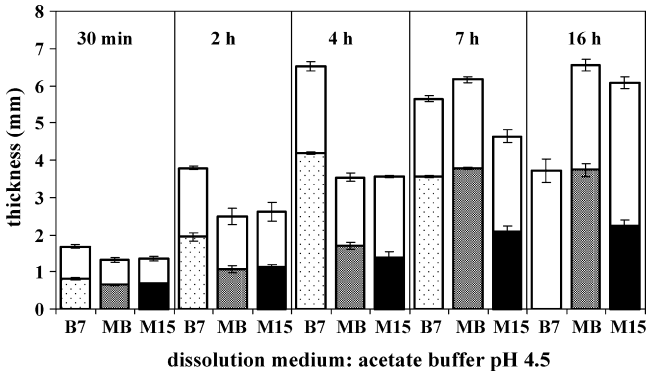

Fig. 7. B7, MB and M15 infiltrated layer (inferior bar) and gel layer (superior bar) thicknesses during the swelling study conducted in acetate buffer at pH 4.5.

B7 samples show a high hydration rate, as it can be seen in the rapid increase of the infiltrated region thickness in the first 4 h (Fig. 7). The following decrease of the two hydrates layers and of the overall dimensions of the tablet can be considered as a consequence of the high solubility of the polymer at this pH value. At the 16th hour the system is totally gelled and its dimensions have undergone to an abrupt decrease. M15 samples show a progressive increase of the infiltrated region and of the gel layer with progressive increase of the tablet dimensions. MB matrices, after the hydration of the structure, reach a gel and infiltrated layer thickness values which remain constant from the 7th hour to the 16th hour.

Polymer relaxation and erosion are the main phenomena involved in drug release process from B7 matrix (n-value is 1.062). The formation and growth of the surface hydrated layer can be observed in the histogram bars. The distance from the gel/core interface to the outer surface of the gel barrier, is the pathway through which the active molecule must diffuse to be released. In this case this drug obligate pathway increases till the fourth hour and then it decreases gradually without the presence of a solid core into the tablet. The mechanism of drug release is thus mainly associated to the polymer dissolution and disentanglement at the surface of the gel layer; macroscopically it is evidenced by matrix erosion. It is clear that M15 gel and diffusion layers increase progressively with time and these conditions are the reason of a continuous enlargement of the diffusional pathway which must be crossed by the active molecule to be delivered; the drug release rate decreases with time and the mechanism is mainly associated to Fickian transport ($n = 0.608$). MB gel and infiltrated layer thicknesses maintain constant values between the 7th and the 16th hour; this results in a combination of diffusion and erosion mechanisms in drug release process. The diffusional pathway of the drug remains constant and the rate of drug release is constant too; the process of drug delivery is governed by a zero-order release kinetics.

In acetate buffer at pH 6.8, the morphological differences among the three formulations are less marked than that described at pH 1, and their behaviour is similar to that shown at pH 4.5 (Fig. 8). All the matrices hydrate, swell and form gel layers at their surface which seem to be characterized by different consistence, but none of them shows detectable evidence of chemical crosslinking.

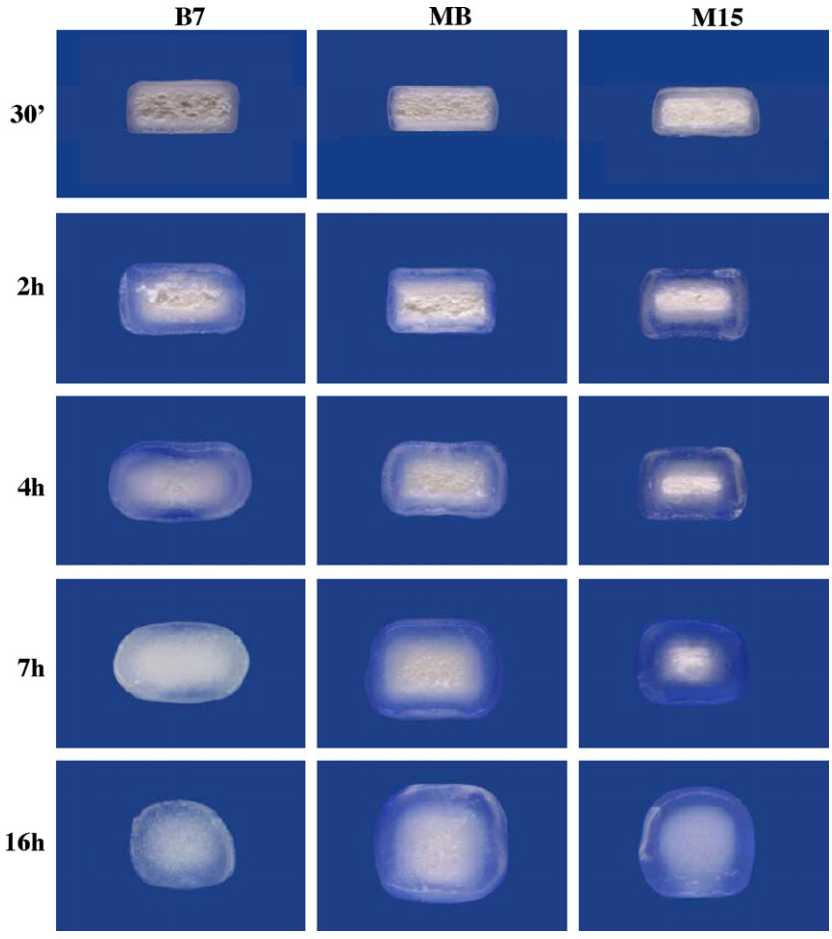

Fig. 8. Photographs taken on B7, MB and M15 systems after 30 min, 2, 4, 7 and 16 h from the beginning of the dissolution test (in acetate buffer at pH 6.8).

B7 systems hydrate rapidly and the fluid penetrates rapidly into the structure of the tablet, in fact, after only 4 h the matrix dimensions increase and the core is completely wetted. After 7 h the system undergoes an erosion process and its dimensions decrease.

M15 shows the typical behaviour of a hydrophilic swellable matrix, after 2 h, its structure is characterized by three phases: a solid core, an infiltrated region of wetted polymer (not gelled yet) and an external gel layer. After 4 h, the gel thickness increases and the dimensions of the core decrease; after 16 h the matrix is swollen and shows a completely wetted core.

The systems containing the mixture of the two polymers show an intermediate behaviour compared to the matrices containing the single polymers. After 2 h, the core is maintained but is partially wetted; after this time the fluid penetrates into the system and at the fourth hour the core is completely wetted. After 16 h the system is swollen, gelled and the presence of a hydrated and wetted core is still evident.

Volume percent variations of the three formulations at pH 6.8 are reported in Fig. 9. A progressive increase of the overall dimensions of the tablet, due to solvent penetration into the matrix structure, characterizes morphological swelling behaviour of samples containing HPMC and HPMC:NaCMC 1:1 mixture. B7 matrix rapidly hydrates and swells reaching 700% of the dry tablet dimensions after 4 h of contact with the dissolution fluid. From the 4th to the 16th hour the systems undergo erosion process with a consequent decrease of the tablet volume.

Fig. 10 illustrates the relative increase of the gel layer and infiltrated layer thickness for the three formulations at pH 6.8 versus time. For B7 matrices between the second and the fourth hour the rate of infiltrated region formation is more rapid. After

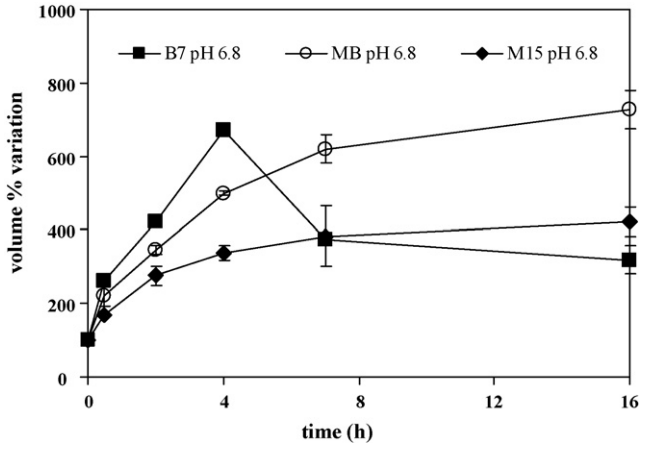

Fig. 9. B7, MB and M15 normalized volume dimensions during the swelling study conducted in acetate buffer at pH 6.8.

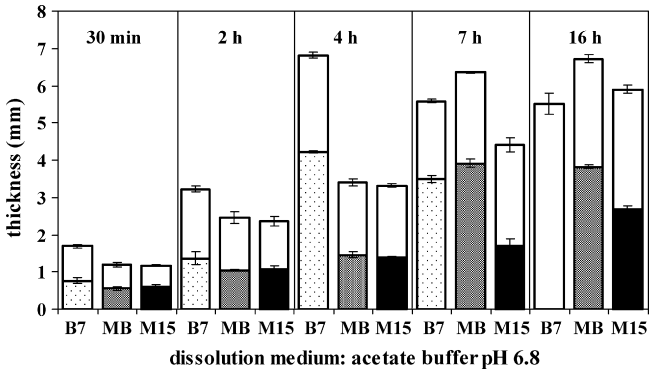

Fig. 10. B7, MB and M15 infiltrated layer (inferior bar) and gel layer (superior bar) thicknesses during the swelling study conducted in acetate buffer at pH 6.8.

this phase a decrease in the gel layer, infiltrated layer and of the overall dimensions of the tablet characterize the morphological behaviour of these matrices. M15 gel and infiltrated layers increase slowly during the test; MB systems show the maintenance of a constant thickness of gel and infiltrated layers between the 7th and the 16th hour.

B7 release behaviour is described as 'super-case II transport' as confirmed by *n*-value of 1.431. Polymer relaxation and erosion of the gel layer drive and determine the drug release profile. As the gel layer and diffusion layer increase with time, the diffusional pathway crossed by the drug increases with time and drug release rate decreases during the dissolution test. MB diffusion and gel layers remain constant between the 7th and the 16th hour: the diffusional pathway of the drug is constant and the drug release rate is constant too. M15 samples behaviour at pH 6.8 is similar to those shown at the other pHs. The *n*-value is equal to 0.656 and it indicates a release mechanism driven by both diffusion and erosion processes.

4. Conclusion

HPMC matrices (M15 samples), upon contact with the three dissolution fluids, hydrate slowly, swell and form a thick gel layer at the tablet surface which is responsible for controlling drug release rate. This polymeric material seems to be not affected by the variation of the dissolution medium pH and this leads to a quite pH independent swelling behaviour.

On the contrary, NaCMC matrices are characterized by a different behaviour as a function of the dissolution fluid pH. At pH 1 tablets swell, forming a sort of chemically cross-linked gel, increase their dimensions but maintain their original shape and the system are elastic. The reached volume is maintained till the end of the test and no erosion phenomenon seems to happen during the dissolution test. This is a consequence of the gel high resistance to erosion process in this fluid which is probably due to the formation of strong ionic cross linkages. Drug release process is driven by a pure diffusion mechanism. At pH 4.5 and 6.8 tablets reach the maximum swelling extent at the fourth hour but then their volume decreases drastically as a result of erosion and polymer dissolution processes.

The matrices containing the blend of two polymers show a similar swelling trend at pH 4.5 and 6.8, while they have different behaviour in acidic fluid. At pH 1, in fact, gel and infiltrated layers increase progressively during the performance of the test; while, in acetate buffer at pH 4.5 and 6.8, NaCMC/HPMC matrices, once hydrated, reach gel and infiltrated layer thickness values which are maintained constant between the 7th and the 16th hour. At pH 4.5, these systems maintain a constant drug release rate coupling the diffusion and erosion mechanisms; moreover, at pH 6.8 the slower release rate obtained is characterized by a good linear profile.

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