ACRYLATES AND METHYLCELLULOSE BASED HYDROGELS. SYNTHESIS, SWELLING PROPERTIES AND APPLICATIONS TO INCLUSION AND CONTROLLED RELEASE OF BIOACTIVE MATTERS

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This manuscript is presented to celebrate the 50th anniversary of Cellulose Chemistry and Technology since its foundation by Prof. Cristofor I. Simionescu and other famous chemists in the field of wood and cellulose chemistry.

Polymeric networks with semi-interpenetrated structure (semi-IPN) have been obtained by crosslinked polymerization of 2-hydroxyethyl methacrylate, acrylic acid and triethylene glycol dimethacrylate, in the presence of methylcellulose. FTIR data confirmed the network formation and indicated strong interactions between the hydrophilic groups of the formed synthetic matrix and methylcellulose. Thermal analysis indicated that single phase materials were obtained with a Tg situated around 125 °C. The kinetics of swelling revealed a non-Fickian diffusion, the values for the diffusional coefficient *n* suggesting that the penetration rate of buffer molecules into the hydrogels and the polymeric network relaxation were comparable; the anomalous behaviour was favoured by the presence of the methylcellulose in the semi-IPN network. The maximal degree of swelling was reached for the hydrogels with increased content of methylcellulose. Carteolol hydrochloride, a beta-adrenoceptor blocking agent was included by diffusion into the hydrogels and drug release studies were performed in a buffered solution. The release profile varied according to the content of methylcellulose, monomers and crosslinker. The presence of methylcellulose and acrylic acid determined the release of the drug due to the interactions between the ionized species. The physico-chemical characteristics and *in vitro* release studies indicate that the prepared hydrogels are promising materials for ophthalmic drug delivery applications.

Keywords: hydrogels, acrylic monomers, methylcellulose, semi-IPN, swelling, drug release

INTRODUCTION

The active control of the site and kinetics of drug release, as well as the improvement of stability prior to delivery of active matter to the target are common aims in the design of efficient drug delivery systems. Moreover, the biocompatibility and biodegradability are properties of major interest for biomedical applications.[1] Among the different systems able to meet such conditions are the interpenetrating networks (IPN). An interpenetrating network is a combination of two polymers exhibiting various characteristics. As a difference from the

copolymerization, which results in a new chemical entity and does not ensure the maintenance of the properties of each polymer, the interpenetration of crosslinked polymers leads to materials that combine the features of both components in a tunable way.[2] For example, when a hydrophilic gelling polymer is interpenetrated with a relatively hydrophobic gelling polymer, the resultant IPN hydrogel is expected to have an improved capability of immobilizing a drug. This would open up new avenues to using IPN in designing novel drug release systems.[3] Semi-interpenetrated hydrogels (semi-IPN) are obtained from tridimensional networks in which a linear polymer is introduced.[4]

Hydrogels are three-dimensional networks that can take up very large amounts of water.[5] They are materials that swell and hold high amounts of water without losing their shape.[6] Polymers and copolymers of acrylamide (Am) are the most commonly used hydrogels and they have been widely studied. Polyacrylamide (PAM) hydrogels have found applications in water purification and irrigation, in improving soil texture, in pesticide formulations to limit spray drift and in medical applications.[7-9] They are also used in molecular biology laboratories as matrices for separating nucleic acid components during DNA sequence analysis and protein identification.[10] PAM hydrogels can absorb relatively high amounts of water; furthermore, their swelling capacity is not very sensitive to pH or electrolytes.[11,12] For some applications, high water absorption capacity is desired because it increases the permeability and the biocompatibility of the hydrogels.[13-16]

Crosslinked poly(2-hydroxy-ethyl methacrylate) [p(HEMA)] hydrogels have been extensively studied in the biomedical and pharmaceutical fields for a variety of applications, including soft contact lenses, tissue engineering and drug delivery devices.[17-20] Due to its mechanical stability, high refractive index and oxygen permeability, crosslinked p(HEMA) has been effective in the ophthalmology field. Swollen p(HEMA) has high light transmission capability in the visible and near-visible region. The water content can be regulated by copolymerization with hydrophilic/hydrophobic monomers or by mixing with natural or synthetic polymers. The balance between hydrophilic/hydrophobic groups and the length between links are designing the swelling properties and interaction with bioactives.[21,22]

Methylcellulose was used as hydrophilic polymer.[23,24] As it is a derivative of a natural polymer, it presents interest due to its biodegradability and biocompatibility.[25] This allows to prepare hydrogels for ophthalmic applications.

The paper reports on the synthesis and the physico-chemical properties of hydrogels based on poly(2-hydroxyethyl methacrylate-co-acrylic acid) and methylcellulose, and the *in vitro* evaluation of the obtained hydrogels as ophthalmic drug delivery systems.

EXPERIMENTAL

Materials

Methylcellulose (molecular weight of 88,000 g/mol, with a methoxy substitution between 27.5 and 31.5% (weight)), monomers and initiating agents were purchased from Sigma Aldrich. Monomers, as 2-hydroxyethyl methacrylate (HEMA) and acrylic acid (AA), were purified by passing them through an inhibitor removal column. Triethyleneglycol dimethacrylate (TEGDMA) was used as a crosslinker, and ammonium persulfate (APS), as well as tetramethylethylenediamine (TEMED), as initiators.

Phosphate buffer solutions (PBS) were prepared from citric acid and disodium phosphate, according to a procedure reported in the literature. The carteolol hydrochloride (a non-selective beta-adrenoceptor) was used as an ophthalmic solution USP, 1% (Bausch & Lomb Incorporated) to be loaded into the hydrogel. The drug had a pKa of 9.74,[26] and its chemical structure is given in Fig. 1.

Preparation of hydrogels

Semi-IPN hydrogel networks of poly(2-hydroxyethyl methacrylate-co-acrylic acid) (HEMA-co-AA) - methylcellulose (MC) were synthesized by crosslinking polymerization of the monomers with triethyleneglycol dimethacrylate (TEGDMA) in the presence of methylcellulose, ammonium persulfate (APS) and tetramethylethylenediamine (TEMED) as initiator systems.

Methylcellulose was added to a stirred aqueous solution of APS (2%, w/w) and homogeneously mixed for a period of time ranging between 10 min and 40 min, depending on the system's viscosity (the mixing time increases with the percent of MC). The addition of the monomers (HEMA and AA) and crosslinking agents TEGDMA and TEMED was consecutively followed by strong mixing of the blend. The resulting compound was poured into glass moulds (50 mm × 50 mm × 0.5 mm) and kept at a temperature of 50 °C for 12 hours.

The formed hydrogels were washed repeatedly in bi-distilled water for 96 hours. The hydrogel was dried at 37 °C, for 24 hours in vacuum atmosphere and stored in a calcium carbonate desiccator.

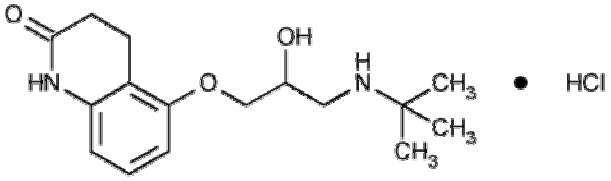

Figure 1: Chemical structure of carteolol hydrochloride

Characterisation of hydrogels

The synthesised hydrogels were analysed by Fourier transform infrared spectroscopy, differential scanning calorimetry (DSC) and their morphology by scanning electronic microscopy (SEM). The swelling properties of the synthesized materials were evaluated in buffered solutions and the equilibrium degree of swelling, *SD*eq (%, weight), was calculated. *In vitro* drug release studies were performed by using a nonselective beta-adrenoceptor (carteolol hydrochloride); the loading and release kinetics were spectrophotometrically obtained. Blank experiments, using drug-free hydrogels, confirmed that there was no interfering background absorption.

Fourier Transform Infrared spectroscopy (FTIR)

FTIR spectra were obtained using a Nicolet Avatar 360 FT-IR Spectrometer in the range of 4000 cm^{-1} to 675 cm^{-1} in the ATR mode: mono reflection device, using a diamond crystal with an incidence angle of 45°.

Scanning Electron Microscopy

Morphology analysis was carried out using scanning electron microscopy (SEM VEGA TESCAN) at 30 kV. The samples were fixed to the substrate and coated by vacuum sputtering an Au/Pa layer (thickness of 3 nm) prior to placing them into the SEM chamber. The analysis provided useful images for better detection of changes in microscale morphology.

Differential Scanning Calorimetry

About 5 mg of each dried hydrogel was analyzed in a Perkin Elmer Differential Scanning Calorimeter (Pyris Diamond DSC, Perkin Elmer, USA). The runs were performed at a heating rate of 10 °C/min, in nitrogen atmosphere with a flow of 20 mL/min.

Swelling properties

The swelling ratio of the hydrogels was studied in a buffer solution (pH 7.4), using the gravimetric method. The dried samples of known weights were soaked in the buffer solution for 24 h at 37°C. At specified time periods they were taken out, blotted carefully (without pressing hard) to remove the surface-adhered solution, weighed and then re-immersed into the aqueous medium.

For the swelling behaviour, the mass equilibrium degree of swelling, SD_{eq} (%), and the kinetics of swelling were investigated using the following relations:

$$SD = \frac{m - m_0}{m_0} \cdot 100 = \frac{m_1}{m_0} \cdot 100 \quad (1)$$

$$F = \frac{W_t}{W_\infty} = k \cdot t^n \quad (2)$$

where m_0 is the dry initial sample weight (g), m is the sample weight at swelling equilibrium (g) at time t (min), F denotes the amount of solvent fraction at time t according to Fick's law, k is the swelling rate constant; n is the swelling exponent; and W_t and W_∞ are the water intakes at time t and equilibrium time, respectively.[27]

Drug loading and drug release studies

A quantity of 0.5 g of dry hydrogel was swelled to equilibrium in distilled water and then kept in 1% (w/vol) carteolol hydrochloride aqueous solution. Hydrogels were maintained in the drug solution for 72 hours, until equilibrium drug diffusion was obtained. After this sequence, the loaded hydrogels were dried at 30 °C, for 48 hours, under vacuum. The quantity of loaded drug was determined spectrophotometrically (λ = 252 nm) as the difference between the initial amount of drug and the one remaining in the supernatant.

The *in vitro* release profile of carteolol hydrochloride was obtained spectrophotometrically: a drug-loaded hydrogel was placed into 25 ml phosphate buffer solution and the time-profile of drug release was determined by observing the absorption at 252 nm. Calibration was performed using a series of phosphate buffer solutions containing known amounts of carteolol hydrochloride (concentrations ranging between 0.001-0.02%, w/w). Blank experiments, using polymer-only films, confirmed that the hydrogels did not contribute to the 252 nm absorption.

Experimental program

An experimental program with 3 variables (MC ratio, HEMA/AA (mol/mol) and TEGDMA concentration (%)), (Table 1) was used to study the composition influence on the characteristics of the hydrogels. The range of the investigated variables and the predicted values for MC (%), HEMA/AA (mol/mol) and TEGDMA (%) are presented in Table 2.

The mathematical model from equation 3 was used to correlate the parameters with properties.

$$Y = a_0 + \sum_{i=1}^{m} a_i x_i - \sum_{\substack{i=1 \\ j>1}}^{m-1} a_{ij} x_1 x_j + \sum_{i=1}^{m} a_{ij} x_i^2 - \ldots \quad (3)$$

where a_i – regression coefficients and x_i, x_j – input variables, previously described, which influence the response variable Y (SD). These functions were estimated and the regression coefficients were determined (Table 3).

RESULTS AND DISCUSSION

Synthesis of hydrogels

Semi-interpenetrated networks were achieved with a network of acrylic monomers (acrylic acid, 2-hydrohyethylacrylate and triethyleneglycol dimethacrylate), and with methylcellulose included into this network. The schematic representation of the semi-IPN hydrogel is given in Fig. 2.

Strong hydrogels with comparable properties have been obtained. In addition, several differences in properties were observed, as detailed below.

FTIR results

The pure MC film had absorption bands related to OH stretching at 3444 cm^{-1}, CH_3 stretching on the anhydroglucose unit at 2926 cm^{-1}, CO carbonyl stretching in the anhydroglucose unit of the cellulose at 1637 cm^{-1}, COH in-plane bend at 1460 cm^{-1}, CH_3 symmetric bend (umbrella mode) at 1381 cm^{-1}, CO stretching from the asymmetric oxygen bridge at 1062 cm^{-1}, and ring stretching at 947 cm^{-1}. The data are in agreement with those reported in the literature.[28]

Table 1
Codification of the parameters

	Coding	Variation of parameters
Percent of methylcellulose in the monomer mixture (% MC)	X_1	5-50%
HEMA/AA ratio	X_2	4-7 mol/mol
Percent of TEGDMA in the monomer mixture	X_3	3-7%

Table 2
Experimental matrix

Sample	MC (%)		HEMA/AA (mol/mol)		TEGDMA (%)		Swelling degree (%)
	Code	Real	Code	Real	Code	Real	
HG1	-1	14.12	-1	4.61	-1	3.81	259
HG2	1	40.87	-1	4.61	-1	3.81	423.8
HG3	-1	14.12	1	6.39	-1	3.81	239.5
HG4	1	40.87	1	6.39	-1	3.81	348.9
HG5	-1	14.12	-1	4.61	1	6.19	222.3
HG6	1	40.87	-1	4.61	1	6.19	383.5
HG7	-1	14.12	1	6.39	1	6.19	179.3
HG8	1	40.87	1	6.39	1	6.19	305.7
HG9	-1.682	5	0	5.5	0	5	170.6
HG10	1.682	50	0	5.5	0	5	428.7
HG11	0	27.5	-1.682	4	0	5	326.2
HG12	0	27.5	1.682	7	0	5	258.0
HG13	0	27.5	0	5.5	-1.682	3	314.7
HG14	0	27.5	0	5.5	1.682	7	244.8
HG15	0	27.5	0	5.5	0	5	239.2
HG16	0	27.5	0	5.5	0	5	236.3
HG17	0	27.5	0	5.5	0	5	235.1
HG18	0	27.5	0	5.5	0	5	244.9
HG19	0	27.5	0	5.5	0	5	237.1
HG20	0	27.5	0	5.5	0	5	238.75

Table 3
Regression, correlation coefficients and asymmetric errors

	a_0	a_1	a_2	a_3	a_4	a_5	a_6	a_7	a_8	a_9	COR	ASE
Swelling degree	238.51	72.91	-24.16	-21.81	21.93	-11.27	1.65	19.26	-3.28	14.90	0.9998	351.2165

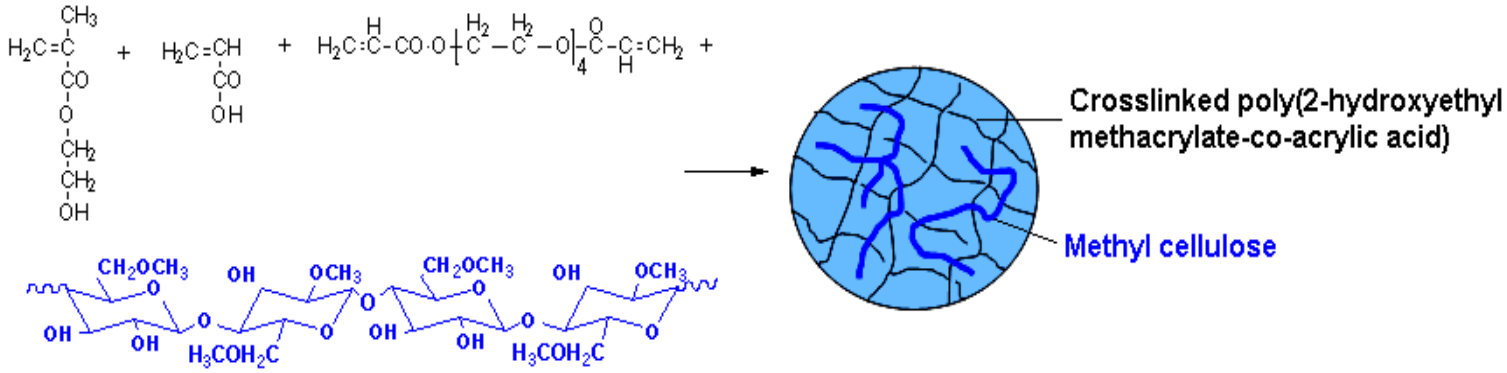

Figure 2: Synthesis of semi-IPN hydrogels

FTIR spectrometric analysis of the polyHEMA-co-AA-MC hydrogels showed an absorption characteristic of both synthetic and natural components: the bands typical of the hydroxyl group are located at 3444 cm^{-1}, 1394.5 cm^{-1} and 1074.35 cm^{-1}, of ether – at 1159.2 cm^{-1}; of carboxylic groups – at 2953.0 cm^{-1}; and of -CH_2, -CH_3 at 1728.2-1485.2 cm^{-1} and 2889.4 cm^{-1}.

DSC data

The thermograms in Fig. 4 show that all semi-IPNs exhibited the same Tg (120-125 °C), which suggests a homogeneous phase morphology characteristic of a semi-IPN. This temperature corresponds to copolymers of acrylic acid and it demonstrates the presence of longer sequences of polymerized acrylic acid with HEMA. Small changes in the Tg values are attributed to the water molecules, which bind to methylcellulose and HEMA regions and act as plasticizer, which influences the reduction in Tg for the higher methylcellulose content hydrogel.

In this experiment, the detection of Tg was hindered because the temperature range was limited to the upper range of 200 °C based upon the observation of Szczesniak *et al.*,[29] who reported cellulose degradation and changes in colour from white to yellow-brown above 180 °C.

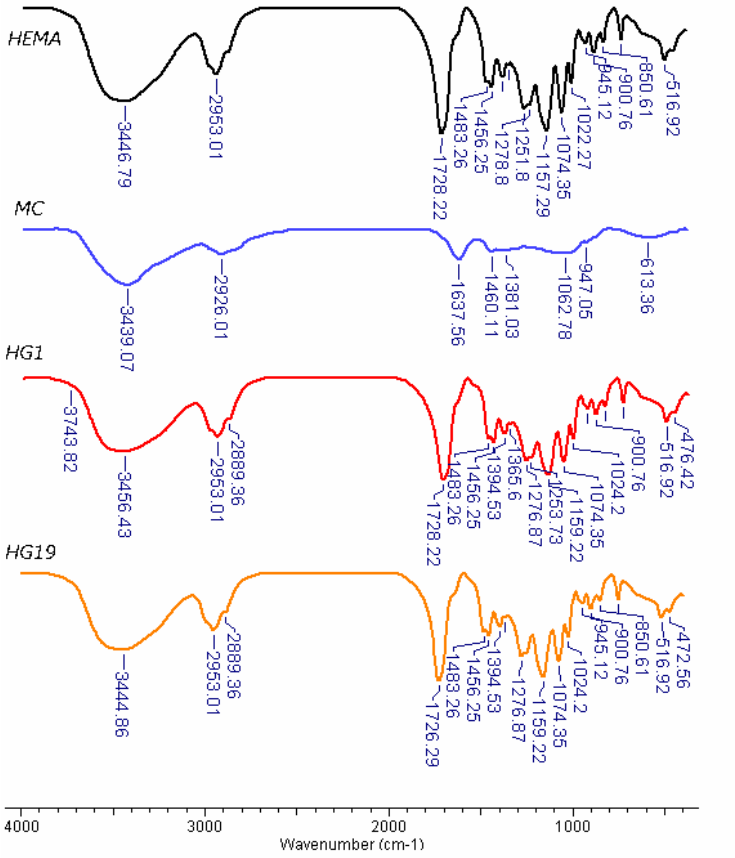

Figure 3: FTIR spectra of HEMA, MC, HG1 (5% MC, HEMA:AA 4:1, 3% TEGDMA) and HG19 (50% MC, HEMA:AA 4:1, 3% TEGDMA)

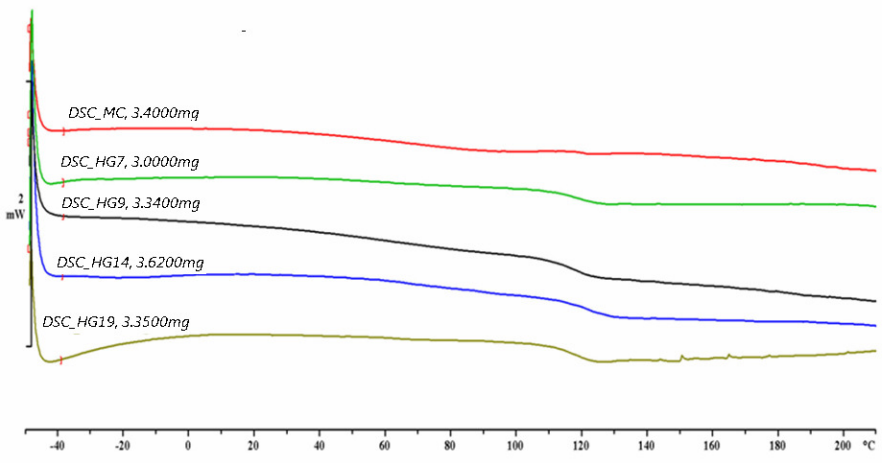

Figure 4: DSC data of MC, HG7, HG9, HG14 and HG19

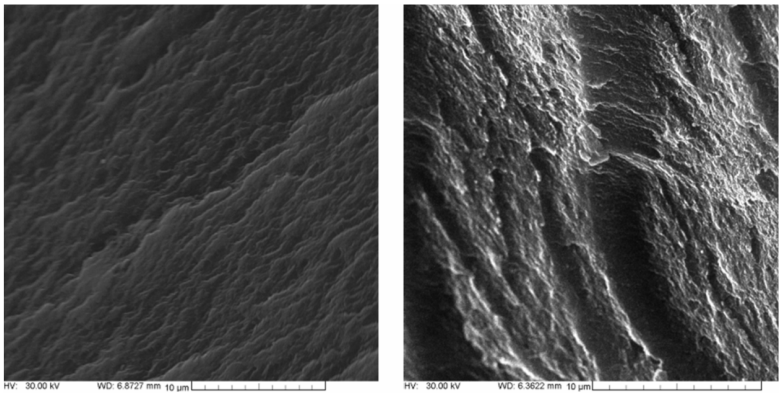

Figure 5: SEM data for HG9 (25% MC, HEMA:AA 4:1, 3% TEGDA) (left) and HG19 (50% MC, HEMA:AA 4:1, 3% TEGDA (right)

Hydrogel surface morphology

Fig. 5 shows the SEM micrographs of hydrogels with different compositions. In general, SEM morphology results are not taken as direct evidence of polymer miscibility, owing to the limit of the scale of phase resolution. As can be seen in Fig. 5, the hydrogels have homogeneous morphology, which confirms the miscibility of the polymers. The content of methylcellulose has a great significance; the hydrogels with 50% MC present a more non-uniform surface, compared to those with lower content of MC in the composition (25%).

Swelling studies

The swelling behaviour of the hydrogels has been studied over a range of pH values (2.4 to 7.4); the effect of the composition on the kinetics of swelling (*SD*) at various pH values is summarised in Fig. 6. The swelling characteristics of hydrogels in biological media are very important for their application as drug delivery systems, especially for drug inclusion/release through diffusional processes.

After immersion of the hydrogels into the buffered solution of pH 2.4, it was observed that the hydrogels with the same amount of polysaccharide, but with different molar ratio of monomers and amount of crosslinking agent, achieved a constant degree of swelling after 40-80 minutes. The hydrogel with the highest content of methylcellulose continued to swell up to 300 minutes, as the polysaccharides acting as a relaxing component for the polymeric network allowed the absorption of larger quantities of buffer into the semi-IPN matrix (MC is very hydrophilic). The behaviour remarked in buffers of pH 5 is close to the results obtained for swelling in a solution of pH 2.4, except the slightly increased values for the swelling degree. The effect is attributed to the carboxylic groups from acrylic acid, which are switched to the

ionized state (the pKa of acrylic acid is 4.25).[30] The ionization of the carboxylic groups has a significant contribution to the behaviour of the hydrogels at pH 7.4 and balances the effect of the polysaccharide relaxation.

Fig. 7 presents the variation of the speed of swelling versus time for the hydrogels analyzed; the curves were obtained by derivatization of the kinetic curves in Fig. 6 (pH 7.4) at various intervals of the swelling process and the highest values for the speed of swelling was observed for the hydrogel with increased content of polysaccharide.

Swelling is a continuous process of transition from an unsolvated state to the relaxed regions of the hydrogels. When a hydrogel is brought into contact with water, water diffuses into the hydrogel and the hydrogel swells. The swelling may be described by Fickian transport with a concentration dependent diffusion coefficient.[31] The reorientation of polymeric molecules can lead to a wide variety of anomalous effects for the swelling experiments.

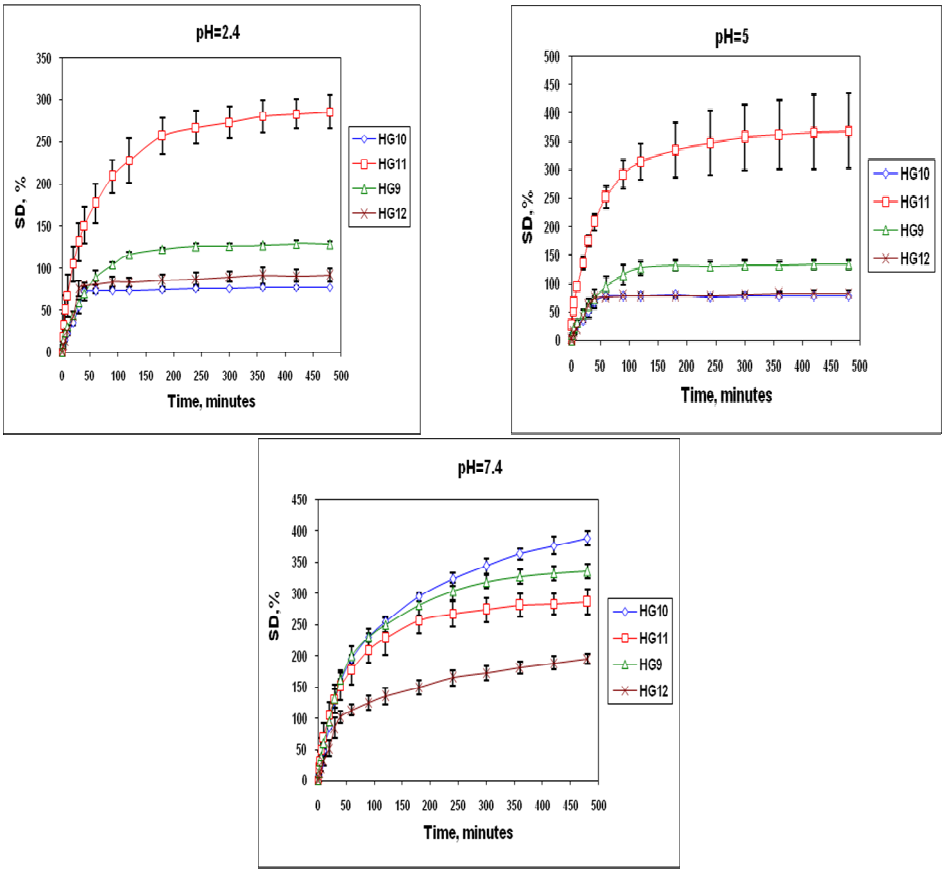

Figure 6: Swelling kinetics of hydrogels at various pH values

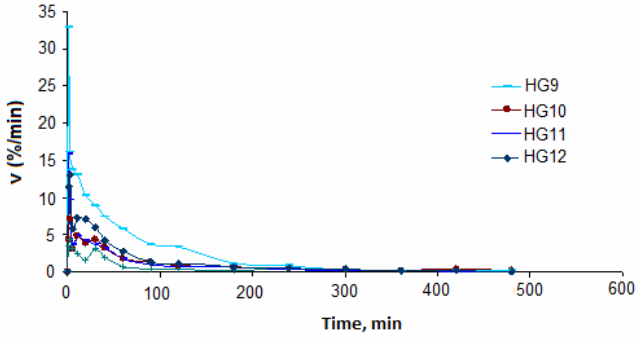

Figure 7: Variation in swelling rate versus time for hydrogels

Table 4
Swelling parameters for hydrogels

Hydrogels	t_{eq} (min)	n	v^* (%/min)
HG5	300	0.539	11.48
HG9	300	0.544	15.854
HG10	300	0.654	4.386
HG11	300	0.613	32.96
HG12	300	0.610	3.47

*v is the initial swelling rate

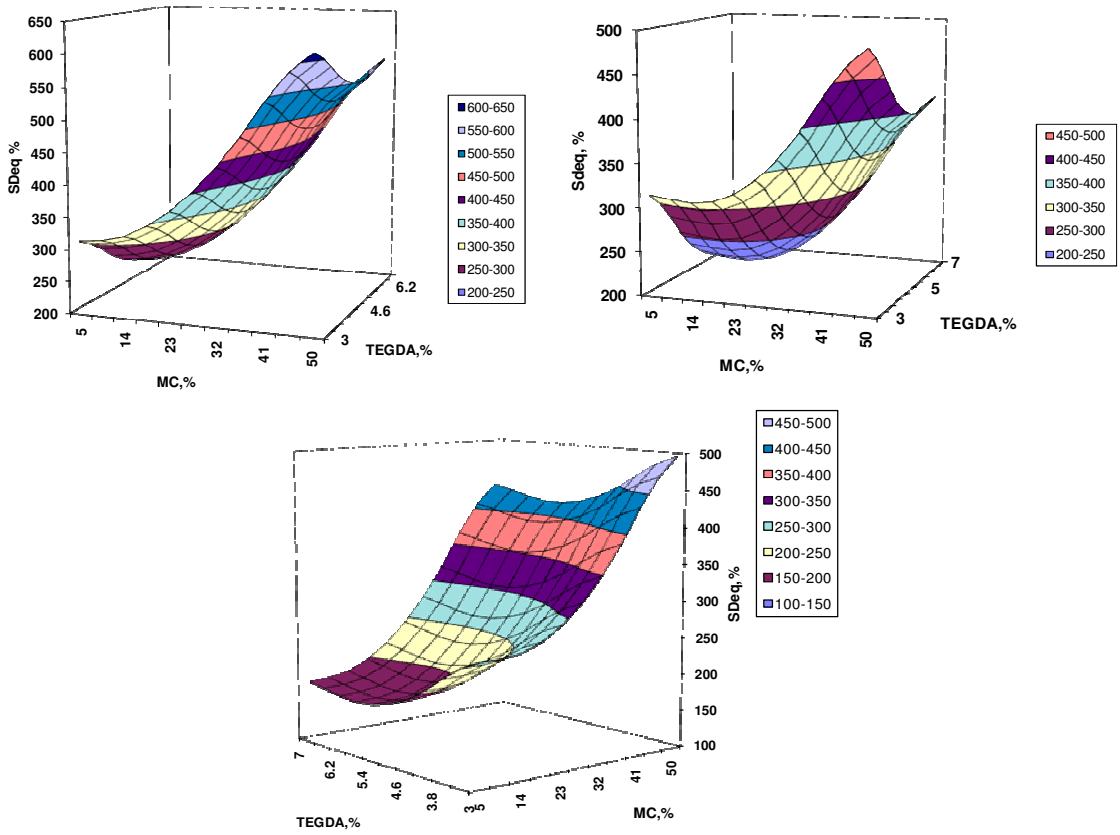

Figure 8: Mass equilibrium degree of swelling, SD_{eq} (%) as a function of MC and TEGDA, at pH 7.4 and various ratios HEMA/AA: a) HEMA/AA=4, b) HEMA/AA=5.5 and c) HEMA/AA=7

The values of the diffusional coefficient (*n* from equation 2) of the buffer with pH = 7.4 for the prepared hydrogels are shown in Table 4.

Depending on the relative rates of diffusion (solvent and polymer relaxation), three classes of diffusion mechanisms are distinguished:[31] 1) Case I or Fickian diffusion, in which the rate of diffusion is much lower than that of relaxation (n = 0.50), 2) Case II diffusion, in which the diffusion is very rapid compared with the relaxation processes (n = 1), and 3) Non-Fickian or anomalous diffusion, which occurs when the diffusion and relaxation rates are comparable (0.50 < n < 1).

Analysing the values for the coefficient of diffusion, it can be concluded that the swelling process is non-Fickian, *n* showing values between 0.539-0.654. These results indicate that the penetration rate of solvent molecules into the meshes of the network and the polymeric network relaxation are comparable. The anomalous behaviour is favoured by the presence of the

methylcellulose in the semi-IPN network; the closest values to 0.5 were observed for the hydrogels with low content of polysaccharide.

The influence of hydrogel composition on the equilibrium swelling degree (SD_{eq}), at pH 7.4, is presented in Fig. 8. The maximal swelling degree increases with methylcellulose content, at constant acrylic monomer content, in relation with the increased hydrophilicity of the network, due to the presence of the polysaccharide. Compared to HEMA, AA induces an increased swelling behaviour, as the maximum values of SD_{eq} were observed for the highest content of AA. Both monomers are hydrophilic, but at pH 7.4, HEMA acts as hydrogen bond generator and AA as ionized monomer. At pH 7.4, a larger concentration of carboxyl groups inside the hydrogels are ionized ($–COO^-$). Due to the increasing density of electrostatic repulsion forces between groups with the same ionic charge, the swelling capacity of the hydrogels reached relatively high values: a swelling osmotic pressure was formed inside the hydrogel. The data reveal that this behavior becomes more pronounced as the crosslinking density of the hydrogels is decreased, presumably, because of the reduced mobility of the methylcellulose chains.

Drug loading and drug release

With the aim to investigate the ability of the prepared methylcellulose/poly(HEMA-AA) hydrogels to act as vehicles for the controlled release of actives, carteolol hydrochloride was incorporated in the system and its cumulative discharged amount was monitored spectrophotometrically. The kinetics of drug loading into the hydrogels is presented in Fig. 9. From the graphs of inclusion, it can be noted that for all hydrogels an initially fast inclusion (up to 300 min) is produced, followed by a slower loading (up to 1000 min), the final concentration of the drug in the aqueous solution having become constant over 1000 min.

Fig. 10 shows the kinetic curves of carteolol hydrochloride release from the hydrogels and the mechanism of drug diffusion.

The kinetics of drug release was measured at 37 °C in a buffered solution medium at pH 7.4, over 24 hours, the time period when the highest values for the degree of swelling of the hydrogel were recorded. An increased amount of the drug was released from the hydrogel with the lowest content of methylcellulose (HG12). It is estimated that the ionized carboxylic groups from acrylic acid had a contribution to the drug retention in the polymeric matrix. Carteolol hydrochloride is a non-selective beta-adrenoceptor blocking agent, extensively used in ophthalmic applications, with a pKa = 9.74 and good water and aqueous solution solubility. At pH 7.4, carteolol hydrochloride is able to interact with the functional groups from the polysaccharide and acrylic acid.

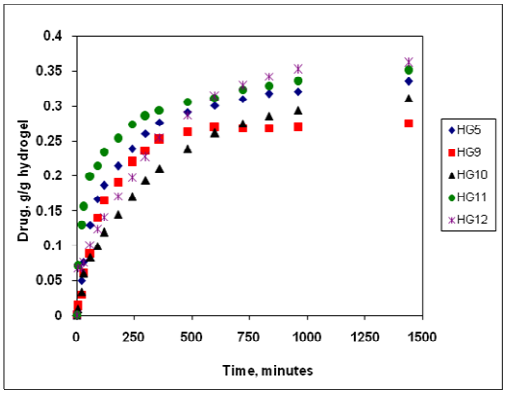

Figure 9: Kinetics of drug loading into hydrogels

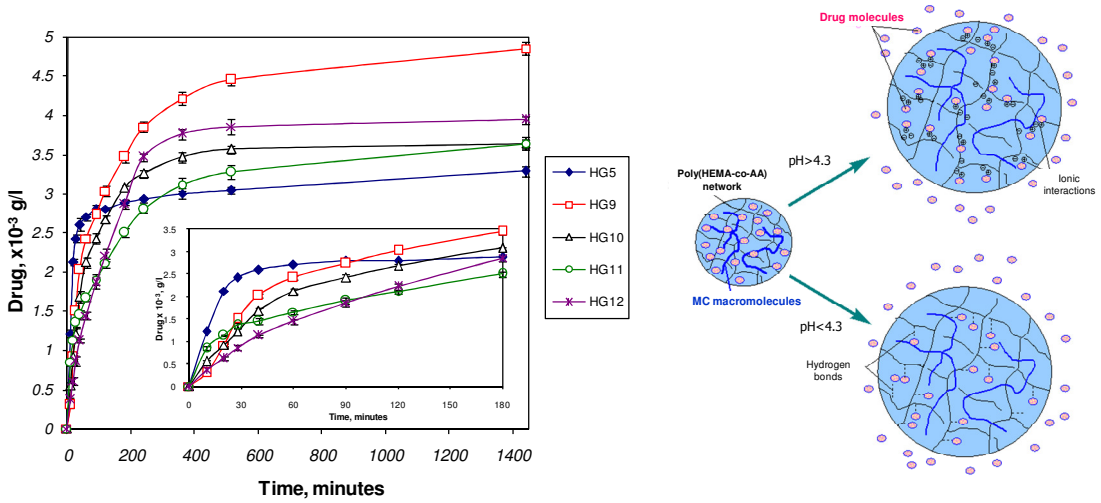

Figure 10: Kinetics of drug release from hydrogels based on methylcellulose and crosslinked poly(HEMA-AA)

Therefore, the drug release from the hydrogels involves:

-drug interaction with the carboxyl functional groups from acrylic acid, which delay drug release;

-molecular diffusion of the carteolol hydrochloride from the crosslinked network, the lower the crosslinking degree, the quicker the process.

The hydrogels release carteolol hydrochloride for more than 9 hours, which makes them very good candidates for controlled release in ophthalmology. This controlled release may be improved using liposomes to avoid the "burst effect" usually observed with such systems.[33]

CONCLUSION

Semi-interpenetrated polymeric networks have been obtained by crosslinked polymerization of monomers (2-hydroxyethyl methacrylate, acrylic acid and crosslinker triethyleneglycol dimethacrylate) in the presence of methylcellulose, and their application as controlled release systems for ophthalmic drugs was tested. FTIR data showed strong interactions between the hydrophilic groups of the poly(2-hydroxyethyl methacrylate-co-acrylic acid), and methylcellulose. DSC analysis enabled the observation of a single Tg at around 125 °C, for all hydrogels, indicating a single phase material. The degree of swelling as measured in aqueous solutions revealed that the hydrogels swelled relatively quickly in acidic medium, and slowly at pH 7.4 (equilibrium is established in more than 8 hours). The maximal degree of swelling is reached for the hydrogels with an increased content of methylcellulose, at constant acrylic monomer proportions. Carteolol hydrochloride, a beta-adrenoceptor blocking agent, was included by diffusion, and drug release studies were performed in a buffered solution for 24 hours at body temperature (37 °C). The release profile varied according to the nature of the matrix. Analysis results have shown that the presence of methylcellulose and acrylic acid delay the release of the drug due to interactions of the ionized species from the drug and the polymer. The *in vitro* release profile indicates that the synthesized hydrogels may be used as controlled release systems for ophthalmic applications.

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