Timolol-Imprinted Soft Contact Lenses: Influence of the Template: Functional Monomer Ratio and the Hydrogel Thickness

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ABSTRACT: Isothermal titration calorimetry (ITC) was used to identify the optimal timolol:functional monomer ratio for preparing soft contact lenses (SCLs) able to sustain drug release. ITC profiles revealed that each timolol molecule required six to eight acrylic acid (AAc) monomers to saturate the binding and that these ratios could be the most suitable for creating imprinted cavities. Various poly(hydroxyethyl methacrylate-*co*-AAc) hydrogels 0.2 and 0.9 mm thick were prepared with timolol:AAc molar ratios ranging from 1 : 6 to 1 : 32 and also in the absence of timolol. The hydrogels were reloaded with timolol by immersion in 0.04, 0.06, 0.08, and 0.10 m*M* drug solutions. Both imprinted and nonimprinted hydrogels showed a high affinity for the drug because of the presence of AAc. Nevertheless, the 1 : 6 and 1 : 8 imprinted hydrogels loaded less timolol but sustained the release better than the other hydrogels. These differences were explained in terms of the different arrangement of the functional monomers along the network. The imprinting effect was more noticeable in the case of the thinnest hydrogels, where the contribution of the diffusion path to the release rate was smaller. The results obtained prove the interest of ITC for the rational design of drug-imprinted networks to be used as medicated SCLs. © 2011 Wiley Periodicals, Inc. J Appl Polym Sci 122: 1333–1340, 2011

Key words: drug delivery systems; hydrogels; molecular imprinting

INTRODUCTION

Soft contact lenses (SCL) have been proposed as drug carriers for sustained release on the precorneal area since decades ago.[1,2] SCLs preferentially release the drug molecules to the postlens tear film, between the cornea and the lens; this results in a prolonged contact with the cornea surface.[3] In this way, the drug escapes from the protective ocular mechanisms, and the sorption through the conjunctiva is also minimized. Therefore, drug-eluting SCLs may be particularly convenient for clinical conditions requiring a high intraocular concentration of drug, such as anterior segment inflammations, angle closure glaucoma, or infections. The immersion of the SCL in a drug solution or the instillation of eye drops on the surface of the lens after insertion have been shown to improve both the ocular bioavailability and pharmacological response of various drug molecules compared to conventional eye-drop administration.[4–7] Thus, the development of a combination product for simultaneous refractive correction and drug release may fill a relevant therapeutic gap.[8,9] Nevertheless, drug-eluting SCLs still have to face up to the fact that if the drug does not interact with the polymeric network, the drug loading and release is only driven by passive diffusion through the aqueous phase of the network. This limits both the amount loaded and the control of the release, which may be insufficient for prolonged delivery.[10,11]

Over the last few years, several approaches have been explored to improve the performance of SCLs as drug-delivery devices: (1) the chemically reversible immobilization of drugs through labile bonds,[12–14] (2) the incorporation of drug-loaded colloidal systems into the lens,[15–18] (3) copolymerization with functional monomers able to interact directly with the drug,[19–21] and (4) molecular imprinting.[22–27] Molecular imprinting technology pursues the optimization of the spatial distribution of monomers able to interact with the

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drug (named *functional monomers*) to achieve the maximum efficiency of the interactions between the drug and the polymeric network. To do that, the drug molecules are used as templates during polymerization with the purpose of creating tailored-active sites or imprinted pockets with the size and most suitable chemical groups to interact with the drug.[28,29] When the drug molecules that served as templates are washed out, the polymer network is expected to recognize the drug when it enters into contact with it again and to accommodate the drug molecules more efficiently than conventional hydrogels prepared in the absence of the drug. Research on drug-imprinted SCLs has focused so far on three therapeutic groups, namely, β-adrenergic antagonists (timolol),[30,31] antimicrobials (norfloxacin),[24] and antihistamines (ketotifen),[32–35] and also on comfort ingredients (hyaluronic acid).[36]

Differently from conventional highly crosslinked imprinted networks, the peculiar optical and mechanical features of SCLs restrict the nature and proportion of the functional monomers and the degree of crosslinking. Thus, the lower physical stability of the cavities in the imprinted lenses has to be compensated by maximization of the affinity for the drug. In this sense, the selection of the optimum drug:functional monomer ratio is a key parameter for the achievement of the imprinting effect and the adequate performance of the SCLs as drug-delivery systems. In addition to the trial-and-error approach, various analytical and computational techniques may provide information about the stoichiometry, strength, and stability of the drug–functional monomer complexes during lens synthesis.[37–41] We have previously seen that isothermal titration calorimetry (ITC) was a suitable technique for identifying the optimal norfloxacin:acrylic acid (AAc) ratio when this antimicrobial agent was used as template of imprinted SCL.[24] The aim of this study was to elucidate the interest of ITC as a tool for the rational design of SCLs that can sustain the release of timolol and to determine to what extent the thickness of the hydrogels affected the role of the imprinted cavities in the drug-release control. Timolol has already been found to be adequate for preparing imprinted networks using as functional monomers those bearing carboxylic acid groups, probably because the ability of timolol to behave as a donor and acceptor of hydrogen bonds.[22,30,31] Thus, first, the stoichiometry of timolol–AAc complexes was determined by ITC, and then, two sets of hydrogels with various timolol:AAc molar ratios and two different thicknesses were synthesized. Concordance between the ITC predictions and the experimental results with regard to the ability of the hydrogels to load timolol and to regulate its release was evaluated.

EXPERIMENTAL

Materials

2-Hydroxyethyl methacrylate (HEMA) and AAc were supplied by Merck (Darmstadt, Germany). Ethylene glycol dimethacrylate (EGDMA), timolol maleate salt (S-[-]-isomer form), and dichlorodimethylsilane were from Sigma-Aldrich (St Louis, MO, USA). 2,2′-Azobis(2-methyl propionitrile) was obtained from Acros (Geel, Belgium). Ultrapure water (resistivity > 18.2 MΩ cm) was obtained by reverse osmosis (MilliQ, Millipore, Barcelona, Spain). All other chemicals were reagent grade.

Calorimetric titration of timolol with AAc

The interactions between timolol and AAc in HEMA solution were evaluated by ITC (VP-ITC, MicroCal, Inc., Northampton, MA). The experiments were carried out in duplicate (reproducibility within ±5%) at 25°C, with the AAc solution (0.50*M*, 0.290 mL) titrated onto the timolol solution (0.01*M*, 1.439 mL). The binding experiment involved sequential additions of 1-μL aliquots of the AAc solution in the reaction cell under continuous stirring at 280 rpm. Control experiments were carried out under identical conditions to obtain the heats of dilution, and mixing involved in the injection of the AAc solution into the HEMA medium. The net reaction enthalpy was obtained by subtraction of the dilution enthalpies from the apparent titration enthalpies.

Synthesis of the hydrogels

AAc (1.87 g) and EGDMA (10.27 g) were mixed with 130 mL of HEMA. To 20-mL aliquots of this solution (0.15 mol of HEMA, $4 \cdot \times 10^{-3}$ mol of AAc, and $8 \times \cdot 10^{-3}$ mol of EGDMA), different amounts of timolol maleate were added to obtain timolol maleate:AAc molar ratios of 0 (nonimprinted networks) or 1 : 6, 1 : 8, 1 : 12, 1 : 16, and 1 : 32 (imprinted networks). All hydrogels, including the nonimprinted networks, contained the same proportion of AAc. 2,2′-Azobis(2-methyl propionitrile) (0.032 g) was added to each solution, and the monomer solutions were immediately injected into molds made of two glass plates separated with silicone frames 0.2 and 0.9 mm thick. The glasses were previously treated with dichlorodimethylsilane, dried for 2 h, and successively washed with distilled water and ethanol four times and dried in an oven.

Polymerization was carried out at 50°C for 12 h and then at 24 h at 70°C. The gels were removed from the molds and immersed in boiling water for 15 min to remove unreacted monomers. Then, 10-mm diameter discs were immediately cut from the gels with a cork borer and washed successively with

water, 0.9% NaCl, 0.1*M* HCl, and distilled water at room temperature. The washing solution was replaced four times a day for a complete washing period of 7 days. The removal of unreacted monomers and timolol was confirmed by the absence in the washing solutions of UV absorption bands between 190 and 900 nm. Then, the hydrogels were dried in an oven for 24 h at 40°C.

Swelling kinetics

The dried hydrogels were weighed (W_0) and placed in vials with 10 mL of water at 25°C. The degree of swelling at various times (Q_t) was calculated as the relative weight gain:

$$Q_t = 100(W_t - W_0)/W_0 \quad (1)$$

The hydrogels were weighed (W_t) on each occasion after careful wiping of their surfaces with a soft tissue.

Timolol loading

The dried hydrogels were weighed, placed in timolol solutions at different concentrations (0.04, 0.06, 0.08, and 0.100 m*M*), and maintained at dark without stirring. The volume of the drug solution was chosen to be proportional to the volume of the hydrogels, that is, 2 mL for hydrogels with a thickness of 0.2 mm and 8 mL for hydrogels with a thickness of 0.9 mm. The experiments were carried out in triplicate for each hydrogel. Timolol concentration in the loading solution was monitored by recording of the absorbance at 294 nm (Agilent 8453 spectrophotometer, Boeblingen, Germany). The amount loaded by equilibrium between the aqueous phase of the network and the loading solution, which led the drug concentration within the hydrogel to be equal to that of the loading solution, could be estimated with the following equation[42]:

$$\text{Loading (aqueous phase)} = (V_s/W_p)/C_0 \quad (2)$$

where V_s is the volume of water sorbed by hydrogel (mL), W_p is the weight of the dried hydrogel (g), and C_0 is the concentration of drug in the loading solution (mg/mL).

Timolol release

After loading, each hydrogel disc was rinsed with distilled water and placed in 2 mL (0.2-mm thickness) or 8 mL (0.9-mm thickness) of a 0.9% NaCl solution. These volumes ensured sink conditions. The medium was gently shaken before sampling. Samples of the release medium (1 mL) were withdrawn at regular time intervals, and their timolol concentrations were measured spectrophotometrically at 294 nm. The samples were returned to the corresponding container immediately after each measurement to maintain the initial volume of 0.9% NaCl. The experiments were carried out in triplicate. The release profiles up to a fraction released of 0.6 were fitted to the square-root kinetics:

$$\frac{M_t}{M_\infty} = K_H t^{1/2} \quad (3)$$

where M_t and M_∞ represent the amount of timolol released at time t and at the end of the release test, respectively. The release rate constant (K_H) was estimated by linear regression.

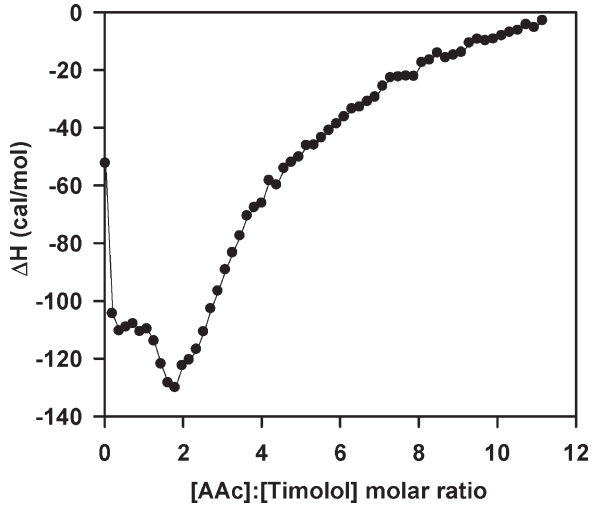

Figure 1 ITC titration at 298 K of 0.01*M* timolol with 0.50*M* AAc in HEMA solution. change in enthalpy (ΔH)

Statistical analysis

Statgraphics Plus 5.1 software (Statistical Graphics Corp.) (Warrenton, VA, USA) was used to carry out analysis of variance of the release rate constants. A multiple-range test was used to identify the systems that were statistically different from each other.

RESULTS AND DISCUSSION

Design and synthesis of the hydrogels

The first step of this study was to identify the optimal timolol:AAc ratio required to form imprinted cavities. Thus, ITC experiments were carried out by titration of the drug with AAc in the same medium (HEMA) where the hydrogels were going to be synthesized. The net reaction enthalpy was obtained by subtraction of the dilution enthalpies from the apparent titration enthalpies (Fig. 1). ITC studies revealed

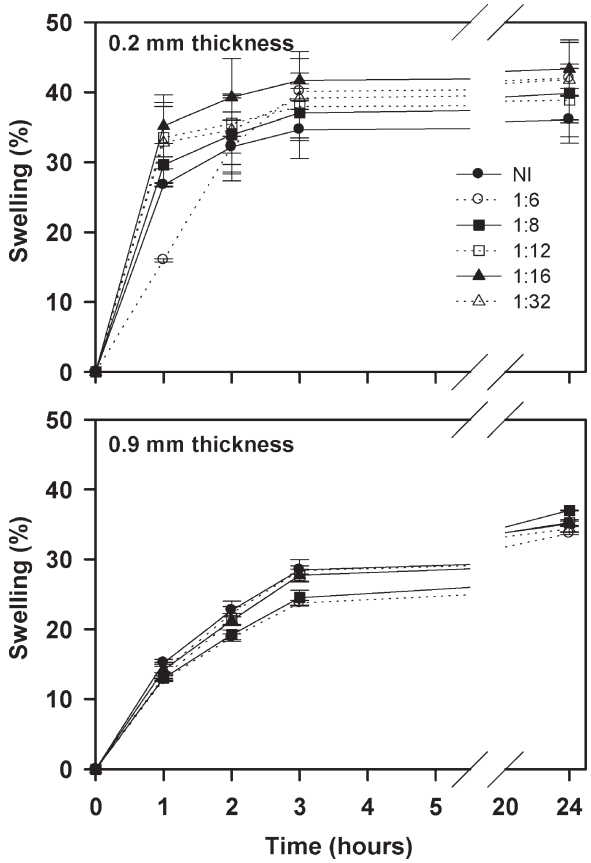

Figure 2 Swelling of the hydrogels in water at 25°C.

that maximum binding interaction between timolol and AAc occurred at a 1 : 2 molar ratio and that the process saturated around a 1 : 8 molar ratio. Thus, hydrogels comprising timolol:AAc molar ratios inside and above this range were synthesized and tested to evidence the imprinting effect. Because timolol maleate was not soluble above 33.3 m*M* in the monomer solution, this concentration was chosen for preparing the hydrogels with the highest timolol proportion, that is, 1 : 6 timolol:AAc.

After polymerization, the hydrogels were boiled in water, which is a common procedure for removing unreacted species and sterilizing SCLs; cut as 10-mm discs; and then, intensively washed to remove the drug template molecules. Nonimprinted hydrogels underwent the same process for comparative purposes. All hydrogels were totally transparent (transmittance > 80% at 600 nm) and swollen up to a similar extent in water (Fig. 2). However, some differences in the swelling rate were observed as a function of the proportion of timolol added during hydrogel synthesis (Fig. 3). These differences, although small, revealed that the imprinted hydrogels prepared with a 1 : 6 timolol:AAc molar ratio required more time to swell, although the degree of swelling at equilibrium was statistically equal for all hydrogels. One could hypothesize that the entrance of water depended on the diffusion path (i.e., the thickness of the hydrogel) and on the conformational changes underwent by the polymer chains as they became hydrated. This last factor may have been affected by the spatial distribution of the ionizable monomers in the chain. In the case of the 1 : 6 imprinted hydrogels, the imprinted cavities may have consisted of six AAc mers quite close in the space and interacting among themselves through hydrogen bonds. Imprinted cavities with a larger number of AAc mers may have led to a not so tight structure. The lower the timolol:AAc molar ratio was, the higher the trend toward a random distribution was. The changes in swelling rate caused by a different merging of AAc mers were particularly evident for the thinnest hydrogels.

Timolol loading

The hydrogels were immersed in timolol solutions of various concentrations with the aim of testing their affinity for timolol. Because all hydrogels (including the nonimprinted ones) had a similar degree of swelling at equilibrium, the same monomeric composition, and the same content of functional monomer (AAc), the differences in the loading (Fig. 4) could be attributed to the arrangement of the functional monomers due to the presence of timolol during polymerization. It should be also noticed that the volume of the drug-loading solution was chosen to be proportional to the volume of the hydrogels, that is, 2 mL for hydrogels with a thickness of 0.2 mm and 8 mL for hydrogels with a thickness of 0.9 mm. In this way, similar drug concentrations at equilibrium could be

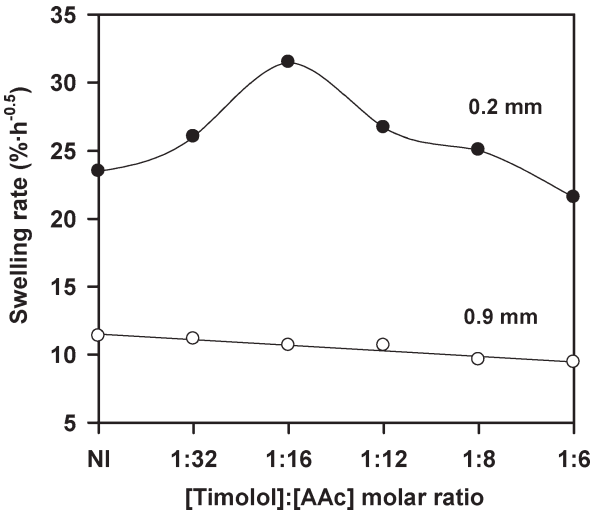

Figure 3 Dependence of the swelling rate obtained by fitting of the water uptake to the square-root kinetics (r^2 > 0.97) on the proportion of timolol incorporated to the hydrogels during synthesis.

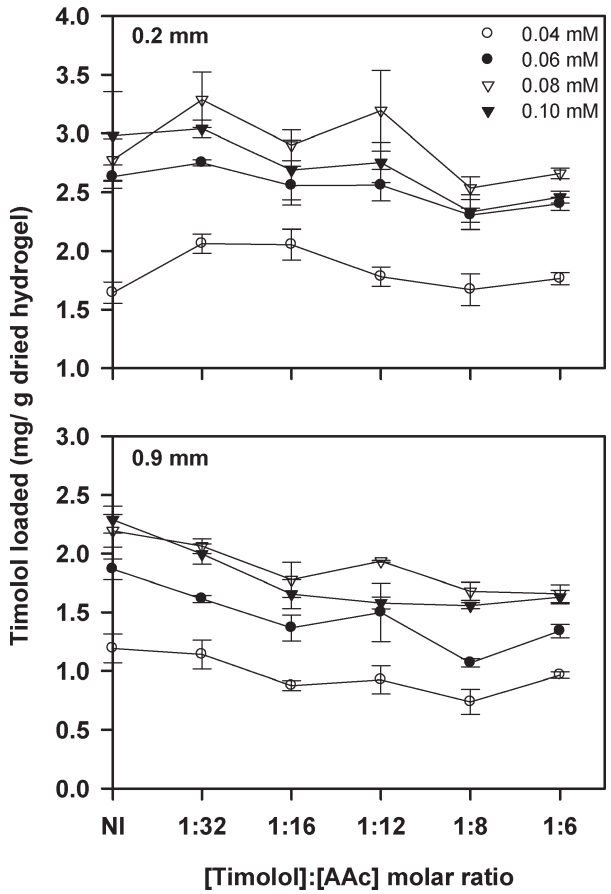

Figure 4 Timolol loaded by imprinted and nonimprinted hydrogels prepared with 200 m*M* AAc and with different thicknesses. The concentrations of the timolol solutions used to load the hydrogels are indicated in the plot legend.

reached, and the results obtained for both sets of hydrogels could be directly compared.

The amounts of timolol loaded were two orders of magnitude above those expected if the drug was only hosted in the aqueous phase of the hydrogels, that is, 0.007, 0.010, 0.014, and 0.017 mg/g for the hydrogels immersed in concentrations of 0.04, 0.06, 0.08, and 0.10 m*M*, respectively. This means that the presence of AAc itself notably enhanced the affinity of the hydrogels for timolol. We previously observed that polyHEMA hydrogels without functional monomer just took up the amount of drug that could be hosted in the aqueous phase.[30]

As expected, the higher the concentration of the drug solution was, the greater the amount loaded was. Nevertheless, the values obtained with the 0.08 and 0.10 m*M* timolol solutions were quite similar or even smaller for the latter, which may have indicated that the hydrogels were close to saturation. For a given concentration of timolol loading solution, it was interesting to note the progressive decrease in the amount loaded as the [timolol] : [AAc] molar ratio increased from 1 : 32 to 1 : 6. Norfloxacin-imprinted SCLs also showed a decrease in the loading as the proportion of template increased.[24] This phenomenon could be attributed to the fact that although the total number of functional groups was the same in all hydrogels, the number of each of them that gathered to form the binding site was different. In the nonimprinted hydrogels, the AAc groups were randomly distributed, and each of them constituted a potential binding site, although of low affinity. In contrast, in the 1 : 6 and 1 : 8 timolol:AAc imprinted hydrogels, each binding site was formed by six or eight AAc mers, which was the number identified as optimum by ITC. Therefore, each timolol molecule reloaded by the optimally synthesized hydrogels consumed six to eight functional groups, and consequently, the total amount loaded was less. The hydrogels prepared with timolol contents between those of the nonimprinted hydrogel and the 1 : 6 and 1 : 8 timolol:AAc imprinted hydrogels, that is, those ranging from 1 : 12 to 1 : 32 timolol:AAc, may have had imprinted cavities with six and eight AAc mers, and also others were constructed with the remanent AAc groups randomly distributed (probably individually or as dimers). As a result, when the hydrogels were immersed in the timolol solution, the drug molecules could be hosted by the imprinted cavities (with a 1 : 6 or 1 : 8 stoichiometry) and by some randomly distributed AAc groups (likely with a lower stoichiometry, e.g., 1 : 1 or 1 : 2); this resulted in a greater loading and one similar to that of the nonimprinted hydrogels. Thus, the lower the amount of timolol added before polymerization was, the lower the number of imprinted cavities was and the higher the number of nonimprinted binding sites was.

On the other hand, the loading rate was mainly conditioned by the thickness of the hydrogels. In the first 48 h, the amount loaded was about 75% of the total amount loaded by 0.2-mm hydrogels and about 50% by 0.9-mm hydrogels. The time required to achieve the equilibrium was 6 days for 0.2-mm hydrogels and 18 days for 0.9-mm hydrogels. This time was remarkably larger than that spent in the swelling, which indicated that the diffusion of the drug into the hydrogels was slower than the movement of water. Timolol is a relatively large molecule (weight-average molecular weight = 432.5 Da). Additionally, the interaction with the AAc mers and the fit into the imprinted cavities may have taken some time. Nevertheless, all hydrogels tested were loosely crosslinked, and thus, the polymeric network was not expected to hinder the diffusion of the drug toward the inner parts of the network. It has been reported that drug equilibration throughout the lens can remarkably determine the performance as delivery device because when the drug diffuses out from the surface layers, it can be

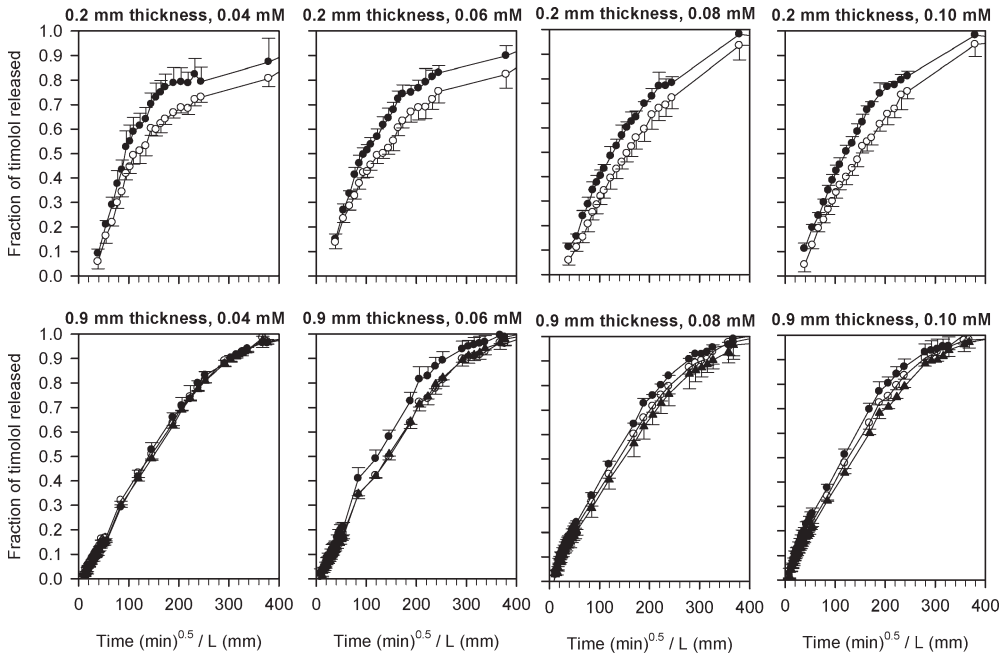

Figure 5 Timolol release profiles in NaCl 0.9% at 37°C from hydrogels of different thicknesses that were loaded by immersion in drug solutions of various concentrations (0.04, 0.06, 0.08, and 0.10 m*M*). Solid circles represent nonimprinted hydrogels, white circles represent the imprinted 1 : 6 hydrogels, and the solid triangles represent the imprinted 1 : 16 hydrogels. The *x*-axis scale corresponds to 27 and 540 h for 0.2-mm (first row) and 0.9-mm (second row) hydrogels, respectively.

replenished from the deeper part, which acts as a reservoir; this makes a more sustained and reproducible release possible.[4,43] Consequently, all hydrogels were loaded until equilibrium before we carried out the release experiments.

Timolol release

An isotonic saline solution was used as the release medium with the purpose of mimicking the ionic strength and pH conditions on the ocular surface. One can expect that the ions disturbed the binding of timolol to the AAc mers by inducing their ionization. However, no burst effect was observed for any timolol-loaded hydrogel. The 0.2-mm hydrogels were able to sustain timolol release for 1 day, whereas the 0.9-mm hydrogels controlled the delivery for 2 weeks. For the aim of clarity, only the release profiles of the hydrogels that behaved more differently are shown, once normalized by half of the thickness, in Figure 5. The release rate constants for all of the hydrogels, obtained by fitting of the square-root kinetics, are reported in Table I. Although both nonimprinted and imprinted hydrogels showed similar release patterns, some differences may be highlighted. In the case of the thinnest hydrogels, the faster release rate was recorded for the nonimprinted networks, and the slower release was achieved with the 1 : 6 and 1 : 8 timolol:AAc imprinted hydrogels (differences with the nonimprinted hydrogels were statistically significant at signification level (α) < 0.01). All other 0.2-mm

TABLE I
Timolol Release Rate Constant Values ($h^{1/2}$) Obtained by Fitting of the Release Profiles to the Square-Root Model

Hydrogel thickness (mm)	Loading concentration (mM)	Timolol:AAc molar ratio					
		Nonimprinted	1 : 32	1 : 16	1 : 12	1 : 8	1 : 6
0.2	0.04	0.067 (0.006)	0.063 (0.003)	0.057 (0.002)	0.049 (0.002)	0.046 (0.001)	0.048 (0.001)
	0.06	0.050 (0.004)	0.046 (0.005)	0.045 (0.004)	0.042 (0.003)	0.035 (0.002)	0.034 (0.001)
	0.08	0.043 (0.001)	0.044 (0.004)	0.041 (0.003)	0.038 (0.002)	0.031 (0.004)	0.036 (0.002)
	0.10	0.044 (0.002)	0.046 (0.005)	0.041 (0.004)	0.041 (0.002)	0.039 (0.001)	0.037 (0.001)
0.9	0.04	0.0087 (0.0002)	0.0081 (0.0003)	0.0079 (0.0001)	0.0079 (0.0003)	0.0080 (0.0001)	0.0080 (0.0001)
	0.06	0.0096 (0.0005)	0.0088 (0.0004)	0.0083 (0.0001)	0.0081 (0.0002)	0.0082 (0.0001)	0.0080 (0.0001)
	0.08	0.0093 (0.0003)	0.0077 (0.0004)	0.0075 (0.0007)	0.0081 (0.0001)	0.0079 (0.0001)	0.0080 (0.0003)
	0.10	0.0118 (0.0009)	0.0109 (0.0006)	0.0099 (0.0001)	0.0099 (0.0004)	0.0098 (0.0011)	0.0107 (0.0004)

Mean values and, in parenthesis, standard deviations

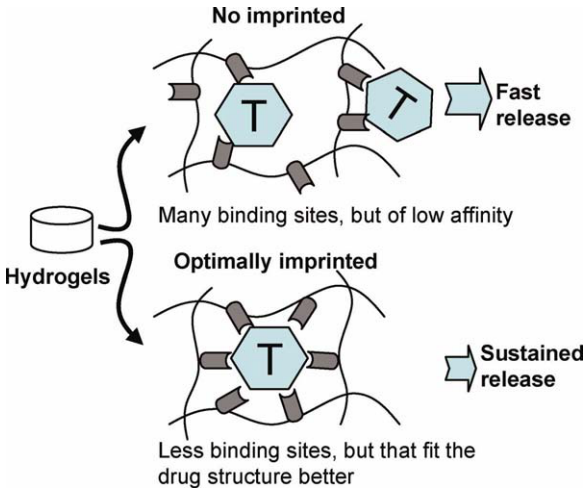

Figure 6 Schematic draw of the influence of the functional monomer arrangement on the control of drug release. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

hydrogels showed intermediate behavior. This finding suggests that the better the imprinted cavities created were, the stronger their affinity for timolol was, and, consequently, the greater their ability to retain the drug was (Fig. 6).

The imprinting effect was somehow attenuated in the thicker hydrogels, probably because of the fact that the release was determined by two factors: the affinity of the drug for the imprinted cavities and the length of the diffusional path through the hydrogel network. The contribution of this latter factor became greater as the thickness of the hydrogel increased. Furthermore, in the case of the 0.9-mm hydrogels, we observed that any imprinted hydrogel released timolol at a slightly slower rate than the nonimprinted ones (release rates from the 1 : 8, 1 : 12, and 1 : 16 hydrogels were statistically different from that of the nonimprinted hydrogels at $\alpha < 0.01$). The release of timolol from the thick hydrogels implied that the drug molecules may have had more chances to find imprinted cavities (or at least AAc mers more or less gathered together) during the movement toward the surface. The drug may have fallen down into the cavity and then escaped from it, to probably enter into another high-affinity region and so on. The interaction with those cavities should have made the movement slower. The higher the number the cavities was, the higher the likelihood of falling into one was. The imprinted hydrogels prepared with 1 : 16 timolol:AAc seemed to be particularly efficient from that point of view. As explained previously, these hydrogels may have combined optimally constructed imprinted cavities (i.e., 1 : 6 or 1 : 8 timolol:AAc) and also a certain number of cavities with fewer AAc mers. We previously observed that imprinted networks prepared with *N*,*N*-dimethylacrylamide, tris(trimethylsiloxy)silylpropyl methacrylate, and a 1 : 16 timolol:methacrylic acid molar ratio provided better control of timolol release than nonimprinted ones.[31]

CONCLUSIONS

The ITC analysis was shown as an adequate tool to elucidate the stoichiometry of the timolol–AAc complexes and to design imprinted lenses with a rational basis. Those imprinted hydrogels prepared with the timolol:AAc molar ratios identified as optimum by ITC (1 : 6 and 1 : 8) consisted of a lower number of imprinted cavities but a higher affinity for the drug. As a result, these imprinted hydrogels loaded lower amounts of timolol but released it at lower rate than the nonimprinted hydrogels. The improvement in the performance as drug-delivery systems of the imprinted hydrogels prepared with the timolol:AAc molar ratio of 1 : 6 was more evident in the case of the thin, 0.2-mm hydrogels. The greater the thickness of the hydrogels was, the slower the water uptake, drug uptake, and release rate were. However, in the case of the thick, 0.9-mm hydrogels, the influence of the timolol:AAc molar ratio was quantitatively less relevant; the hydrogels with more cavities, although with lower affinity, sustained drug release as well as (or even better than) those hydrogels possessing the best formed imprinted cavities. This effect was explained by the greater likelihood of the drug falling down and escaping from the imprinted cavities as the drug molecules moved through the thicker network toward the hydrogel surface.

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