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# High molecular weight polyethylene oxides (PEOs) as an alternative to HPMC in controlled release dosage forms

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**Abstract**

High molecular weight polyethylene oxides (PEOs) have recently been proposed as an alternative to hydroxypropylmethylcellulose (HPMC) in controlled release matrix tablets. In this study, we compared the performance of PEO and HPMC polymers when employed in the Geomatrix® [1] technology, a versatile, well-known method to achieve extended release of drugs at a constant rate. Four core formulations were prepared, containing a soluble drug (diltiazem) and, alternatively, PEO or HPMC of two different viscosity grades. These formulations have the same composition except for the polymer employed. Similarly, four barrier formulations were also prepared, which only differ in the kind of polymer employed. Three-layer Geomatrix® systems were then prepared using these core and barrier formulations. The release profiles of the different three-layer systems obtained were compared, to verify if PEO could efficiently replace HPMC in this type of dosage form. The results show that slower release rates can be obtained from the plain matrices containing HPMC compared to PEO, moreover HPMC, used in the barrier formulations, is generally more efficient in controlling drug release rate in three-layer Geomatrix systems. 

*Keywords:* Polyethylene oxides; Hydroxypropylmethylcellulose; Hydrophilic matrix; Three-layer system; Controlled release

## 1. Introduction

Among the various hydrophilic polymers employed for drug release control, hydroxypropylmethylcellulose (HPMC) is the most commonly used polymer in matrices for extended release of drugs, due to its versatility, compatibility with many drugs and safety (Alderman, 1984). Nevertheless, high molecular weight polyethylene oxides (PEOs) have recently been proposed as an alternative to HPMC for controlled drug delivery (Royce, 1993; Kim, 1995, 1998). Apicella et al. prepared extended release hydrophilic matrices, which contain high molecular weight PEOs as the hydrophilic polymer, and demonstrated that this kind of delivery system shows a non constant release rate (Apicella et al., 1993). Yet, drug release at a constant rate is often desirable, to

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[1] Geomatrix® is a registered trademark of Skye Pharma AG, Muttenz, CH.

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maintain the plasmatic levels of the drug in the therapeutic range, thereby avoiding the peak and valley profile characteristics of conventional dosage forms in a multidose regimen.

Table 1
Percent composition of different core formulations

| Core | $CY_1$ | $CM_1$ | $CY_2$ | $CM_2$ |
|---|---|---|---|---|
| PEO (Polyox WSR N60K) | 38.2 | | | |
| HPMC (Methocel K4M) | | 38.2 | | |
| PEO (Polyox WSR 303 NF) | | | 38.2 | |
| HPMC (Methocel K100M) | | | | 38.2 |
| Diltiazem hydrochloride | 49.3 | | | |
| Lactose | 11.0 | | | |
| Magnesium stearate | 1.0 | | | |
| Colloidal silicon dioxide | 0.5 | | | |

Table 2
Percent composition of different barrier formulations

| Barrier | $bY_1$ | $bM_1$ | $bY_2$ | $bM_2$ |
|---|---|---|---|---|
| PEO (Polyox WSR N60K) | 45.0 | | | |
| HPMC (Methocel K4M) | | 45.0 | | |
| PEO (Polyox WSR 303 NF) | | | 45.0 | |
| HPMC (Methocel K100M) | | | | 45.0 |
| Lactose | 45.0 | | | |
| Hydrogenated castor oil | 8.5 | | | |
| Magnesium stearate | 1.0 | | | |
| Colloidal silicon dioxide | 0.5 | | | |

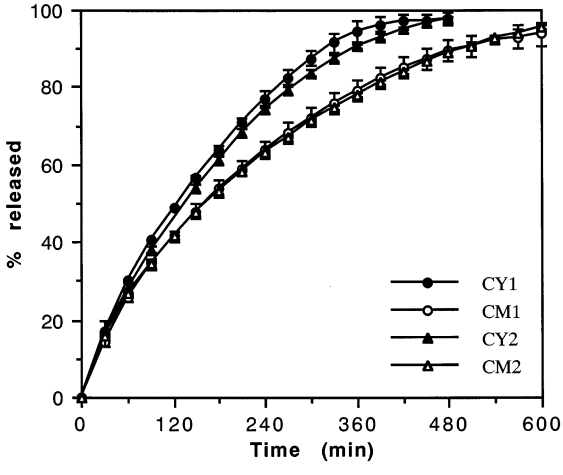


Fig. 1. Release profiles of the core formulations $CY_1$, $CM_1$, $CY_2$ and $CM_2$.

Geomatrix® technology is widely employed to obtain constant drug release (Conte and Maggi, 1998). This drug delivery system consists of two or three-layer tablets in which the outer layers are drug-free modulating barriers, while the active ingredient is contained in the central layer (or core). All the layers contain a hydrophilic polymer, usually HPMC (Conte et al., 1994). The multi-layer design and the use of polymeric barriers allow the drug release profile to be modulated in a wide range. The barrier layers reduce the surface of the core exposed to the outer environment and, by controlling water penetration in the matrix, they modulate the drug release rate (Conte et al., 1993).

In this study, high molecular weight PEOs were used as the hydrophilic polymer in the core and/or in the barrier layers of Geomatrix systems, in particular, Polyox® WSR N60K (molecular weight $2 \times 10^6$) and Polyox® WSR 303 (molecular weight $7 \times 10^6$), which are believed to be comparable to Methocel® K4M and Methocel® K100M (Union Carbide bulletin, 1993). These four polymers were used to prepare two PEO and two HPMC plain matrices (cores of the Geomatrix systems), which have the same composition except for the kind of polymer contained. As a model drug, a well-known soluble drug (diltiazem hydrochloride) was employed. The dissolution behaviour of these formulations in the form of plain matrices without barrier layers was compared. Three-layer Geomatrix tablets were then prepared, employing the previously detailed core formulations and four different types of barriers containing PEO or HPMC. The release profiles of the different three-layer systems were compared to verify if PEO could efficiently replace HPMC in this type of drug delivery system. The influence of polymer type and viscosity grade on drug release rate and kinetics was evaluated.

## 2. Experimental

### 2.1. Materials

Diltiazem hydrochloride was supplied by Profarmaco S.p.A. (Milan, Italy). HPMCs (Methocel

Table 3
Times (min) at which 75% of the drug is released ($t_{d75}$) from different core and three-layer systems (mean value, $n = 3$)

| Formulation | Plain matrix no barriers | Geomatrix three-layer systems | | | |
|---|---|---|---|---|---|
| | | $bY_1$ | $bM_1$ | $bY_2$ | $bM_2$ |
| $CY_1$ | 222 | 505 | 616 | 624 | 792 |
| $CY_2$ | 246 | 559 | 687 | 657 | 946 |
| $CM_1$ | 324 | 651 | 724 | 715 | 1013 |
| $CM_2$ | 357 | 629 | 782 | 761 | 1199 |

K4M and Methocel K100M) were supplied by Colorcon (Orpington, UK) while PEOs (Polyox WSR 303 and Polyox WSR N60K) were supplied by Union Carbide Corp. (Danbury, CT, USA).

Polyox WSR N60K (molecular weight $2 \times 10^6$) is characterised by a viscosity grade comparable to Methocel K4M. A 2% (p/v) water solution of Polyox WSR N60K has a viscosity range of 2000 and 4000 cP (Brookfield viscometer, with a No 3 spindle at 10 rpm, 25°C, Union Carbide bulletin, 1993), and a 2% (p/v) water solution of Methocel K4M has a viscosity of 4000 cP (Ubbelohde tube, 20°C, Colorcon bulletin, 1992). Polyox WSR 303 (molecular weight $7 \times 10^6$) is believed to be comparable (Union Carbide bulletin, 1993) to Methocel K100M.

The other excipients were lactose and magnesium stearate (C. Erba, Milan, Italy), hydrogenated castor oil (Cutina HR, Henkel Chimica, Milan, Italy) and colloidal silicon oxide (Syloid 244, Grace GmbH, Worms, Germany).

### 2.2. Methods

The four cores and the four barrier formulations were prepared by mixing the drug (only in the case of core formulations), the hydrophilic polymer and the excipients for 30 min (Turbula, Bachofen, Basel, CH Switzerland). The compositions of the various mixtures are reported in Tables 1 and 2.

The core matrices were prepared by direct compression of the powder mixtures. A single punch reciprocating tablet machine (Korsh EK0, Berlin, Germany), equipped with convex punches of 10 mm in diameter was used. The tablets weighed 244 mg $\pm$ 1% and the thickness is 3.63 mm $\pm$ 1%. The PEO tablets ($CY_1$ and $CY_2$) showed a crushing strength of 98.3 $\pm$ 2.9 N, while this parameter was 172 $\pm$ 5.2 and 195 $\pm$ 7.1 N for the core matrices containing Methocel K4M or K100M, respectively. To prepare three-layer Geomatrix tablets, the die was accurately and progressively filled with weighed amounts of the different mixtures (barrier, drug formulation and barrier again). The powders were manually layered and the compression cycle was activated. The resulting tablets weighed 504 mg $\pm$ 1% and the tablet thickness was 6.30 mm $\pm$ 2%. The crushing strength was 177 $\pm$ 14 N for Geomatrix tablets with PEO cores and the four different barriers and 289 $\pm$ 15 N for those with HPMC cores and the four different barriers, respectively.

All systems contain 120 mg of diltiazem hydrochloride as active.

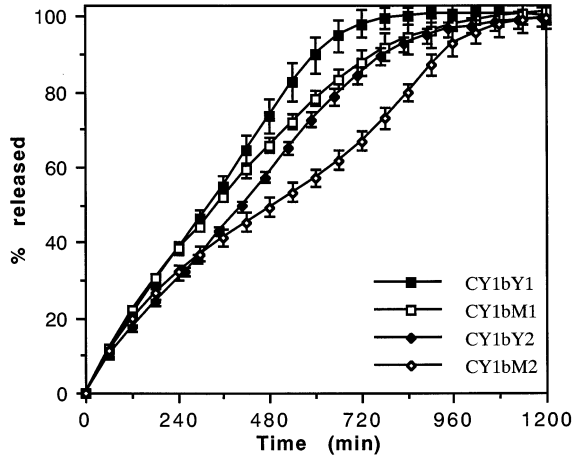


Fig. 2. Release profiles of Geomatrix three-layer systems with $CY_1$ cores and the four different barrier formulations.

Table 4
Prevailing release kinetics (correlation coefficients, $R^2$) of the different three-layer Geomatrix systems

| Formulation | $bY_1$ | $bM_1$ | $bY_2$ | $bM_2$ |
|---|---|---|---|---|
| $CY_1$ | Anomalous (0.994) | Anomalous (0.997) | Anomalous (0.999) | Anomalous (0.996) |
| $CM_1$ | Anomalous (0.999) | Anomalous (0.999) | Anomalous (0.994) | Anomalous (0.998) |
| $CY_2$ | Linear (0.997) | Linear (0.999) | Linear (0.999) | Higuchi (0.998) |
| $CM_2$ | Linear (0.998) | Linear (0.999) | Linear (0.999) | Linear (0.998) |

In vitro dissolution tests were performed in 1 l of distilled water at 37°C, with the USP apparatus 2 (paddle), at 100 rpm (three replicates). The amount of drug released was assessed by UV detection at 236 nm (Spectracomp 602, Advanced Products, Milan, Italy).

The release data were fitted using the well-known empirical equation proposed by Korsmeyer and Peppas (1983)

$$\frac{M_t}{M_\infty} = kt^n \quad (1)$$

where $M_t/M_\infty$ is the fractional drug release, $t$ the release time, $k$ is a kinetics constant and $n$ the diffusion exponent, characteristic of the release mechanism. For a cylindrical matrix that can swell, $0.89 < n < 1.0$ indicates a zero order release, while $0.45 < n < 0.89$ shows anomalous release kinetics (Ritger and Peppas, 1987; Peppas and Sahlin, 1989).

A linear regression analysis of the logarithmic form of Eq. (1) was carried out, and a correlation coefficient ($R^2$) > 0.99 was obtained in all cases.

The significance of the differences between the various formulations in terms of time at which 75% of the drug is released ($t_{d75}$) was evaluated (Student's $t$ test).

It is known that polyethers can undergo chain cleavage through autooxidation (Union Carbide bulletin, 1993). This degradation causes a reduction of the molecular weight of the polymer and, as a consequence, may influence the controlled release efficiency of the matrix. For this reason, the dissolution profiles of all the systems considered were evaluated after the tablets had been stored for 1 year in polyethylene bottles at room temperature.

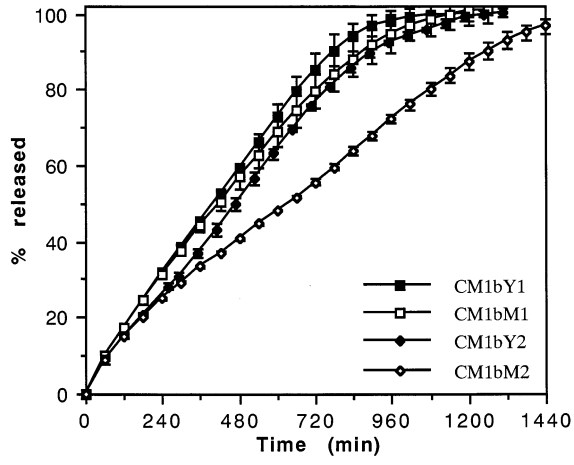


Fig. 3. Release profiles of Geomatrix three-layer systems with $CM_1$ cores and the four different barrier formulations.

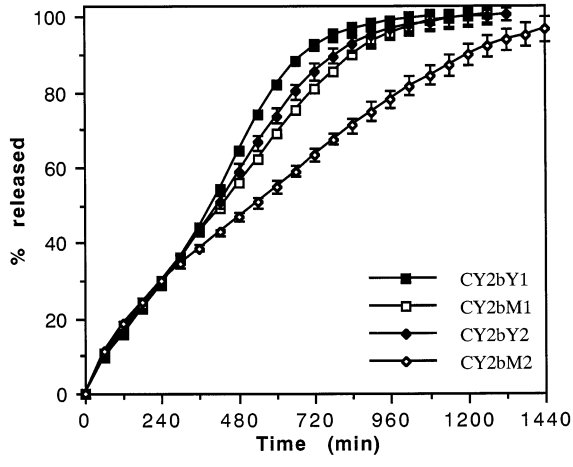


Fig. 4. Release profiles of Geomatrix three-layer systems with $CY_2$ cores and the four different barrier formulations.

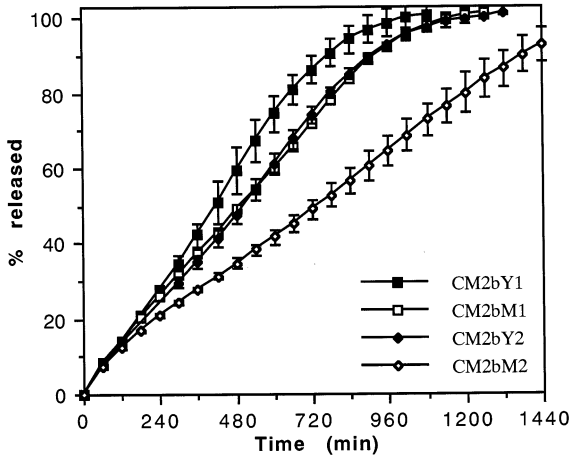


Fig. 5. Release profiles of Geomatrix three-layer systems with $CM_2$ cores and the four different barrier formulations.

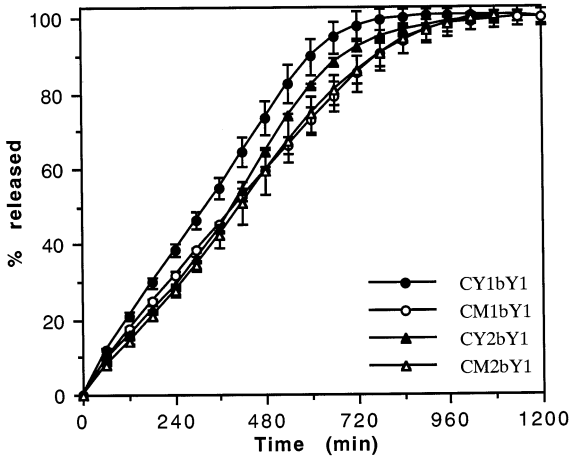


Fig. 6. Release profiles of Geomatrix three-layer systems with $bY_1$ barrier and the four different core formulations.

To study the morphological behaviour of the different type of polymeric material during the dissolution test, some plain tablets, made of pure polymers, were also prepared. These tablets were placed in dissolution in the same conditions as previously detailed, sampled after different time intervals and sectioned. The photomicrographs of these pure polymeric tablets were evaluated according to a method previously described (Conte and Maggi, 1996), using a video microscope and an image analyser (CV9000, FKV SRL, Sorisole, BG, Italy). From the images the height and diameter of the tablets can be measured to evaluate the volume increase during dissolution test.

## 3. Results and discussion

The results of the dissolution tests performed on the four different core formulations showed that the diltiazem release rate from the two matrices containing HPMC is slower compared to

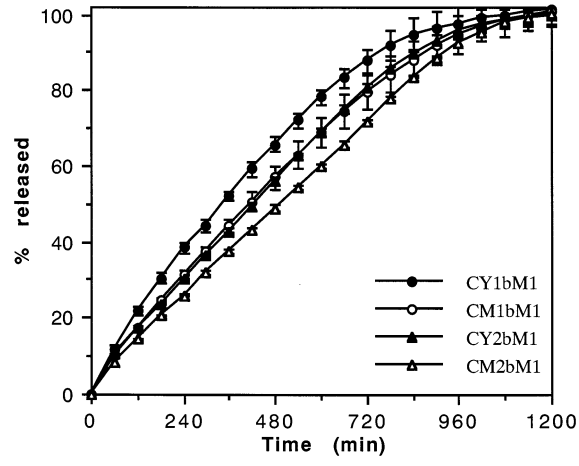


Fig. 7. Release profiles of Geomatrix three-layer systems with $bM_1$ barrier and the four different core formulations.

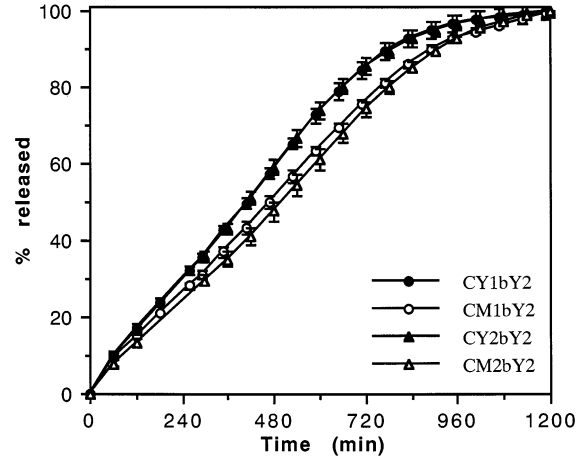


Fig. 8. Release profiles of Geomatrix three-layer systems with $bY_2$ barrier and the four different core formulations.

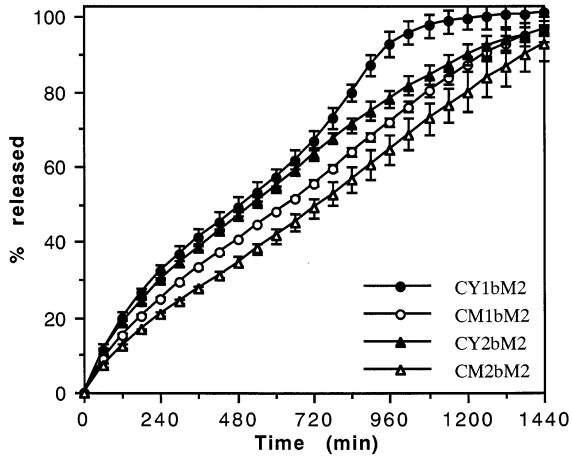


Fig. 9. Release profiles of Geomatrix three-layer systems with $bM_2$ barrier and the four different core formulations.

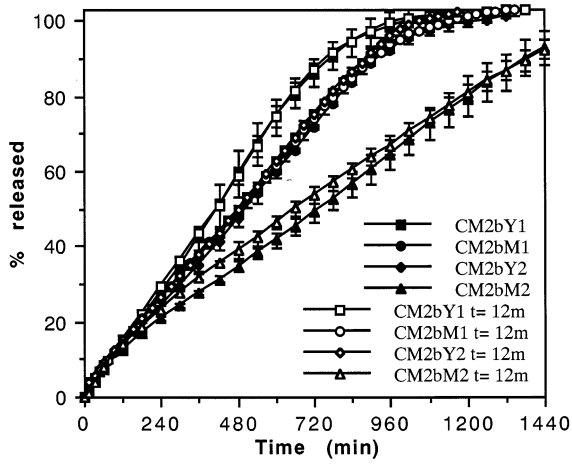


Fig. 10. Release profiles of Geomatrix three-layer systems with $CM_2$ cores and the four different barriers at time zero and after 1 year of storage at room temperature.

the release rate of PEO matrices (Fig. 1). The *t* tests showed significant differences in $t_{d75}$ between $CY_1$ and $CM_1$ and between $CY_2$ and $CM_2$ formulations ($P < 0.01$, Table 3). On the other hand, by comparing the dissolution behaviour of the core formulation containing Methocel K4M to that of the core composition containing Methocel K100M, no significant difference between the dissolution profiles of these formulations can be evidenced. Similar considerations can be made in the case of $CY_1$ and $CY_2$ cores. Thus, the viscosity grade of the polymer contained in these matrices seems to have slight influence on the release profile of the core formulations. For all the core tablets, the kinetics which best fits the release data is the Higuchi ($R^2 \geq 0.999$). This means that the drug is mainly released by Fickian diffusion.

The application of the different barrier layers causes a strong reduction in the drug release rate in all the core formulations (Table 3). In particular, the application of $bM_1$ barriers to the different cores, doubles the $t_{d75}$ of the plain matrices, while the $t_{d75}$ of Geomatrix systems with $bM_2$ barriers are three-fold compared to that of the core tablets. On the other hand, the barriers made of PEO of comparable viscosity are less efficient in reducing drug release rate.

The release profiles of the three-layer tablets with $CY_1$ as core layer and with the four different barrier formulations are compared in Fig. 2. As expected, barriers containing polymers of higher viscosity ($bY_2$ and $bM_2$ barriers) are more efficient in controlling drug release rate compared to those containing polymers of lower viscosity ($bY_1$ and $bM_1$, $P < 0.01$). Moreover, diltiazem release from the devices with $CY_1$ cores and HPMC barriers is slower than the release from systems with $CY_1$ core and PEO barriers of comparable viscosity. This trend is more evident for the barriers containing polymers of higher viscosity ($P < 0.05$ between $bY_2$ and $bM_2$ barriers, while $0.05 < P < 0.1$ between $bY_1$ and $bM_1$ barriers).

The above mentioned systems show anomalous release kinetics as shown in Table 4, and also the Geomatrix systems with $CM_1$ cores and the four different barriers show anomalous release kinetics (Table 4). The dissolution profiles of three-layer matrices with $CM_1$ cores and $bY_1$, $bM_1$ or $bY_2$ barriers are very similar (Fig. 3). On the contrary, the application of the barrier layers containing HPMC of higher viscosity ($bM_2$), causes a stronger reduction in drug release rate compared to the other $CM_1$ three-layer tablets ($P < 0.05$). Similar behaviour was shown by the three-layer systems containing $CY_2$ cores and the four different barrier formulations (Fig. 4). $CY_2bY_1$, $CY_2bM_1$ and $CY_2bY_2$ dissolution patterns are very similar, while $bM_2$ barrier seems to be more efficient in controlling drug delivery rate in this

Table 5
Times (min) at which 75% of the drug is released ($t_{d75}$) from different core and three-layer systems stored for 1 year at room temperature (mean value, $n = 3$)

| Formulation | Plain matrix no barriers | Geomatrix three-layer systems | | | |
|---|---|---|---|---|---|
| | | $bY_1$ | $bM_1$ | $bY_2$ | $bM_2$ |
| $CY_1$ | 223 | 528 | 586 | 632 | 835 |
| $CY_2$ | 278 | 560 | 708 | 667 | 951 |
| $CM_1$ | 309 | 616 | 703 | 765 | 1089 |
| $CM_2$ | 357 | 632 | 759 | 792 | 1186 |

core formulation. On the contrary, the release profiles of three-layer matrices with $CM_2$ cores and the four different barriers compared to $CM_1$ and $CY_2$ three-layer devices are more differentiated (Fig. 5).

The three-layer devices containing in the core the polymers of higher viscosity, release the drug at a lower rate compared to the systems containing the polymers of lower viscosity (Table 3; Figs. 4 and 5). For all cases, the best fit was determined to be linear (Table 4) except for $CY_2bM_2$ which best fit is the Higuchi type.

The barriers made of HPMC seem more efficient in reducing drug delivery than PEO barriers, and their efficiency in drug release modulation depends on the viscosity grade of the polymer (Table 3).

By comparing the dissolution behaviour of the Geomatrix three-layer systems with the same barrier but with cores containing the four different polymers, very similar dissolution patterns were obtained (Figs. 6–8). This means that the core composition has less influence on the drug delivery modulation in this kind of device, while the barriers play the leading role in controlling drug release from the Geomatrix three-layer systems. Only in the case of the barrier containing HPMC of higher molecular weight a rank order can be evidenced as a function of the viscosity grade of the polymer contained in the core (Fig. 9).

The stability test does not evidence any problem related to possible oxidation of the PEO chain. The dissolution profiles of all the systems considered at time zero and after 1 year of storage at room temperature, are completely superimposable (three-layer systems with $CM_2$ cores and the four different barriers are reported in Fig. 10 as example). No significant difference could be evidenced in $t_{d75}$ (Table 5).

The results of the swelling studies performed on the plain tablets made of pure polymer evidence quite different morphological behaviour of HPMCs and PEOs during hydration. In fact, HPMCs tablets showed a slow and continuous volume increase, up to four-fold (Methocel K4M) or six-fold (Methocel K100M) the volume of the dry tablet, after 20 h in distilled water (Fig. 11). On the other hand, tablets made of pure PEOs swell rapidly (up to six-fold or two-fold in the case of Polyox WSR 303 or Polyox NF-60K tablets, respectively, after 8 h), but these polymers form a weaker gel, tend to be eroded much more quickly and the tablet volume decreases progressively (Fig. 11).

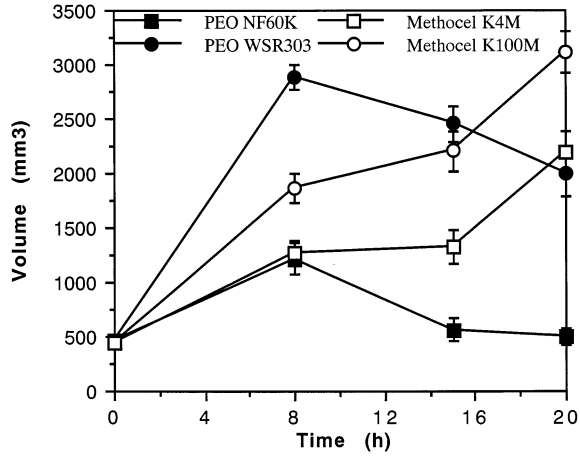


Fig. 11. Swelling study, volume increase of the tablets made of pure polymer.

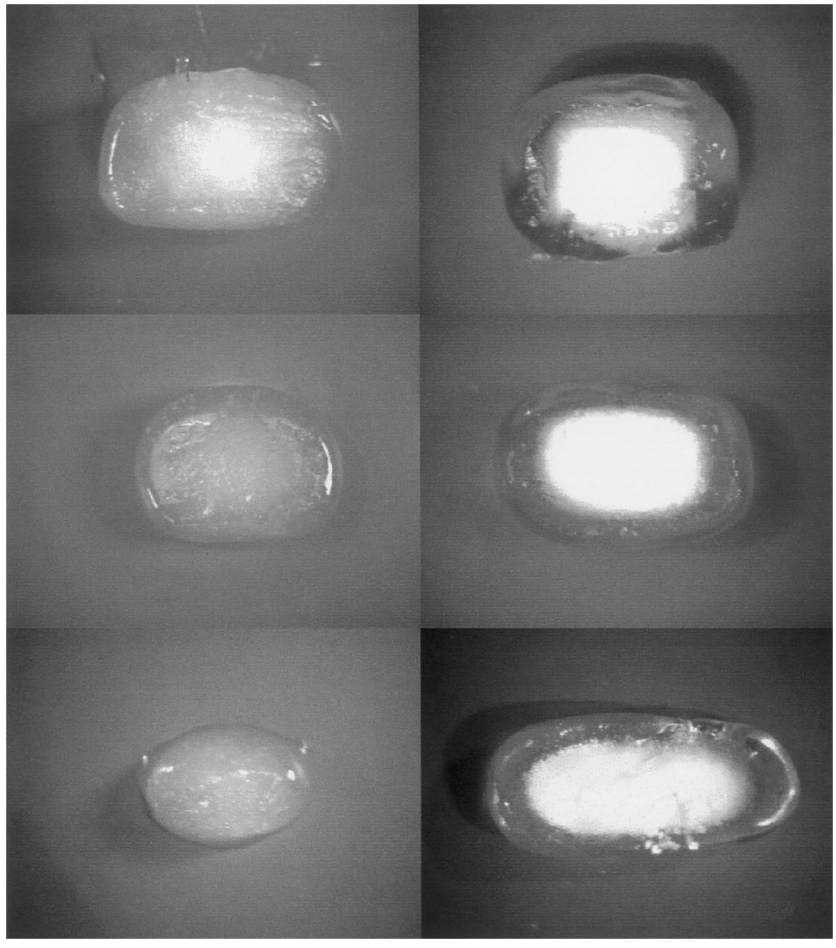

Fig. 12. Photographs of the tablets made of pure polymer during dissolution. Left column, Polyox WSR N60K; Right column, Methocel K4M. From top to bottom, after 8, 15 and 20 h.

Moreover, the photomicrographs of the tablets made of pure HPMCs evidenced a slow hydration rate: after 20 h a bulky glassy core could still be evidenced in both Methocel K4M (Fig. 12) and Methocel K100M tablets (Fig. 13). Methocel K100M showed a stronger resistance to erosion compared to Methocel K4M, as evidenced by the presence of a gel layer characterized by a considerable thickness at the tablet surface (Fig. 13).

On the other hand, PEOs showed a faster hydration rate: after 15 h in water only a small portion of the tablet made of Polyox WSR 303 was still in the glassy state (Fig. 13), and the Polyox NF-60K tablet was completely gelled (Fig. 12). After 20 h both polymers were fully gelled, but Polyox WSR 303 was eroded at a slower rate because it seems to form a stronger gel compared to Polyox NF-60K. The volume of the Polyox WSR 303 tablet was about five-fold compared to that of the tablet made of PEO of lower viscosity after 20 h in water (Fig. 11).

As expected, HPMC and PEO of higher viscosity grade are characterised by a slower hydration rate and by a stronger resistance to erosion compared to the corresponding polymers of lower viscosity.

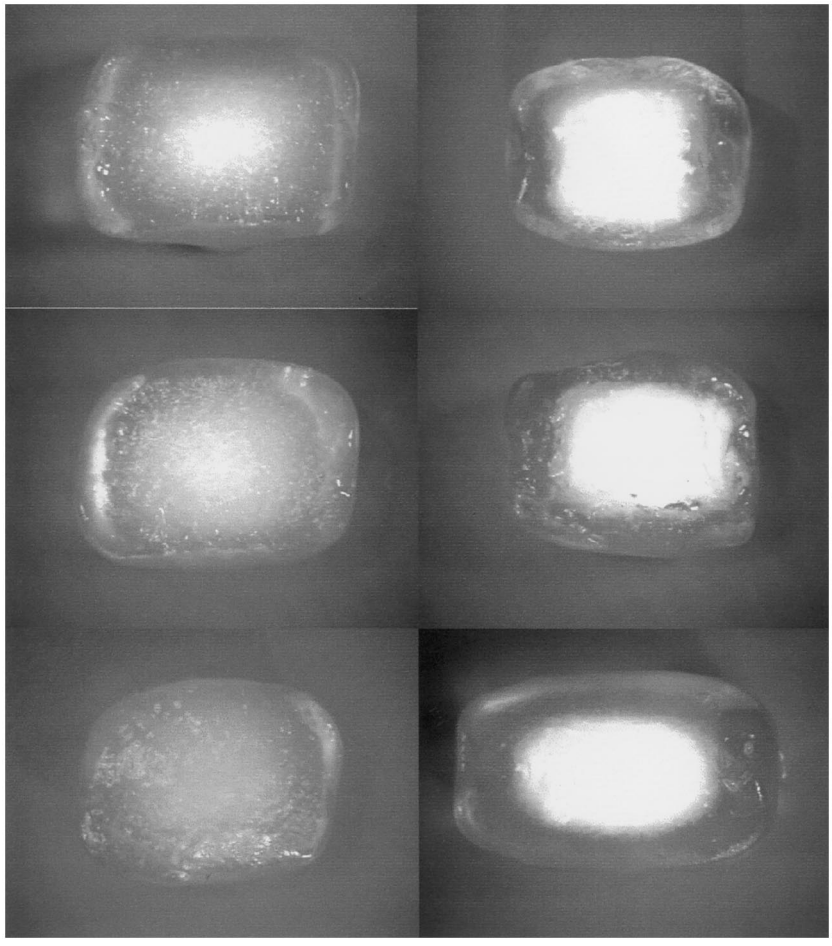

Fig. 13. Photographs of the tablets made of pure polymer during dissolution. Left column, Polyox WSR 303NF; Right column, Methocel K100M. From top to bottom, after 8, 15 and 20 h.

## 4. Conclusions

PEOs appear to be less efficient when compared to HPMCs in reducing the delivery rate of a soluble drug as diltiazem hydrochloride, probably because they form a weaker gel layer than HPMCs of comparable viscosity. A softer gel can be more rapidly removed by the dissolution medium, and therefore, the matrix system more easily susceptible to an erosion process.

However, the active core and barrier layer design of the Geomatrix technology allows a stronger control of the release kinetics and an optimal modulation of the dissolution profiles can be easily achieved whether PEOs or HPMCs are used. The storage at room temperature has little, if any, influence on the controlled release efficiency of all the systems considered.

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