N,N-DIMETHYLACRYLAMIDE HYDROGELS FOR CONTROLLED DRUG DELIVERY. INFLUENCE OF NETWORK STRUCTURE AND DRUG SOLUBILITY ON THE LOAD AND RELEASE MECHANISMS

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***Abstract*—The aim of the present work was to synthesize sustained-release hydrogels based on *N,N*-dimethylacrylamide (DMA) to study the effect of the polymer matrix structure and the solubility of drugs on the load and release mechanisms. A series of crosslinked DMA hydrogels were synthesized with different monomer concentration and crosslinker to monomer ratio by free radical aqueous solution polymerization at 37ºC using *N,N*-methylen-bis-acrylamide as crosslinking agent. The effect of total monomer concentration and degree of crosslinking on the water absorption, glass transition temperature values, mechanical properties, and load/release of different drugs was studied. Main results showed that: a) the structure of the network, obtained by varying the monomer and crosslinking agent concentration, is a factor that governs the chemical and physical properties of the hydrogel (water absorption, glass transition temperature, storage and loss moduli, network parameters), b) the rate and amount of drug released from swellable hydrogels depend on both the degree of hydrogel crosslinking and the water solubility of the drug. In all cases, as the concentration of the crosslinker agent increased, the swelling capacity of the hydrogels was reduced and drugs with high solubility in water were more easily released, probably due to their greater affinity for the medium.**

***Keywords*—*N,N*-dimethylacrylamide hydrogels; Swelling kinetics; Mechanical properties; Drug release.**

I. INTRODUCTION

Hydrogels are three-dimensional hydrophilic polymer networks that swell but do not dissolve when put in contact with water due to the presence of chemical or physical crosslinks, which provide the network structure and physical integrity (Lowman and Peppas, 1999). Since the development of the hydrogel of poly(2-hydroxethyl methacrylate) in 1960s, hydrogels have been employed in a wide range of biomedical and pharmaceutical applications due to their high water content and, hence, excellent biocompatibility (De Rossi *et al.*, 1991; Lowman and Peppas, 1999; Ende and Mikos, 1997; De Loos *et al.*, 2005). Some applications of hydrogels include contact lenses, biosensors, sutures, dental materials, and controlled drug delivery devices (Caló and Khutoryanskiy, 2015). The properties of hydrogels are strongly dependent on the chemical nature of the polymer as well as on the structure and morphology of the network. The properties of hydrogels mostly arise from their cross-linked structure, which is influenced by the nature and concentration of both the monomers and the employed crosslinker. To understand the structure of the gel, the swelling behavior is normally studied (Kim and Peppas, 2002). Then, the hydrogel can be manipulated to enable the diffusion of drug in a desired way (Gander *et al.*, 1989).

Poly(*N,N*-dimethylacrylamide) (PDMA) is a useful hydrophilic biocompatible polymer. Linear polymers, interpenetrating polymer networks, and blends based on PDMA find numerous applications in molecular biology, DNA sequencing, medical and pharmaceutical fields including the delivery of drugs and the production of contact lenses (Algi and Okay, 2014). However, the controlled synthesis of PDMA hydrogels, its effect on the application properties and the materials characterization have been poorly studied. In the current investigation, covalently crosslinked *N,N*-dimethylacrylamide (DMA) hydrogels are prepared by aqueous solution free radical polymerization at 37ºC using *N,N'*-methylene-bis-acrylamide (BIS) as crosslinking agent, and potassium persulfate/*N, N, N', N'*-tetramethylethylenediamine (KPS/-TEMED) redox couple as initiation system. The aim of this work is to synthesize sustained-release hydrogels to analyze the influence of i) the hydrogel structure, and ii) the drug solubility on the load and release behaviour. Ranitidine hydrochloride, Atenolol and Paracetamol were selected as model drugs, due to their different solubility in water.

II. MATERIALS AND METHODS

A. Synthesis of the Hydrogels

The monomer *N,N*-dimethylacrylamide (DMA), the crosslinker *N,N*-methylene-bis-acrylamide (BIS), and the redox initiator pair potassium persulfate/*N,N,N',N'*-tetramethylethylenediamine (KPS/TEMED), all from Sigma Aldrich, were used as received. Distilled and deionized water was used throughout the work.

The mass fraction of monomer in water was selected as 5, 10, 15 or 20 wt%, and the molar ratio crosslinker/monomer was varied from 0.5 to 6 mol% for each monomer concentration. The synthesis procedure first involved the dissolution of DMA, BIS and KPS in water, and then the addition of TEMED under stirring. Finally, the resulting solution was poured into syringes (12 mm in diameter). Free-radical polymerization proceeded then for 4 h at 37 ºC. Upon reaction completion, the produced

hydrogels were cut into disks and immersed in excess of water to wash out any residual monomers, initiator, and crosslinking agent. Then, the hydrogel samples were dried up to constant weight.

B. Characterization of the Hydrogels

Swelling and Structure

The swelling behavior of hydrogels was gravimetrically analyzed and their structure was observed by scanning electron microscopy (SEM) using a Zeiss (LEO) 1450VP equipment.

To the kinetics of swelling, completely dry hydrogels of known weight were placed in water (swelling solution) at room temperature. Swollen samples were periodically removed from the swelling solution, dried with filter paper for removing the excess of solution on the surface, accurately weighed, and placed again in the same swelling solution. The weight swelling ratio at any time t (SR); the equilibrium weight swelling ratio ($Q_{w,e}$); the equilibrium swelling ratio (SRe) and the equilibrium water content (EWC), were calculated through the following equations:

$$SR = W_t/W_d \quad (1)$$

$$Q_{w,e} = W_e/W_d \quad (2)$$

$$SRe = [(W_e - W_d)/W_d] \quad (3)$$

$$EWC = [(W_e - W_d)/W_e] \quad (4)$$

where W_t is the weight of the swollen hydrogels at time t, W_d is the weight of the dried hydrogels, and W_e denotes the weight of the gels at equilibrium swelling.

The water diffusion rate within the hydrogels was determined using Eq. (5), where M_∞ is the mass of water that diffuses into the matrix at the equilibrium, k is a constant associated with the network structure, and exponent n is a number related to the type of diffusion. This equation is applicable during the initial stages of swelling (<60%).

$$F = \frac{M_t}{M_\infty} = k \times t^n \quad (5)$$

The diffusion type (n) and k were calculated from the slope and intercept of the straight line, respectively, obtained from the plot of ln F *vs* ln t. The parameter n, can take different values: n=0.45 corresponds to Fickian-type diffusion (diffusion), 0.45< n<0.89 corresponds to non-Fickian diffusion (diffusion and relaxation), 0.89< n<1 responds to a diffusion type II (relaxation) and n>1 corresponds to a super type II (plasticization) (Peppas *et al.*, 2000; Primo *et al.*, 2015).

Determination of Network Parameters:

The more important parameters used to characterize network structure are the polymer volume fraction in the swollen state (ϕ), the polymer-solvent interaction parameter (χ), the molecular weight of the polymer chain between two neighboring crosslinks ($\overline{M}_c$), the crosslinking density (δ) and the corresponding mesh size (ξ). They were calculated by the swelling equilibrium method (Katime and Diaz de Apodaca, 2000; Lira *et al.*, 2009; Rao and Ha, 2009; Singhal *et al.*, 2009).

Table 1. Molecular weight and solubility in water of the employed drugs

Drug	Molecular Weight (g/mol)	Solubility in Water*
Atenolol	266.3	poorly soluble
Paracetamol	151.2	soluble
Ranitidine	350.9	very soluble

*solubility according to Convention of the United States Pharmacopoeia (USP)

Glass Transition of Xerogel

DSC was used to determine the Tg of the DMA hydrogels. Measurements were carried out using a DSC30 calorimeter from the Mettler TA3000 system. The sealed capsules were subjected to the following thermal treatment. A first heating run was realized from room temperature to 453 K with a linear heating rate of 20 K/min. Then, samples were immediately cooled up to 233 K with a cooling rate of 30 K/min, and finally a second heating run from 233 to 473 K was realized. The Tg values were determined from the inflection points of the thermograms obtained in the second heating runs.

Rheological Properties

The rheometer Anton PaarPhysica MCR 301 equiped with parallel plates of 8 mm diameter was used for rheological characterization. Hydrogels swollen to equilibrium were carefully deposited on the bottom plate of the rheometer and then the top plate was moved down and put in contact with the gel. Two types of measurements were carried out to each sample. The first one was a dynamic strain sweep (% strain) from 0.1% to 20% with a constant frequency (ω) equal to 10 s^{-1}, to determine the linear viscoelastic range (LVR) defined as the range where the storage modulus (G') and the loss modulus (G'') have a linear parallel behavior (Okay, 2000). The second type of measurements involved a dynamic frequency sweep between 0.1 and 400 s^{-1}, with a constant strain value, which was also carried out to obtain G', G'' and the damping factor (tan $\delta = G''/G'$) of the DMA hydrogels. The strain and deformation amplitude were selected to ensure that the oscillatory deformation was within the linear regime.

C. Drug Loading and Release

The synthesized hydrogels with 10% DMA and different BIS concentration were evaluated as matrices for controlled release of three model drugs of low molecular weight: Atenolol, Paracetamol and Ranitidine. Molecular weights and solubilities of the 3 different drugs are shown in Table 1.

The loading of drugs into the DMA hydrogels was carried out by the swelling equilibrium method. To this effect, dry hydrogels (xerogels) were swollen in a drug solution of known concentration (5 mg/mL for Atenolol and Ranitidine, and 10 mg/mL for Paracetamol) until equilibrium at room temperature (27ºC), and then dried to constant weight. The amount of drug loaded by each hydrogel was calculated as the difference between the initial amount of drug in solution and the amount remaining after loading, obtained by UV-Vis spectroscopy (Perkin

Elmer Lambda 25) previous calibration. The results were fit to four transport models, Zero-Order, First-Order, Higuchi, and Korsmeyer-Peppas, using non-linear least-squares regression (Higuchi, 1963; Korsmeyer *et al.*, 1983; Dash *et al.*, 2010).

III. RESULTS AND DISCUSSION

A. Synthesis of the Hydrogels

During the DMA homopolymerization by the free radical mechanism, poly(DMA) macroradicals were produced, which in presence of the BIS crosslinker, gave place to a three-dimensional network, the so called DMA hydrogels. As shown in Fig. 1, the transparency of the synthesized hydrogels decreased from a transparent to an opaque gel as the concentration of the crosslinking agent was increased; and it was due to changes in the structure, pore size and degree of homogeneity of the polymer network. In contrast to ideal gels, real ones exhibit an inhomogeneous crosslinking density distribution, known as the spatial gel inhomogeneity. This mainly originates from irregularities in the structure in form of multifunctional cross-links or entanglements; free chain ends (unreacted functionalities) and chain loops. In general, the gel inhomogeneity increases significantly with the crosslinking density (Khare and Peppas, 1995; Lin *et al.*, 2005). All polymers were obtained in rod form and were able to maintain the macroscopic structure after extraction from the syringes. The consistency of the obtained hydrogels depends on the DMA/BIS ratio used for their synthesis. At small concentrations of either DMA or BIS, gelatinous hydrogels were obtained which cannot be handled, but they became more rigid and fragile at higher concentration of such reagents due to lower extensibility of chains.

B. Characterization of the Hydrogels

Swelling and Structure

Table 2 summarizes the results of the kinetics of swelling. In the specific case of the hydrogels synthesized with 15-20% of DMA concentration and 4-6% of BIS molar ratio, swelling results could not be determined since the hydrogels showed degradation during the experiments.

Figure 2 shows the swelling kinetics of hydrogels synthesized by varying both DMA and BIS concentrations. The values of *SR* increased with time up to a plateau where constant swelling was observed, which were considered as the equilibrium swelling ratio (*SRe*). Different values of both the rates of swelling and their maximum values were observed for hydrogels synthesized

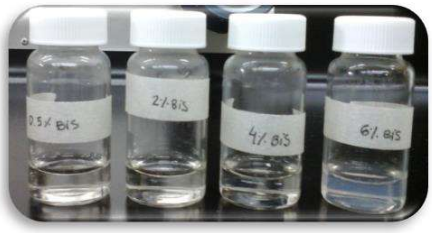


Figure 1. Photography of DMA hydrogels synthesized with 10% monomer concentration and different crosslinker to monomer molar ratio.

Table 2. Swelling Parameters of DMA Hydrogels

%DMA	%BIS	$Q_{w,e}$	*SRe*	*EWC*
5	0.5	21.75	20.75	0.95
	2	17.35	16.35	0.94
	4	16.03	15.03	0.94
	6	13.57	12.57	0.93
10	0.5	14.01	13.01	0.93
	2	11.21	10.21	0.91
	4	8.36	7.36	0.88
	6	6.68	5.68	0.85
15	0.5	12.82	11.82	0.92
	2	8.13	7.13	0.88
20	0.5	0.91	9.92	0.91
	2	0.86	6.12	0.86

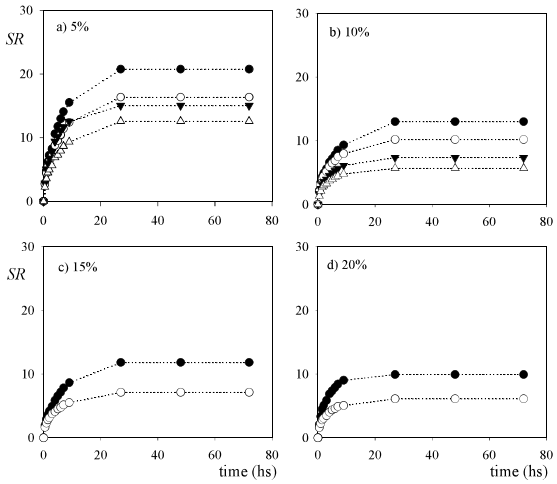


Figure 2. Swelling kinetic curves of DMA hydrogels with 0.5% (●); 2% (○); 4% (▼) and 6% (△) crosslinker, and different monomer concentration a) 5%; b) 10%; c) 15% and d) 20%.

with varied percentages of crosslinking agent. In all cases, swelling values were 60-80% of *SRe* after 9 hours, and reached their maximum value at 24 hs approximately.

The influence of both DMA and BIS concentrations on *SRe* are shown in Table 2 and Fig. 3. Notice that, an increase in the BIS molar ratio (for a given DMA concentration), gave rise to a lower swelling ability of the network that could be physically correlated to the lower extensibility of chains, reducing their flexibility and solving ability. Similarly, working at a given BIS molar ratio, the decrease of DMA concentration produced higher swelling at equilibrium conditions. It is believed that as the DMA concentration is increased, the expansion of the network structure and the free volume within the hydrogel network are reduced, and hence the swelling capacity of the hydrogel is also reduced (Baker *et al.*, 1994; Funke *et al.*, 1998; Okay, 2000). Additionally, the reduced swelling of highly crosslinked networks has been attributed to the glassy inner core of dried hydrogels. Prior to swelling, there are strong intermolecular (polymer–polymer) interactions in the xerogel, which remain in a glassy state as it will be then shown from the *Tg* values. Thus, macromolecular interactions are enhanced in hydrogels with higher crosslinking, which lead to a signifi-

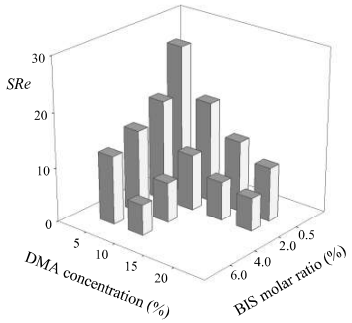


Figure 3. Equilibrium swelling ratio for DMA hydrogels as a function of monomer mass concentration and crosslinker molar ratio.

cant reduction in water uptake (Funke *et al.*, 1998).

Knowing the type of water (n) diffusion within the hydrogel is important a parameter for determining the interaction that occurs between the swelling solvent and the polymer chains. In the samples analyzed, n ranged between 0.58 and 0.89 (data not shown) indicating that the mechanism of penetration of water is controlled by diffusion and polymer chain relaxation (non-Fickian). Hydrogels in dry state have mostly hydrophobic chain-chain interactions. Upon contact with them, water molecules must break these interactions to favor the water-polymer interactions and generate more access or incorporation. Thus, each water molecule entering into the matrix produces a net pressure on the overall structure. Hydrogel chains must take time to respond to the swelling pressure and order themselves to reorder water molecules that enter and allow the entrance of more water within the structure.

Figure 4a shows the dependence of the equilibrium water content on the BIS concentration for swollen DMA hydrogels prepared with 5% and 10% monomer concentration as expected. It is observed that hydrogels with lower crosslinking density gave place to higher swelling. The reduction in swelling when increasing the BIS concentration could be due to the increase in the number of crosslinks in the gel network which results in a reduction of the pore size of the voids available between network chains (Fig. 4b and c). This leads to a slow diffusion of water molecules into the network and restricts relaxation of network chains in the hydrogels (Yazdani-Pedram *et al.*, 2000).

The hydrogels with higher swelling parameters values (Table 2) shows higher pore sizes (Fig. 4b and 4c). With the addition of more BIS y/o DMA, swelling parameters values and pores size decrease, reflecting their structural architecture. Thus, pore size can be related to the space available to the entrance of water into the material. Pore size observed by SEM is in agreement with the swelling parameters values shown in Table 2.

The behavior previously described is emphasized in Fig. 5, where the measured diameter of discs, using a digital caliper, is plotted against the fraction of BIS for hydrogels prepared with 5% and 10% monomer concentration. For a given DMA concentration, the network must

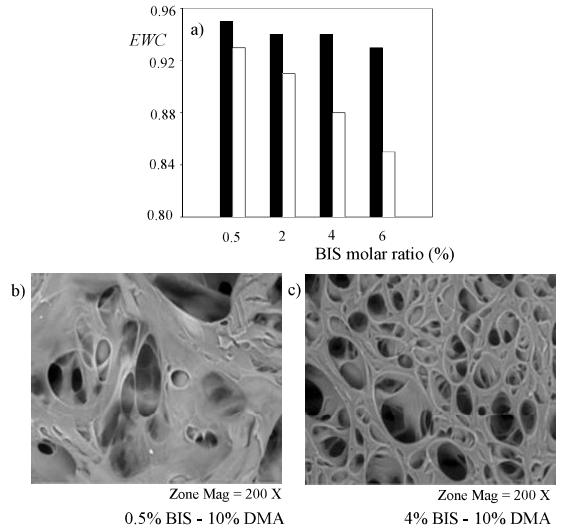


Figure 4. a) Dependence of the equilibrium water content on the BIS molar ratio for DMA hydrogels prepared with 5% (■) and 10% (□) monomer concentration; b) and c) scanning electron microscope (SEM) images of DMA hydrogels synthesized with 10% monomer concentration and 0.5% and 4% crosslinker ratios.

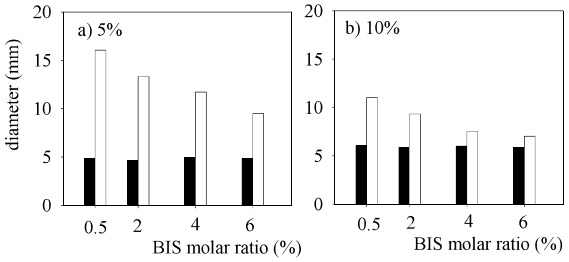


Figure 5. Variation of the expansion diameter of discs as a function of the crosslinker ratio for DMA hydrogels prepared with 5% (a) and 10% (b) monomer concentration: (■) xerogel and (□) hydrogel.

be sufficiently crosslinked for maintaining its dimensional stability, but avoiding large dimensional changes. During the swelling process, it was also observed that the discs having relatively low concentration of crosslinker were deformed at their boundaries, which could be attributed to the faster rate of swelling at boundaries than in the center of the discs.

Determination of network parameters

Table 3 shows the network parameters of DMA hydrogels. The results show that the increase in monomer and crosslinker concentrations influenced the network parameters (Li *et al.*, 2006). Thus, for a fixed monomer concentration, δ increased when augmenting the crosslinker concentration. At lower crosslinker concentration, hydrogels exhibitted lower crosslinking density and hence higher swelling capacity. Also, hydrogels produced with higher crosslinker concentrations exhibited higher crosslinking density, causing a decrease in the distance between crosslink points, and lowering the swelling capacity.

Table 3. Network parameters of DMA hydrogels calculated from swelling data

DMA (%)	BIS (%)	ϕ	χ	$\overline{M}_c$ (g/mol)	$\delta \times 10^6$ (mol/cm^3)	ξ(nm)
5	0.5	0.04	0.51	784.89	1.54	186.59
	2	0.05	0.52	337.66	3.58	113.43
	4	0.05	0.52	250.99	4.82	95.23
	6	0.06	0.52	134.28	9.01	65.85
10	0.5	0.06	0.52	240.09	5.04	88.99
	2	0.07	0.52	103.43	11.70	54.17
	4	0.10	0.53	33.91	35.69	28.08
	6	0.13	0.54	14.22	85.11	16.84
15	0.5	0.07	0.52	225.60	5.36	83.73
	2	0.10	0.53	39.95	30.29	30.19
20	0.5	0.08	0.53	148.95	8.12	64.44
	2	0.12	0.54	28.99	41.74	24.58

Both ξ and $\overline{M}_c$ regularly decreased when increasing the crosslinker concentration. It must be noted that most hydrogels used in biomedical applications have mesh size ranging from 5 to 100 nm in their swollen state (Singh and Sharma, 2014).

Finally, χ was studied to check the interaction between hydrogels and solvent (water). It was observed that $\chi > 0.5$ for all cases, indicating the water insolubility of hydrogels.

Glass Transition of Xerogel

The resulting Tg values for DMA xerogels with 10% monomer concentration and 0.5, 2, and 4 % crosslinker concentration were 126.8, 133.8 and 143.8 ºC, respectively. As all samples were synthesized under the same conditions of temperature, monomer and initiator concentrations, it is clear that, as expected, Tg was increased with increasing BIS content. Higher crosslinking densities restrict the movility and flexibility of the polymer chains thus producing higher Tg values.

Rheological Properties

Rheological properties were studied for DMA hydrogels synthesized with 10% DMA and different BIS concentration. First, the LVR was determined by measuring G' as a function of the strain amplitude. For all the analyzed hydrogels, it was observed that G' was practically independent of the strain amplitude up to 1% (Fig. 6b), beyond which G' abruptly decreased, indicating that a structure breakdown occurred as a consequence of the large deformations imposed (Fig. 6a). It can be assumed that beyond the LVR, the hydrogels become mechanically unstable which results in a decrease in the elastic strength of the hydrogels. Therefore, 1% strain was used for all the following measurements, in order to remain in the linear regime and preserve the hydrogels internal structure.

In the dynamic frequency sweep, G' was higher than G'' in all cases and both were parallel to each other (Fig. 6c). Since G' was higher than G'' in the whole LVR, the elastic behavior predominated over the viscous one (Zhang *et al*., 2003; Caykara *et al.*, 2006).

In turn, when increasing the BIS concentration, the G' and G'' values were distanced relative to one another (Table 4). Generally speaking, the crosslinking density of the polymer network and the flexibility of the polymer chains have a great influence on the rheological properties of the hydrogel. The magnitude of the viscoelastic response of a hydrogel is first governed by the flexibility of the polymer chains and then by the imposed mechanical motion. The increase of the BIS concentration enhances the density of the polymer network and decreases the flexibility of chains, resulting in an increase in the elastic modulus (Wang *et al.*, 2008; Guilherme *et al*., 2010; Hosseinzadeh, 2010; Ganjil, 2010). The polymer chain segments between crosslinks are longer for the less crosslinked networks and, thus, will give origin to lower molecular motion frequencies than those arising from the highly crosslinked networks. However, at higher frequencies, long chains fail to rearrange themselves in the time scale of the imposed motion and, therefore, stiffen up, giving place to a more "solid-like" behavior that is characterized by a sharp increase in G', because shorter polymer chains resulting from highly cross-linked networks exhibit smaller relaxation times (data not shown). Also, when increasing the degree of crosslinking it will result in a stronger gel. However, a higher degree of crosslinking creates a more brittle structure.

C. Drug Loading and Release

The loaded hydrogels were visually similar to the no loaded ones but orange in appearance in the case of hydrogels loaded with Ranitidine.

The "*in vitro*" release of the entrapped drug was carried out by placing the xerogels loaded with the drug into water at 37 ºC. At periodic intervals, 1 mL of solution

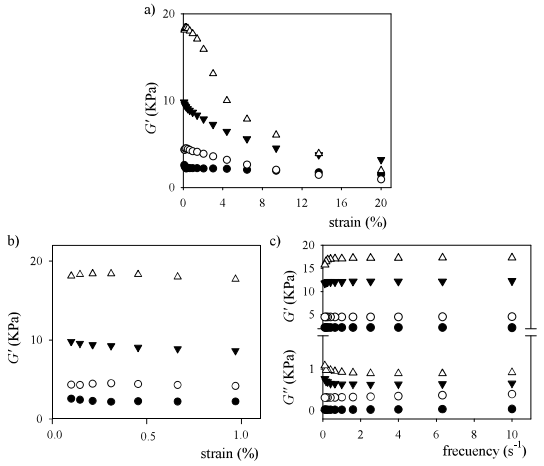


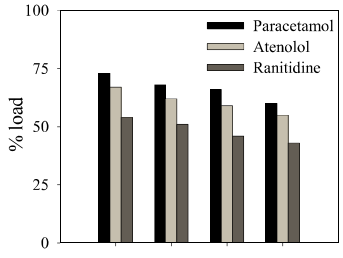
Figure 6. G' as a function of strain (frequency = 10 s^{-1}): a) strain amplitude from 0.1 to 20%; b) strain amplitude below 1 %; and c) G' and G'' as a function of frequency (strain = 1%) for DMA hydrogels produced with 10 % monomer concentration and 0.5% (●); 2% (○); 4% (▼) and 6% (△) crosslinker concentration.

Table 4. Rheological properties of DMA hydrogels produced with 10% monomer concentration (strain 1% -frequency 10s^{-1})

%BIS	0.5%	2%	4%	6%
G'	2.21	4.49	12.11	16.96
G''	0.03	0.33	0.66	0.94
tan δ	0.01	0.07	0.05	0.06

Table 5. Percentage of loading of drugs respect to initial concentration

Drug	%BIS			
	0.5	2	4	6
Paracetamol	73	68	66	60
Atenolol	67	62	59	55
Ranitidine	54	51	46	43



% BIS	0.5	2	4	6
SRe	13.01	10.21	7.36	5.68
ξ	88.99	54.17	28.08	16.84
Mc	240.09	103.43	33.91	14.22
G′	2.21	4.49	12.11	16.96
G″	0.03	0.33	0.66	0.94

Figure 7. Effect of crosslinker concentration on the structural hydrogel parameters and load capacity for the three drugs studied.

containing drug were withdrawn and 1 mL of water was added to keep constant the volume of releasing solution (10 mL). The amount of released drug was quantified by UV-Vis spectroscopy by using an appropriate calibration curve.

It was observed that each hydrogel was able to effectively load the different drugs into its network from aqueous solutions. Table 5 shows that as BIS concentration in the hydrogel was increased, the percentage load of drug in the hydrogel was decreased. As crosslinking increases, the possibility of drug diffusion through the hydrogel pores became reduced due to the steric hindrance provided by polymer chains within the crosslinked networks (Chien-Chi and Andrew, 2006). When increasing the crosslinker concentration, both the crosslinking density and the swelling capacity are increased (see item B). With a lower swelling a reduced amount of aqueous solution and drug get into the hydrogel, thus reducing the load of drugs.

Figure 7 shows a summary that compares the structural data and parameters with the percentage of load of the different drugs studied.

In release assay, for each experiment, the total amount of drug released was compared to the amount that was loaded into hydrogels from the loading solution. Representative drug release profiles are shown in Fig. 8, where the percentage release of the drug from the hydrogel is plotted against the time.

The drug concentration in the release solution at a given time was normalized to the equilibrium drug concentration in the release solution and plotted as a function of time for each crosslinker concentration (data not

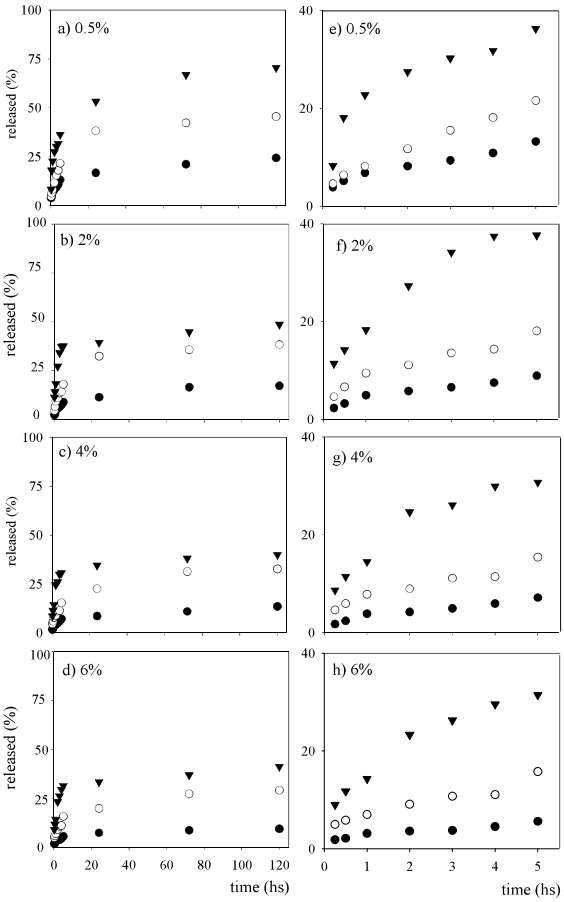


Figure 8. In vitro Atenolol (●); Paracetamol (○); and Ranitidine (▼) release profiles from DMA hydrogels with different crosslinker concentration: 120 hs (a, b, c, d), and first 5 hs (e, f, g, h). The average error of drug release profiles was ± 0.2%.

shown). Normalization was used to eliminate the dependence on the release of the initial concentration of drugs in the gel. Nonlinear least squares adjustments were made for the four transport models (Zero-Order, First Order, Higuchi and Korsmeyer-Peppas) for each crosslinker concentration. The R-squared values resulting from the adjustments for the release of Atenolol, Paracetamol and Ranitidine are shown in Table 6. Both the Higuchi model and the Korsmeyer-Peppas one demonstrated high correlation to the experimental data. However, the Korsmeyer-Peppas model was selected for analysis diffusivity from the n parameter. In all cases, the average n values were between 0.58 and 0.89 (data not shown) indicating that the transport mechanism is non-Fickian or anomalous (Korsmeyer *et al.*, 1983; Peppas *et al.*, 2000). Therefore, the mechanism of drug release is governed by diffusion and swelling, with the rates of such processes being comparable. The rearrangement of polymeric chains occurring slowly and the diffusion process simultaneously caused the time-dependent anomalous effects.

It is shown the release behavior was strongly correlated to the swelling behavior for these gels. The overall drug release rate from hydrogels decreased as their BIS content increased. During release, the water penetrating

Table 6. R-squared values of release profiles for each model considered

%BIS	Zero-Order	First-Order	Higuchi	Peppas
		Atenolol		
0.5	0.826	0.839	0.974	0.993
2	0.847	0.810	0.985	0.993
4	0.732	0.818	0.986	0.991
6	0.786	0.870	0.950	0.986
		Paracetamol		
0.5	0.937	0.903	0.996	0.995
2	0.845	0.799	0.981	0.991
4	0.796	0.829	0.957	0.991
6	0.776	0.874	0.943	0.982
		Ranitidine		
0.5	0.899	0.886	0.995	0.998
2	0.900	0.921	0.988	0.994
4	0.913	0.885	0.994	0.996
6	0.914	0.894	0.995	0.998

Table 7. Percentage release of drugs respect to load from DMA hydrogels after 120 hours

Drug	%BIS			
	0.5	2	4	6
Atenolol	35	24	16	13
Paracetamol	72	53	45	40
Ranitidine	82	75	61	62

the hydrogel caused the gels to swell and the network chains were stretched until a balance was reached (*SRe*). An increase in the molar concentration of the crosslinker decreased the molecular weight between crosslinks, which in turn resulted in a smaller network pore size, and a less flexible structure. As a result, drug release from hydrogels produced with high BIS concentration was more obstructed and consequently it was slower than from hydrogels synthesized with low BIS concentration (Table 7). When the glassy polymer comes into contact with an aqueous solution, it begins to imbibe water. This water uptake can lead to considerable increase in the macromolecular mobility of the network and therefore to a considerable volume expansion (swelling). Due to the swelling action, liquid penetrates the matrix and dissolves the drug, which then diffuses into the exterior liquid through pores. Thus, the release was dependent on both the degree of crosslinking and the solubility of the drug in the medium.

As presented in Fig. 8, the release profile for Ranitidine showed that significantly, higher percentages of release were achieved and its release from all hydrogels was faster than that observed for Atenolol or Paracetamol. As expected, hydrophobic molecules released more slowly than hydrophilic ones, because they will try to minimize their contact with water molecules. In general, the release kinetics of the drug do not only depends on the diffusion of the drug; but also on the dissolution of the drug in the gel layer and the relaxation of the polymer. Due to the swelling action, the drug which is dispersed in the polymer begins to diffuse out. Thus, drug release depends upon two simultaneous rate processes: water diffusion into the polymer and chain relaxation. It can be clearly seen that for lower BIS, degree of crosslinking is low and hence the polymer chains are relaxed to a greater, thus causing a faster diffusion of water into the polymer matrix.

However, in all cases, immediately upon placement in the release medium, an initial large bolus of drug is released before the release rate would reache a stable profile. For the three drugs studied, at 5 hours it was released almost half of the drug released at 120 hours at the end of the test (Fig. 8 e, f, g, h). Some suggested explanations are: a) some drugs becomes trapped on the surface of the polymer matrix during the loading process and are released immediately upon activation in a release medium; and b) migration of drugs during drying and post-load storage may result in a heterogeneous distribution of drug in the polymer matrix. The diffusion and migration of drugs may occur during the drying process as water moves to the gel surface and evaporates. Drugs may diffuse with water by convection, leaving an uneven drug distribution across the gel, with higher concentrations at the surface.

IV. CONCLUSIONS

The development of sustained release formulations is currently one of the most important challenges in pharmaceutical research. Hydrophilic matrices are widely used for controlling drug release, but the mechanisms involved in drug release from these matrix systems are complex and depend on many factors. The aim of the present work was to synthesize sustained-release hydrogels based on DMA to study the effect of the polymer matrix structure and the drugs characteristics on the load and release mechanisms. Thus, a series of DMA hydrogels were synthesized with different monomer concentration and crosslinker to monomer ratio by free radical aqueous solution polymerization. In all cases, as the crosslinking concentration of the hydrogels was increased, the expansion of the network structure and the free volume within the hydrogel network was reduced, and hence the swelling capacity of the hydrogels was also reduced. The characteristics of the DMA hydrogels appeared to influence the degree of swelling, the load capacity, and the release rate. Each produced hydrogel was able to effectively load the three considered drugs from the solution into the network. The loading percentage was 73-60%; 67-55% and 54-43% for Paracetamol, Atenolol and Ranitidine, respectively. The load percentage of hydrophylic drugs was lower probably because they will try to maximize their contact with water molecules. The increase in the BIS concentration produced a greater crosslinking of the polymer chains, decreasing the porosity, and therefore preventing the release of drugs through the gel. In general, drugs with high solubility in water were more easily released. Finally, Ranitidine showed higher percentages of release after 120 hours than observed for Atenolol or Paracetamol (82-62%; 72-40% and 35-13% for Ranitidine; Paracetamol and Atenolol, respectively), probably due to their greater affinity for the medium.

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