Release of Timolol maleate from pH-sensitive Poly(methacrylic acid - co-2-hydroxyethyl methacrylate)

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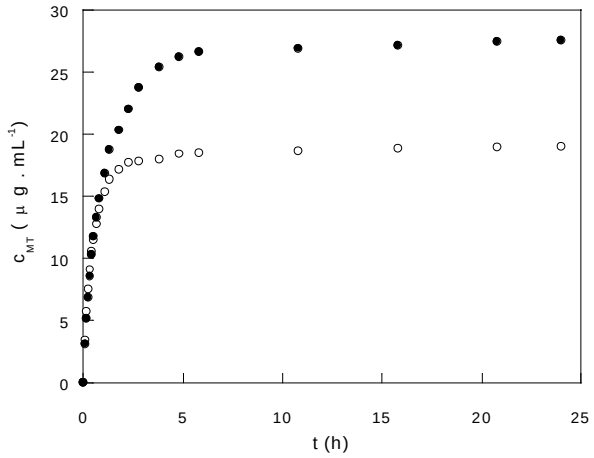
This work describes the swelling behaviour of methacrylic acid (MAA) and 2-hydroxyethyl methacrylate (HEMA) copolymers. Many commercial soft contact lenses are based on HEMA and monomers such as acrylic or methacrylic acid hydrogels. Dry hydrogels, i.e. xerogels, have the ability of absorbing very large volumes of water (i.e. swelling) whilst retaining some physical integrity. Hydrogels have been extensively used as controlled delivery devices for a number of drugs. Therefore, contact lenses could be loaded with therapeutic agents during the swelling process that could then be delivered directly to the eye during the normal use of the contact lenses. Timolol maleate is a non-selective beta-adrenergic receptor blocking agent which is a common treatment for glaucoma. Timolol maleate was selected as model drug and its release profile from HEMA/MAA hydrogels was also investigated.

The copolymers were prepared by free-radical copolymerization in water at 60.0 ± 0.1 ºC for 24 hours. The mixtures were poured into glass tubes and BIS (0.25 wt%) and KPS (1.0 wt%) were added. Nitrogen was bubbled through the mixture for 10 min. to remove dissolved oxygen. The resultant hydrogel rods were washed for 15 days to remove any unreacted materials, finely sliced, dry at room conditions for 24 hours and finally placed in a vacuum oven at 25ºC until constant weight. The dry disks (xerogels) were polished to achieve a smooth and uniform surface of 1.00 ± 0.05 mm thickness. Dynamic swelling studies were performed gravimetrically by placing pre-weighed xerogel disks in 10 mL of PBS at pH 1.0, 4.0, 7.4 and 8.5 at 37 ºC.

Table 1. Maximum water content W∞

	W_∞ in PBS solutions		
Samples	**MAA (wt%)**	**pH = 7.4**	**pH = 8.5**
M_1	0	1.14	3.93
M_2	10	2.21	8.09
M_3	30	5.46	10.69
M_4	50	7.96	12.83
M_5	70	9.6	14.86
M_6	90	13.12	16.23
M_7	100	16.36	19.27

Polymer - drug conjugate was prepared by adding 0.2 mL of a 5.0 $mg.mL^{-1}$ timolol maleate solution to the xerogel (triplicates) until complete absorption. Release experiments were performed by placing the polymer-drug conjugate into pyrex glass tubes with 10 mL of PBS at pH 7.4 at 37 ºC. UV analyses were carried out at 294 nm using a Secoman S 1000 spectrophotometer. The system was calibrated with timolol maleate solutions. Concentration of timolol maleate in solution was determined in aliquots of the swelling medium taken at time intervals. The release studies were carried out for 24 hours.



The effect of hydrogel composition on the release of timolol maleate was investigated. Two extreme compositions were selected for this particular study, i.e. M_1 and M_7 (see Table 1). The figure shows the release profile of timolol maleate for this two hydrogels (see Table 2), in PBS pH = 7.4 at 37°C, conditions very similar to those found *in vivo* in the tear fluid.. Table 2 summarises the weight percentage of drug delivered over a 24 hours period.

Table 2. Timolol maleate released after 24 hours at pH = 7.4 and 37 ºC

Samples	Timolol maleate released (wt%)
PHEMA (○)	38.00 ± 0.01
PMAA (●)	56.00 ± 0.02

The kinetic treatment of the early stages of the delivery process can be described using Fick´s second law:

$$\frac{M_t}{M_\infty} = 4\sqrt{\frac{D_{iL}t}{\pi l^2}}$$

where, M_t is the drug delivered at time t, M_∞ the total drug in the hydrogel, $D_{i,L}$ is the diffusion coefficient in the early stages of the swelling, t time and l the initial thickness of the sample. The following equation was proposed by Fick to describe the diffusion process from thin films at long release times

$$\ln\left(\frac{M_\infty - M_t}{M_\infty}\right) = \ln\frac{8}{\pi^2} - \frac{\pi^2 Dt}{l^2}$$

where M_t is the delivered drug at time t, M_∞ is the total drug in the hydrogel, $D_{f,L}$ is the diffusion coefficient at advanced stages of the delivery process, t time and l the final thickness of the sample.

Table 3. Diffusion coefficients of timolol maleate at pH = 7.4 and 37 ºC

Samples	D_{iL} x 10^7 (cm^2 sec^{-1})	D_{fL} x 10^7 (cm^2 sec^{-1})
PHEMA	0.53 ± 0.02	1.76 ± 0.02
PMAA	0.57 ± 0.01	3.67 ± 0.01

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