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Matrices containing NaCMC and HPMC 1. Dissolution performance characterization

S. Conti [a,*], L. Maggi [a], L. Segale [a], E. Ochoa Machiste [a], U. Conte [a], P. Grenier [b], G. Vergnault [b]

[a] *Department of Pharmaceutical Chemistry, Via Taramelli, 12, I-27100 Pavia, Italy*
[b] *SkyePharma AG, Eptingerstrasse, 51, CH-4132 Muttenz, Switzerland*

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Abstract

In this study hydroxypropylmethylcellulose (HPMC) and sodium carboxymethylcellulose (NaCMC) were used as polymeric carriers to improve controlled release performances of matrix tablets containing a soluble drug. The drug release behaviour of the systems containing these two polymers mixture and each material separately was investigated. To evaluate the effect of the dissolution medium pH, on the drug release performance, release tests were conducted at pH 1, 4.5 and 6.8. In vitro release studies demonstrated that the mixture of the two cellulose derivatives enables a better control of the drug release profiles at pH 4.5 and at 6.8 both in term of rate and mechanism. Texture analysis on the swollen tablets helps to understand drug release kinetic and mechanism. In fact, the results obtained confirm that a gel, which is characterized by high strength and consistence is less susceptible to erosion and chains disentanglement and the drug release mechanism is mainly governed by diffusion. On the contrary, gels, which show a low strength and texture, have low resistance to the fluid erosion action and the release of the active molecule is manly due to polymer relaxation and chains disentanglement moving the drug delivery kinetic towards an erosion/relaxation mechanism.

Keywords: Hydroxypropylmethylcellulose; Sodium carboxymethylcellulose; Zero order release kinetic; Controlled drug release

1. Introduction

The use of hydrophilic matrices has become extremely popular in controlling the release rate of drugs from solid dosage forms. These systems are attractive approaches from an economic as well as process development view point (Juarez et al., 2001; Vazquez et al., 1992).

A sustained release matrix tablet consists of a compressed compact containing a mixture of one or more active ingredient(s) (API) with one or more gel forming agent(s), which retards the release of the drug (Rao et al., 1988). For many reasons, oral drug delivery continues to be the preferred route of drug substances administration (Bae et al., 1991; Deshapande et al., 1996).

During the last two decades, hydrophilic swellable polymers have been widely used to control the release of a drug from matrix tablet formulations (Alderman, 1984; Nerurkar et al., 2005) and the increasing need for suitable polymers to achieve the desired drug release profile conducted the pharmaceutical research to widely screening a large variety of both synthetic and natural polymers which show drug release retarding ability. Because of the cost of both synthesis of new polymeric materials and testing their safety, a new focus has been directed towards investigation of the use of polymer blends of pharmaceutically approved polymeric materials as matrix functional excipients to enhance single polymer performance (Ebube and Jones, 2004).

Although various types of polymers, used as rate controlling agents in hydrophilic matrices, have been extensively reviewed (Neau et al., 1999; Madhusudan Rao et al., 2001; Rao et al., 2001; Zhang and Schwarts, 2003), water soluble polymers, such as cellulose ethers, are probably the most frequently encountered in pharmaceutical literature and have gained popularity in the formulation of oral hydrophilic matrices, due to their swelling properties. Additionally, cellulose ethers have good compression characteristics such that they can be directly compressed to form sustained release swellable matrices (Vueba et al., 2004; Hayashi et al., 2005). Their popularity derives from

* Corresponding author. Tel.: +39 382 987359; fax: +39 382 987382.
E-mail address: stefania.conti@unipv.it (S. Conti).

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their non-toxic nature, their ability to accommodate a large percent of drug and negligible influence of the processing variables on drug release rates (Skoug et al., 1993; Saha et al., 1993; Yang et al., 1996; Khurahashi et al., 1996; Reynolds et al., 1998).

When a matrix containing a swellable glassy polymer comes into contact with a solvent, a progressive change from the glassy to the rubbery state leads to a swelling process. The individual chains, originally in an imperturbate state, absorb water so that their end-to-end distance and radius of gyration expand to a new solvated state. This is caused by the lowering of the transition temperature of the polymer, which is controlled by the characteristic and concentration of the swelling medium and depends on temperature and thermodynamic interactions of the polymer–water system (Siepmann et al., 2002). Macroscopically this phenomenon is evidenced by the formation of a thick gel layer on the surface of the tablet, which is responsible of the drug release rate control. In the gel phase, polymer chains slowly begin to unfold and gradually become solvated; however, the presence of physical entaglements between neighbouring chains hinders polymer dissolution. At the outer surface, the polymer is diluted to the point where the chains disentangle; the polymer has no longer structural integrity and dissolves as single molecules or as discrete agglomerates (Maggi et al., 2002). The rapid formation of this viscous gel layer upon hydration has been regarded as an essential first step in achieving controlled drug release from matrix tablets (Siepmann and Peppas, 2001).

The following possible mechanisms may lead to a proper drug release from polymeric matrices: (a) the first and the most often encountered mechanism is drug diffusion through the outside gelled layers, also known as 'Fickian release' or 'case I' mechanism (Korsmeyer et al., 1983); (b) 'non Fickian' or 'anomalous transport'; (c) 'zero-order release' or 'case II' mechanism (Maroni and Ghebre-Sellassie, 1995)

For matrix devices, drug is often released by diffusion, because a sort of receding drug boundary comes to exist within the device. This boundary moves inward, with increasing dissolution time, and, at the same time, the thickness of the gel layer increases with time. In this way, the distance each drug molecule must cross increases and API flux towards the external environment becomes inversely proportional to gel layer thickness increase.

Depending of the strength of the gel layer formed, drug release is controlled by different mechanism with diverging kinetics. Using gelling agent of low viscosity grades, erosion of the swollen polymer represents the release mechanism and generally leads to a zero-order release kinetic. If high viscosity polymers are applied, as the embedding material, a stable gel is formed and polymer dissolution is negligible. The drug is released from the swollen matrix principally through a diffusion-controlled mechanism. In fact, the drug, following the well-known Fick's law, diffuses through the stable gel layer according to square root time dependence. Often, both diffusion and erosion contribute to the release of the incorporated drug. This transition, between the two mechanisms, results in a kinetic in-between square root time dependence and zero-order generally described as 'anomalous transport', used when contribution of both diffusion and relaxation happens (Zulenger and Lippold, 2001).

Drug release rate is often difficult to control when very soluble drugs are used, moreover drug absorption from a matrix tablet is influenced heavily by its transition through the gastrointestinal tract. For these reasons, dissolution tests at different dissolution pHs should be considered, in a preformulation study, to asses the good functionality of the therapeutic system.

With the aim to achieve a constant release rate, a number of matrix devices have been formulated using different polymeric excipients but, in this study, hydroxypropylmethylcellulose and sodium carboxymethylcellulose were proposed as polymeric carriers for Diltiazem HCl. Drug release behaviour of delivery systems containing either a mixture of these two polymers or each material separately as control–sample has been investigated. To evaluate the effect of the medium pH on drug release performance, the release tests have been conducted in hydrochloric acid at pH 1, acetate buffer at pH 4.5 and in acetate buffer at pH 6.8.

Starting from the hypothesis that the gel strength can strictly influence the drug release kinetic, the assessment of the mechanical property of the gel layer, formed at the tablet surface, has been carried out on samples kept in the same conditions of the dissolution tests.

2. Materials and methods

2.1. Material

Diltiazem HCl was used as very soluble 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 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 sieved and then mixed together in a Turbula apparatus (Turbula T2A, Bachofen, Basel, CH) for 10 min. In Table 1 formulations are reported in terms of percentage composition. Mixtures were directly compressed

Table 1
% composition of B7, MB and M15 formulations

Formulation	Components	% 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

Table 2
Variation of n values with drug release mechanism

n	Mechanism	dM_t/dt dependence
0.5	Fickian diffusion	$t^{-0.5}$
$0.5 < n < 1.0$	Anomalous diffusion	t^{n-1}
1.0	Case II transport	Zero order
$n > 1.0$	Super case II transport	t^{n-1}

with a single die tabletting machine (Kilian, Coln, D) instrumented with piezoelectric load washer (Kistler, Winterthur, CH) for compression force measurements and fitted with flat-faced 9.8 mm punches. A compression force of about 2500 kg has been applied and recorded. The obtained cylindrical tablets weight 329 mg.

2.3. Release test

Release tests (six replicates) were performed in hydrochloric acid pH 1, acetate buffer pH 4.5 and in acetate buffer pH 6.8 (37 °C, $V = 1000$ ml) using USP 26 apparatus 2 with the paddle rotating at 100 rpm. The amount of drug released was determined by UV detection (Spectracomp 602, Advanced Products srl, Milan, Italy) at 246 nm.

2.4. Model used for analysis of drug release kinetics

The dissolution data 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 is 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 (Table 2). The exponent, n, depends on the polymer swelling characteristics and the relaxation rate at the swelling front. A higher k value may suggest burst drug release from the matrix. The equation is, however, valid only for the early stages ($\leq$70%) of drug release. According to the criteria for release kinetics from swellable systems, a release exponent value, $n = 0.45$, $0.45 < n < 0.89$, and $0.89 < n < 1.0$ indicates Fickian (case I) diffusion, non-Fickian (anomalous) diffusion and zero-order (case II) transport, respectively (Peppas, 1983; Ritger and Peppas, 1987).

2.5. Gel texture analysis

The samples were placed in the same conditions described in the release test section and, to avoid deformation during texture analysis, one planar base of the tablets was stocked to a metal flat base. The swollen tablets were sampled from the dissolution apparatus at the fourth hour for texture analysis. This time value has been chosen because it seems to represent a crucial point in the swelling performance of the tablets. The texture (strength) of the gel, during swelling process, was tested in triplicate using the Texture Analyzer (TA.XT2, Stable Micro System, Goldalming, UK), which provided force-time curves recorded during the penetration process. The penetration of a flat-tipped round steel probe (4 mm diameter and 30 mm length) into swollen matrices was determined at a constant speed of 0.1 mm/s, under increasing load. Data collection and analyses were performed by a computer equipped with Texture Expert® software. A predetermined maximum penetration of 2 mm was established in order to prevent the contact of the probe with the glassy core.

3. Results and discussion

3.1. Kinetic and mechanism of drug release from NaCMC and HPMC matrices

Fig. 1 shows the release profiles of the three formulations in hydrochloric acid at pH 1. By comparing Diltiazen HCl release performance from matrix containing HPMC, NaCMC, and their 1:1 mixture, no valuable changes are observed. At this pH value, the two polymers seem to behave in the same way in modulating the drug release rate and no significant changes in the dissolution trend are observed. Furthermore, the matrices containing the mixture of the two polymers show a dissolution profile similar to those of the systems containing either HPMC or NaCMC. In all the three cases, almost the total amount of drug loaded in the delivery systems is released in about 24 h. The nature of the polymer used as release modulator has no influence on the dissolution rate of these systems at pH 1. For these three formulations the n exponent value ranges from 0.554 to 0.716 indicating that the release mechanism of Diltiazem from these matrices is anomalous non Fickian and suggesting that both diffusion of the drug in the hydrated matrix and chains relaxation process affect the drug release process (Table 3).

In Fig. 2 the results of dissolution test, conducted in acetate buffer pH 4.5, performed on matrices containing Diltiazem HCl and HPMC, NaCMC, and their mixture are reported. In these experimental conditions, the active principle is released from NaCMC matrices faster than from HPMC ones; in fact, from NaCMC systems the total drug loaded is released in about 20 h

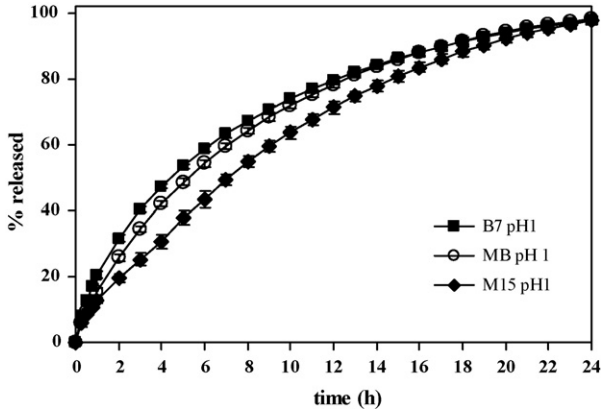

Fig. 1. Dissolution profiles of B7 (NaCMC–drug), MB (NaCMC–HPMC–drug) and M15 (HPMC–drug) in hydrochloric acid at pH 1.

Table 3
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

with a mechanism mainly governed by polymer relaxation and erosion (*n* is 1.062). On the contrary, the amount of drug released from HPMC K15M matrices increases according to a diffusive process during the test (*n* value is 0.608 and indicates an anomalous non Fickian mechanism mainly influenced by Fickian diffusion). The initial burst effect is probably due to the fact that the gel layer, which controls the release of the drug, needs some time to become effective. The mixture of the two polymers, used as release modulator agents, enables the system to reach a nearly zero-order release kinetic (*n* is 0.956). Interactions between HPMC and NaCMC provide to the gel, formed on the surface of the tablet, the ability to overpass the burst effect of HPMC systems. In this way, a combination of the two release mechanisms is realized and the drug is delivered at a nearly constant rate. The total amount of the active molecule, loaded in the matrices, is released in about 24 h.

In Fig. 3 the dissolution profiles in acetate buffer pH 6.8 of matrices containing Diltiazem HCl and HPMC, NaCMC, and their mixture are reported. NaCMC matrices release the active much more quickly than HPMC systems. The value of *n* exponent is 1.431, typical of a dissolution behaviour characterized by a sigmoid, *S*-shaped, curve. The high release rate is due to the high solubility of NaCMC at this pH value. This polymer characteristic gives to the matrix a quick gel erosion rate and a high erosion degree of the overall system. The tablets containing NaCMC, in fact, show a relative slow initial drug release during the first hour but then the release rate increases quickly; 80–85% of the total content is delivered within 8 h. For matrices containing HPMC the release of the drug is predominantly attributable to the contribution of Fickian diffusion (*n* value is 0.656) with a minimal contribution of polymer relaxation and

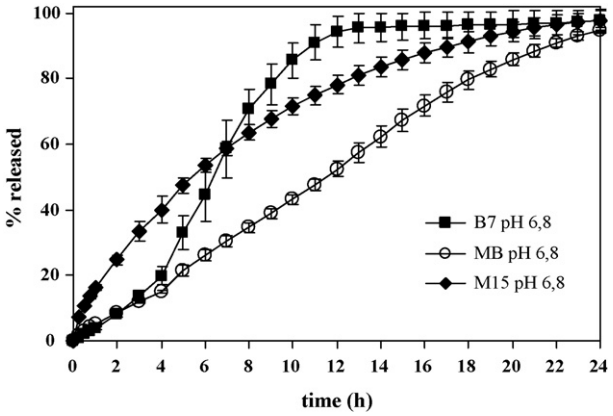

Fig. 3. Dissolution profiles of B7 (NaCMC–drug), MB (NaCMC–HPMC–drug) and M15 (HPMC–drug) in acetate buffer at pH 6.8.

matrix erosion. In the case of MB systems, the *n* value (0.990) indicates a zero order release kinetic. The drug release rate is nearly constant and the release process is slower compared to that of the matrices containing the single polymers. This could be due to the interactions between NaCMC chains, ionic polymer, and HPMC chains, non-ionic polymer, which are probably enhanced at this pH value.

In order to highlight the differences found in the dissolution profiles of the three different formulations, *t*20 and *t*90 have been calculated and their values are reported in Fig. 4 as a function of the system and of the pH in which the dissolution tests have been carried out. *t*20 and *t*90 are considered as the time needed by the systems for the delivery of 20% and 90% of the total amount of drug contained in the tablet.

All the systems show a lower *t*20 value at pH 1; a burst release upon hydration of the tablet occurs in hydrochloric acid, it means that the drug release rate, in this brief initial period, is higher compared to the drug release rate of the overall process. When these matrices come into contact with this dissolution medium, the gel hydration rate is slower and the active molecules present at the surface of the tablet can dissolve and pass into the fluid. The system containing the blend of the two polymers shows an in-between behaviour compared to the control–HPMC and NaCMC–systems.

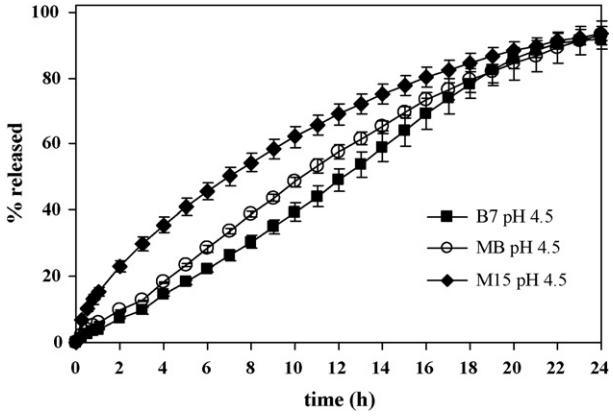

Fig. 2. Dissolution profiles of B7 (NaCMC–drug), MB (NaCMC–HPMC–drug) and M15 (HPMC–drug) in acetate buffer at pH 4.5.

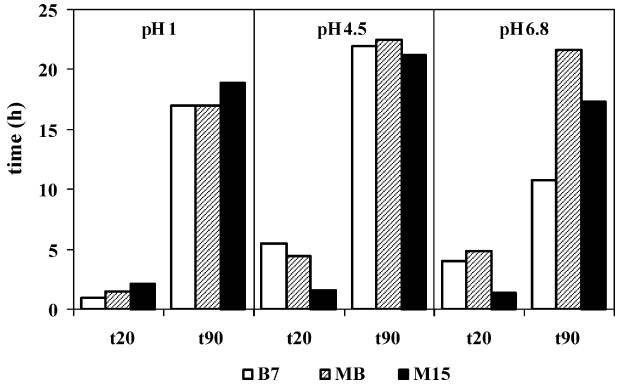

Fig. 4. *t*20 and *t*90 of B7, MB and M15 formulations calculated from the dissolution profiles at pH 1, 4.5 and 6.8.

*t*90 values, in this dissolution fluid, do not show noteworthy differences; the three formulations behave in the same way in modulating drug delivery and the overall drug release rates are comparable.

In acetate buffer at pH 4.5 a low *t*20 value is observed for HPMC matrix systems. In this dissolution fluid, HPMC shows a slow gel layer formation rate and it results in the high initial drug release rate (burst release). On the contrary, a higher *t*20 value is noticed for NaCMC formulations. These systems are subjected to a lag time in the release of the drug upon contact with the dissolution fluid. Probably, the high hydration rate of the polymer causes the formation of a thick gel layer able to slow down the drug dissolution rate at the beginning of the process. The systems obtained by mixing the two polymers overcome the burst release and the lag time of the control–systems. The drug delivery rate is assessed at a value, which remains constant till the end of the dissolution test. Although the differences at the beginning of the test and the diverging mechanisms, which govern the process, *t*90 values are comparable, it means that the drug release rates are similar.

In acetate buffer at pH 6.8, MB systems show higher *t*20 and *t*90 value compared to those of the single polymers–control–matrices. *t*20 is really similar to that of B7 samples; the systems seem to be more influenced by the ionic component in this phase of the dissolution test. *t*20 of HPMC systems is the lowest, even in this case. HPMC matrices are not influenced, in their dissolution behaviour, by the pH of the fluid, probably as a consequence of the pH independent nature of the carrier polymer.

Significant differences can be observed in *t*90 values. NaCMC value is the lowest. In fact, at this pH the dissolution rate is the highest for these systems. The increasing solubility of the polymer with the pH increase is probably the cause of this behaviour.

MB systems show the higher *t*90value. A synergistic effect in modulating drug release rate can be noticed. Mixing the two cellulose ethers polymers, ionic and non-ionic, for the formulation of hydrophilic matrices, a valuable decrease of drug release rate can be achieved.

3.2. Texture analysis

Texture analysis is a technique that has been extensively employed in the mechanical characterization of food materials and, in the last few years, it has emerged also as a useful technique in the field of pharmaceutical gel studies.

Compression analysis experiments have been carried out on the matrix sample withdrawn from the fluid after 4 h of contact with the medium. From a typical compression experiment, the following parameters can be acquired: (1) system hardness, i.e., the maximum positive force required to obtain a given deformation, F_{max}; (2) work of cohesion, given by the positive area under the force–time curve that represents the work needed to overcome the internal bonds of the material; (3) work of adhesion, given by the negative area under the force–time curve, it represents the work needed to pull the probe away from the sample.

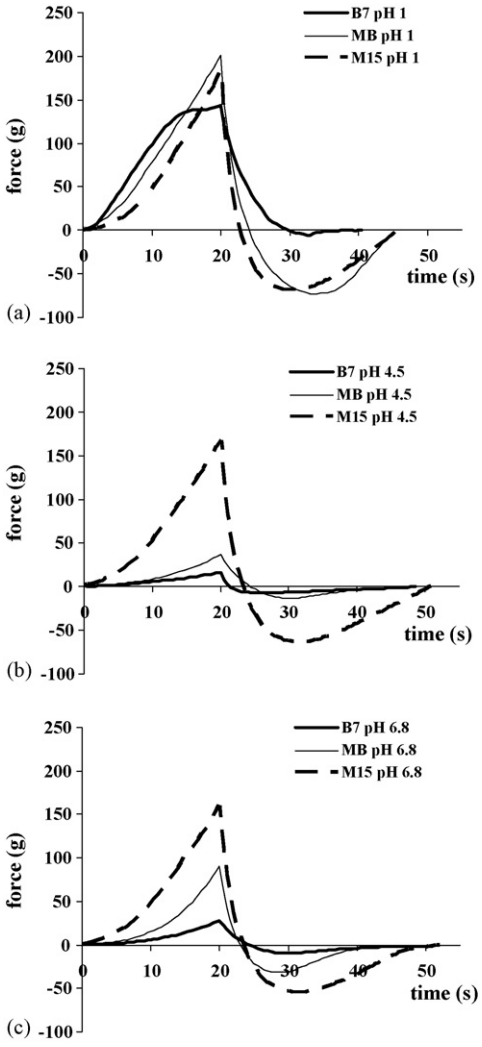

Fig. 5. Texture profiles obtained from B7, MB and M15 formulations in hydrochloric acid at pH 1 (a), in acetate buffer at pH 4.5 (b) and in acetate buffer at pH 6.8 (c).

In Fig. 5a texture profiles obtained analyzing the three formulations at pH 1 are reported. The different shape of B7 texture profile is evident; in fact the texture of this system is different from the other two, containing only HMPC and the mixture NaCMC–HPMC. B7 morphological behaviour is more similar to that of a chemically cross linked hydrogel rather than a physical gel. In fact during the dissolution test at pH 1, B7 samples maintain their shape and consistence during all the performance of the test. The negligible work of adhesion is due to the fact that this kind of gel is more elastic than plastic. MB and M15 sample texture profiles are similar; the consistence of the gel seems comparable. By considering the slope of the first tract of penetration curve as a qualitative parameter to describe gel strength, B7 gel seems to be stronger than MB one, which is stronger than M15 one.

The texture profiles of the three formulations at pH 4.5 and 6.8 show the typical trend of a physical gel (Fig. 5b and c).

Fig. 6 reports the positive areas under the force–time curve, for each formulation, as a function of dissolution medium pH. Higher cohesion values are evident for B7 and MB matrix tablets

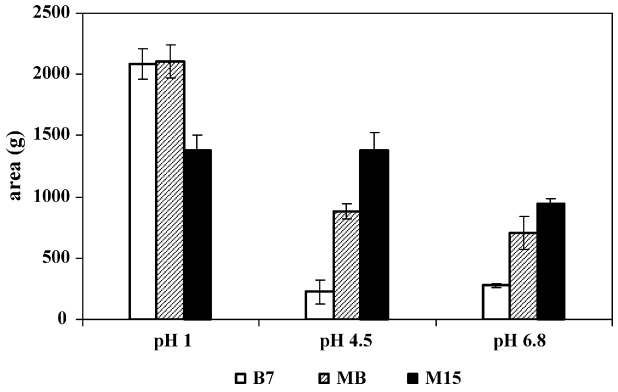

Fig. 6. Positive areas under the force–time curve, for B7, MB and M15 formulations, as a function of dissolution medium pH.

at pH 1 compared to the other pH and to M15 formulation. In this dissolution condition, B7 and MB systems let the formation of a thick and consistent gel layer upon hydration. This gel shows textural properties that prevent its erosion caused by the fluid. In this case, the gel forming rate is higher than the rate of erosion. Thus the drug is delivered by diffusion through the firm gel layer. In this way the rate of drug delivery is higher at the beginning, when the gel layer is thinner and then it decreases because of the increase of the thickness of the gel zone. The drug release data are well fitted by square root time dependence and they are well explained by Fickian diffusion. On the other hand for M15 matrices, the area under the force–time curve is lower compared to B7 and MB, and maintains quite the same values at the three pHs. The matrix systems containing HPMC, as carrier polymer, are not influenced by the dissolution medium hydrogenionic concentration. The drug release process is linked both to the diffusion of the drug in the gel layer and to polymer chains relaxation and dissolution from the tablet surface ($n = 0.716$). At higher pH (4.5), B7 area value is very low compared to the other systems. The gel layer of this system is formed as quickly as it is eroded. This is evidenced by the drug dissolution behaviour, mainly connected to chains relaxation process ($n = 1.062$). MB matrix samples show an intermediate cohesion value and consequently an intermediate dissolution trend. The mixture of the two polymers leads to the obtainment of a zero-order release kinetic. At pH 6.8 the gel strength of M15 matrices is maintained while for MB and for B7 samples this value is very low. The dissolution trends are in agreement with the results of the texture analysis; in fact drug is released by B7 sample mainly through erosion which leads to a very fast delivery of the total dose while the systems containing the two polymers blend show an intermediate behaviour that maintains the advantages of the other two systems with a more extended release at a constant rate.

4. Conclusion

In vitro release studies demonstrated that the release of diltiazem HCl from all the systems considered is sustained. The mixture of the two cellulose ethers, ionic and non-ionic, used as polymeric carriers in hydrophilic matrices, enables to obtain a zero order release kinetic at pH 4.5 and 6.8 at a slow rate.

The use of texture analysis on the swollen tablet reveals to be a good approach to understand drug release kinetic and the mechanism of drug delivery from a swellable matrix system. In fact the results obtained confirm that a gel characterized by a higher strength is less susceptible to erosion and chains disentanglement. In this case the drug release mechanism is mainly governed by diffusion of the active molecule through the gel barrier formed at the tablet surface. On the contrary gels which show a low strength have low resistance to the fluid erosion action. In this case the release of the drug is manly due to polymer relaxation and matrix erosion.

The mixture of hydroxypropylmethylcellulose and sodium carboxymethylcellulose (1:1) matrix systems enable the over passing of the negative effect of the control–NaCMC and HPMC–systems, burst effect and lag time and they shift the mechanism from diffusion to a coupling of diffusion and erosion, and thus zero-order kinetics, while prolonging the drug release process.

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