# Drug Dissolution Profiles from Polymeric Matrices: data *versus* numerical solution of the diffusion problem and kinetic models

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## Abstract

This paper presents a comparative study between the data collected in a drug dissolution experiment and the predictions obtained from simple mathematical approaches of drug diffusion in the delivery device but also with the results achieved from available kinetic models for dissolution processes. The controlled release of timolol maleate from a hydrogel disc, obtained by thermal copolymerization of hydroxyethyl methacrylate and methacrylic acid, was used as the case study.

The equilibrium parameter (drug partition coefficient) used to model the mass transfer process dictates the predictions' accuracy. When this parameter is calculated from the drug release experiment, the diffusion equation with a Robin boundary condition type gives good predictions of the dissolution process. Predictions obtained with zero-sink condition in the release medium resulted in an overestimation of data.

Several kinetic models available in the literature to describe drug release were used to correlate data. All the models tested describe the data adequately, but the Weibull model was the one that had the best correlation performance.

*Keywords:* Dissolution profiles; Diffusion in polymeric matrices; Dissolution models

## 1. Introduction

For a drug to be effective and simultaneously cause no (or little) toxic effects, it must be dosed in such a way that ensures that its concentration is within the therapeutic drug range. The drug administration in a single dose is responsible for a peak of drug concentration

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followed by a period of decreasing concentration to sub-therapeutic levels of drug in the body. The administration of several doses could prevent both over-doses and under-doses as well as maintain the drug concentration within therapeutic levels, but drug concentration fluctuation is unavoidable. In order to achieve a controlled active principle concentration with an effective level during long periods, the controlled release of drugs from delivery devices have been successfully applied to overcome the drawbacks of the administration in several doses ([1], [2]).

Drug delivery technology requires the contribution of several scientific areas of knowledge and research to develop devices with optimal characteristics for drug controlled release. Polymeric systems have been used successfully for this purpose with the incorporation of the drug during polymerization (in-situ drug loading) or added after the preparation of polymeric matrices by absorption (post drug loading).

Several physical and chemical phenomena dictate the kinetics during drug release from the delivery devices ([3]). The drug dissolution profile assessment is a quality parameter not only used in the development of new formulations, optimization of existing formulations but it is also used during routine quality control of drug delivery systems production ([4]). In dissolution studies an extensive series of experiments, which follow the accumulated amount of drug delivered into the release medium over time is required. The drug concentration quantification in the solution during dissolution is a time consuming procedure.

The clinical studies can not be replaced by models, but predicting the drug release behavior from controlled delivery systems could be a useful tool in pharmaceutical products development. Although the drug transport through the polymeric matrices used frequently as delivery devices is a phenomenon that depends on such as factors as polymer swelling extension and drug-polymer interactions, the assumption of a mass transfer process controlled by drug diffusion can be appropriate. More detailed and realistic models are synonymous of additional complexity ([5], [6]) not always followed by an improvement in predictions' accuracy.

The use of semi-empirical/empirical mathematical equations or equations with theoretical support has been widely disseminated as an easier way of quantitatively interpreting data obtained in dissolution experiments. With the semi-empirical/empirical models available the insight into drug release parameters dependence will be low but these are very useful in the establishment of similarities between dissolution profiles.

This study presents a comparison between the data collected during a drug release experiment monitored continuously and the predictions obtained from: $i$) a diffusional model to describe the drug transfer through the release device and $ii$) different semi-empirical/empirical models available in the literature. Several boundary conditions con-

cerning the external conditions of the release device are used in the mathematical modeling in order to have a progressively more realistic representation of the phenomena and simultaneously to better understand its influence on the mass transfer process.

## 2. Procedures and methods

In the present work a case study with the timolol maleate release from a small polymer disc made with a methacrylate based hydrogel is used.

The timolol active ingredient is commonly used in the glaucoma treatment. Recently therapeutic contact lenses were used as an efficient delivery device of this medication into the eyes. Poly(hydroxyethyl methacrylate) (polyHEMA) have been used as a main polymer in the preparation of therapeutic lenses, which is complemented with a small amount of methacrylic acid (MAA) in order to enhance the hydrogel drug load capacity.

The drug dissolution experiment described uses a small disc made of polyHEMA and MAA (3%, w/w) prepared by thermal copolymerization using ethylene glycol dimethacrylate (EGDMA) as a cross-linking agent. The timolol maleate containing the active ingredient was incorporated in the mixture before polymerization (in-situ loading).

Several small discs with the same polymeric formulation but without the addition of the active ingredient were also prepared to be used in equilibrium experiments for the timolol maleate partition coefficient determination.

### 2.1. Dissolution experiments (data)

An experimental technique with continuous measurement of drug concentration in the release medium has been implemented and described in [7]. The hydrogel film with the timolol maleate incorporated, a disc shape about 18 mm in diameter and 0.5 mm thickness, was immersed in the release medium (an aqueous solution of NaCl with a concentration of 9 g/L and pH $= 5.62 \pm 0, 14$) during 48 hours. The release medium temperature was maintained constant at $36\,^{o}$C by means of a thermostatic bath and the medium agitation was ensured by a magnetic stirrer. The release medium flowed in a closed circuit with the help of a peristaltic pump and passed through a flux cuvette located inside a spectrophotometer where the solution absorbance was continuously measured at 292 nm (the wavelength of maximum absorbance for timolol maleate).

The drug dissolution profile was obtained from the absorbance data acquired every 300 s (using the HiperTerminal emulator to connect to a computer), during the drug release experiments and trough using a calibration curve (absorbance *versus* drug concentration) obtained previously. The release experiments were repeated 3 times in similar conditions

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in order to show that reproducible drug dissolution profiles were produced with less than 5% relative standard errors.

## 2.2. Drug diffusion in the delivery system and numerical approach

The mass transfer mechanism of drugs in polymeric delivery devices is usually controlled by diffusion ([6], [8], [9]) and Fick's second law written as,

$$\frac{\partial C_A}{\partial t} = D\frac{\partial^2 C_A}{\partial x^2}, \text{ in } \Omega, \, t > 0, \tag{1}$$

can be used to represent the drug release process from plane sheets of solid membranes, where $C_A$ represents the drug concentration in the delivery device, $D$ is the drug diffusion coefficient, $t$ is the time with $\Omega = (-\ell, \ell)$ and $\ell$ is the semi-thickness of the polymer. Equation (1) defines a one-dimensional transient diffusional problem and $x$ stands for the direction in which mass transfer occurs. As thin discs of polymeric matrices are being dealt with, radial and circumferential drug concentration gradients can be discarded in relation to the gradients developed in the axial direction $(x)$.

The initial and boundary conditions for this problem can be written as:

$$C_A = C_{Ai}, \text{ in } [-\ell, \ell], \, t = 0, \tag{2}$$

$$\frac{\partial C_A}{\partial x} = 0, \text{ in } x = 0, \, t > 0, \tag{3}$$

$$C_A = C_{AS} \simeq 0, \text{ in } x = \ell, \, t > 0. \tag{4}$$

The initial condition (Eq. (2)) assumes initial uniform drug concentration throughout the small disc, from the lower surface $(x = -\ell)$ up to the upper surface $(x = \ell)$. The boundary condition presented in Eq. (3) describes the disc midplane $(x = 0)$ symmetry requirement. The zero-sink boundary condition (Eq. (4)) represents the drug concentration in the polymeric matrix on its surface $(C_{AS})$ which is assumed to be constant and virtually zero as a first approximation to resolve the unsteady state diffusion problem. This condition corresponds to a situation where the release medium volume is sufficiently large for the amount of drug released from the solid matrix to significantly modify the drug concentration in the (well stirred) release medium and it also considers that the drug mass transfer resistance outside the polymeric matrix is negligible (infinite mass transfer coefficient). Besides the initial period of the dissolution process, the approximation referred was not legitimate because a small volume of release medium was used in the experiments.

In order to improve the boundary condition two more realist assumptions were introduced. Considering a finite mass transfer coefficient for the release medium $(k_L)$, new conditions were used establishing that the drug flux on the delivery device surface, coming

from the polymer interior by diffusion, is transferred by convection through the release medium. Equation (5) presents the boundary condition with the assumption of negligible drug concentration in the bulk of the release medium:

$$-D\frac{\partial C_A}{\partial x} = k_L(C_{AS}^{\text{r.m.}} - 0) = \frac{k_L}{K}(C_{AS} - 0), \text{ in } x = \ell, \, t > 0 \tag{5}$$

and the condition in Eq. (6) considers a time-dependent quantity increasing during the dissolution process,

$$-D\frac{\partial C_A}{\partial x} = k_L(C_{AS}^{\text{r.m.}} - C_{A\infty}^{\text{r.m.}}) = \frac{k_L}{K}(C_{AS} - C_{A\infty}^*), \text{ in } x = \ell, \, t > 0. \tag{6}$$

In Eq. (5) and Eq. (6) the driving force for mass transfer in the release medium was expressed in terms of drug concentrations in the polymeric matrix using the drug partition coefficient $K$ and $C_{A\infty}^*$ represents the drug concentration in the solid that would be in equilibrium with the bulk drug concentration in the release medium. The evolution of $C_{A\infty}^{\text{r.m.}}$ over the dissolution process is obtained by a drug mass balance performed to an infinitesimal period of time $dt$,

$$2\dot{m}_A|_{x=\ell} \times dt = -2DA\left(\frac{\partial C_A}{\partial x}\right)_{x=\ell} \times dt = V dC_{A\infty}^{\text{r.m.}}, \tag{7}$$

where $\dot{m}_A|_{x=\ell}$ is the drug mass transfer rate crossing the delivery device surface at $x = \ell$ (which due to the symmetry requirement is equal at $x = -\ell$) and $A$ is the surface area of the polymeric matrix exposed to the release medium with volume $V$.

The numerical predictions were obtained using a simple finite difference method for the drug concentration in the polymer disc, where a central difference formula of second order is used to discretize the second order derivative (Eq. (1)). For time integrations (Eq. (7)) the Euler method of first order was used. When the boundary condition in Eq. (6) was considered, the numerical method applied to approximate the solution of the diffusional problem used a backward difference to discretize the flux on the boundary. The numerical computation developed used Matlab technical language.

### 2.3. Modeling of dissolution profile

The in vitro dissolution experiments are a useful tool for the development of drug delivery devices or the optimization of existing formulations. Over the last decades, several theoretical or empirical models have been proposed to describe the drug dissolution process as an alternative to the time-consuming kinetic experiments.

The most relevant and the most commonly used drug dissolution models are presented and discussed at the review work of [10]. Some models were derived with theoretical

Table 1: Drug dissolution models used to correlate data for timolol maleate release from the polymeric matrix based on methacrylate hydrogel.

| Model | Equation | Parameters | |
|---|---|---|---|
| First-order | $F = F_{max}\left[1 - \exp(-kt)\right]$ | $F_{max}; k$ | Eq. (8) |
| Weibull | $F = F_{max}\left[1 - \exp\left(-\dfrac{t^{\beta}}{\alpha}\right)\right]$ | $F_{max}; \alpha, \beta$ | Eq. (9) |
| Logistic | $F = F_{max}\dfrac{\exp[\alpha + \beta\log(t)]}{1 + \exp[\alpha + \beta\log(t)]}$ | $F_{max}; \alpha, \beta$ | Eq. (10) |
| Gompertz | $F = F_{max}\exp\{-\alpha\exp[-\beta\log(t)]\}$ | $F_{max}; \alpha, \beta$ | Eq. (11) |
| Probit | $F = F_{max}\phi[\alpha + \beta\log(t)]$ | $F_{max}; \alpha, \beta$ | Eq. (12) |

support, such as the case of zero-order, first-order (Eq. 8), Korsmeyer-Peppas, Baker-Lonsdale and Hopfenberg models, but other (empirical) models were obtained from known mathematical equation adaptations, for example the Weibull (Eq. 9), logistic (Eq. 10), Gompertz (Eq. 11) and probit (Eq. 12) models. The models presented in Table 1 were used to correlate the experimental data obtained during timolol maleate release from the polymeric matrix based on the methacrylate hydrogel used in this study.

Most of the equations used to model drug dissolution processes are nonlinear. Some efforts have been made to develop more user-friendly and versatile software to optimize nonlinear data fitting for drug release studies ([11], [12]) as an alternative to commercial statistical software packages. The add-in program DDSolver ([12]) is a supplement for Microsoft Excel and is a good example of the results achieved. When launched with Excel, this supplement can be easily accessed and a pull-down menu where a library with several dissolution models is presented. A nonlinear least-squares curve fitting is used by DDSolver which minimizes the sum of squares differences between the observed (data) and the predicted dissolution values with the best model parameters determination. The nonlinear optimization technique used the Nelder-Mead simplex algorithm which has some advantages ([12], [13]) compared to more classical ones (as Gauss-Newton and Marquardt algorithms). Additionally, DDSolver calculates several parameters allowing the statistical fitness evaluation of the model. Some of the most popular tests are ([10], [12]): the coefficient of determination ($R^2$), or the adjusted coefficient of determination ($R^2_{adjusted}$) when comparing models with different numbers of parameters; the correlation coefficient ($R$); the sum of squares of residues (SSR); the Akaike Information Criterion (AIC) ([14]) and

the Model Selection Criterion (MSC) ([15]). The most appropriate model to fit dissolution data shall give the smallest value of AIC and the largest value of MSC (in general, values greater than 2-3 indicate a good fit ([16]).

The models presented in Table 1 were fitted to the data obtained in the timolol maleate drug dissolution experiments using the DDSolver add-in program.

## 3. Results and discussion

### 3.1. *Data* versus *numerical solutions of the diffusion problem*

When the polymeric delivery device with the incorporated drug is immersed in the release medium, a dissolution process is initiated with the development of a drug concentration gradient within the polymeric matrix which promotes the diffusion process. The drug is transferred from the interior towards the delivery device's exterior surface and the drug concentration profile changes with time. Predictions were made using the numerical approach presented before, which was used to resolve the differential equation describing the diffusion problem with the boundary and initial conditions.

The equilibrium and mass transfer parameters, the dimensional characterization of the polymeric disc and the timolol maleate concentration incorporated inside it used to obtain the predictions are presented in Table 2. The information about the HEMA/MAA disc, corresponds to the one used in the dissolution experiment described. The diffusion coefficient of timolol maleate in the polymer disc was obtained from data collected during the dissolution experiment as described by [7]. The partition coefficient $K$ was experimentally obtained by immersion of blank polymer discs (without drug incorporated) in concentrated aqueous solutions of timolol maleate until saturation. The drug absorbed by the discs was calculated from the difference between the amount of timolol maleate in the liquid at the beginning and after 7 days of soaking; the timolol maleate concentration in the solution was obtained by spectrophotometry. A partition coefficient of $9.02 \pm 0.26$ results from 8 independent absorption experiments. The mass transfer coefficient used for the liquid phase ($k_L$) was estimated from a correlation for external forced convection flow over a flat plate. The average liquid velocity was calculated with the dimensions and the rotational speed of the magnetic stir bar used to stir the released medium during the experiment. The Schmidt number was obtained with the timolol maleate coefficient diffusion in the released medium predicted using the Wilke-Chang equation ([17]).

The timolol maleate concentration profiles corresponding to different dissolution times, which were predicted with the simple mathematical approach presented previously, are shown in Figure 1. Three different external boundary conditions (Eq. (4) to Eq. (6)) were

Table 2: Parameters and conditions used to obtain the predictions, which correspond to the dissolution experiment conditions.

| | | |
|---|---|---|
| timolol maleate diffusion coefficient in the polymeric matrix ($\mathrm{m^2/s}$) | | $2.33 \times 10^{-12}$ |
| Schmidt number in the release medium | | 866 |
| mass transfer coefficient in the release medium (m/s) | | $2.11 \times 10^{-5}$ |
| polymer disc dimensions | - thickness (m) | $0.5 \times 10^{-3}$ |
| | - diameter (m) | $16.85 \times 10^{-3}$ |
| initial timolol maleate concentration in the polymer disc (mg/mL) | | 5.62 |
| partition coefficient from drug load experiments | | $9.02 \pm 0.26$ |

used to obtain Figures 1 a), b) and c). Initially, the drug concentration is uniform throughout the polymer, but then the concentration starts to decrease from the external surface of the delivery device in contact with the release medium to its interior. As expected, symmetric parabolic concentration profiles are developed within the polymeric matrix, which become flatter as the dissolution process continues. After 12 hours of immersion in the release medium, the concentration profiles are virtually coincident (for all the boundary conditions used) indicating that no more timolol maleate is released from the polymer.

An obvious conclusion can be drawn from the concentration profiles obtained with the three scenarios, no significant changes in the timolol maleate concentration distribution within the polymeric matrix were observed. However, a residual uniform concentration of drug in the delivery device resulted from the predictions, when an increase in drug concentration in the release medium (proportional to the amount of drug released from the polymer disc) was considered in the boundary condition applied in the mathematical approach (see Figure 1 c)). Effectively, when a zero-sink boundary condition is used, theoretically all the drug loaded into the delivery device can be released if the dissolution process is long enough.

The release profile of the timolol maleate from the polymer disc obtained in the dissolution experiment is presented in Figure 2 along with the predictions from the different mathematical approaches. After the initial burst of drug release, the increase of timolol maleate in the release medium starts slowing down and for a time of dissolution greater than 12 hours the amount of drug dissolved remains almost constant. This behavior is reported in both situations: the dissolution experiment and the numerical approaches. However, the amount of drug released is overpredicted by the theoretical approach. After an initial period (about 4 hours), the boundary condition used at the delivery device's surface starts to influence, albeit to a small extent the drug release rate from the polymer disc. This happens when the mass transfer driving force, $C_{AS}^{\mathrm{r.m.}} - C_{A\infty}^{\mathrm{r.m.}}$, predicted for the
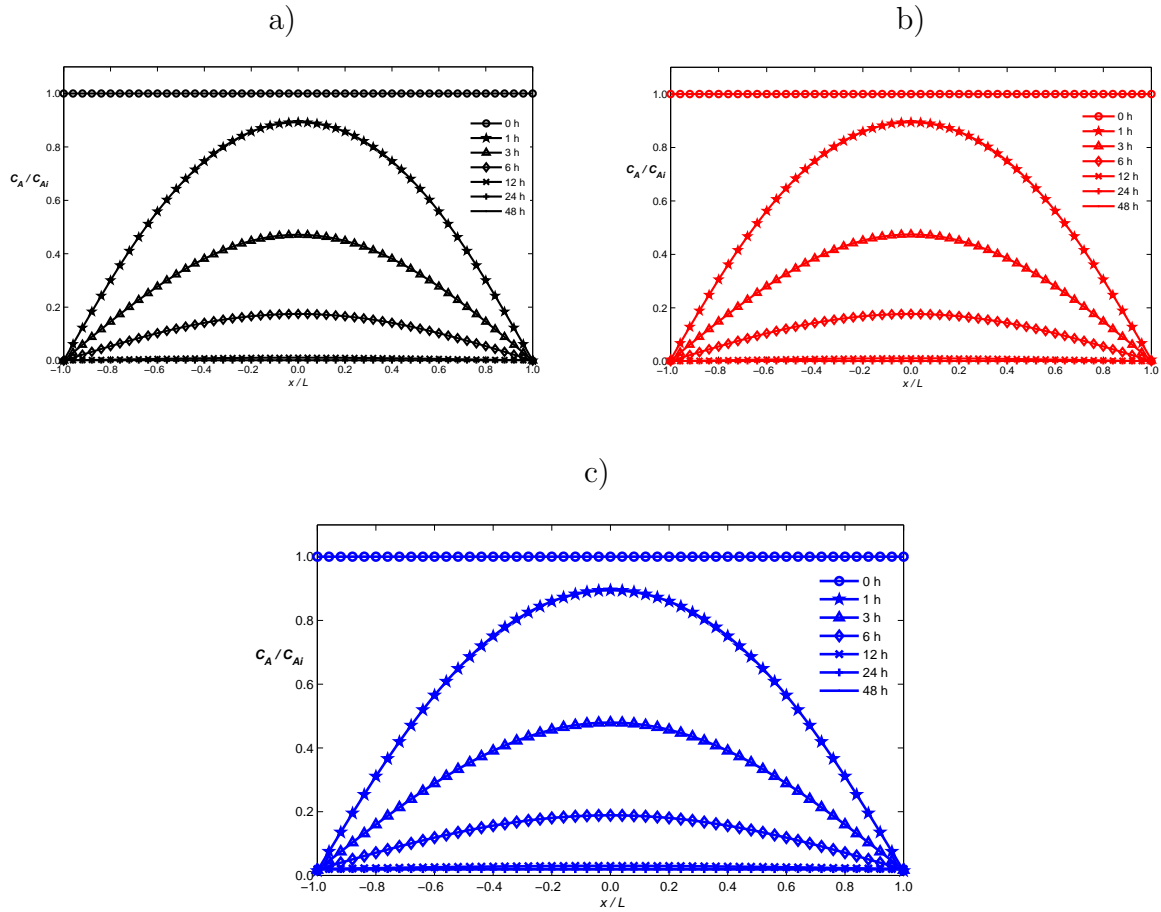
a)

b)

c)

Figure 1: Timolol maleate concentration profiles developed within the polymeric matrix based on methacrylate hydrogel for different times of dissolution and predicted using different boundary conditions at the interface: a) Eq. (4), b) Eq. (5) and c) Eq. (6). The partition coefficient used in the predictions was obtained from drug load experiments ($K = 9.02$).
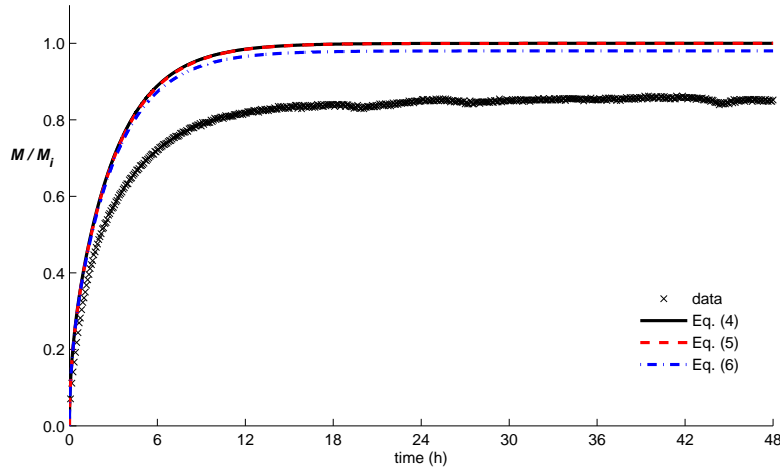
Figure 2: Timolol maleate release profiles obtained from the dissolution experiment and predicted using the mathematical approach with different boundary conditions at the interface, represented by Eq. (4) - Eq. (6). The partition coefficient used in the predictions was obtained from drug load experiments ($K = 9.02$).

release medium becomes virtually zero as the equilibrium (dictated by the partition coefficient $K$) between the timolol maleate in the solution and within the polymeric device has been reached.

The $M/M_i$ ratio limit value reached with the predictions using a zero-sink boundary condition is 1.0, indicating that all the drug loaded into the polymeric device was released into the solution. This result was expected and it is independent of the magnitude of the equilibrium constant used.

The predictions show that drug transfer in the release medium is not the rate-limiting step as the assumption of negligible external mass transfer resistance and the different solution drug concentration do not affect very significantly the predicted dissolution profile (comparison of profiles obtained with Eq. (4) through Eq. (6)). However, as expected the predictions obtained with the zero-sink boundary condition deviate more from the data because they were obtained with the highest possible driving force for mass transfer in the release medium during the whole dissolution process. When a nonzero drug concentration in the release medium was used, the predicted amount of drug delivered decreased, approaching (although slightly) the profile obtained from the dissolution experiment.

The drug equilibrium coefficient $K$ between the hydrogel and the external solution dictates the solute concentration on the external delivery device boundary and the drug flux across the interface. When the drug does not interact with the polymer chains, the solute

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partitioning phenomena is a reversible equilibrium. Some works ([18], [19]) refer favorable interactions between ionic and nonionic water soluble drugs and the internal polymer network of HEMA and MAA copolymers through specific adsorption or ion binding.

The pH and ionic strength of the medium have a great influence on the timolol maleate uptake by the polymeric matrix and on the release process from soft contact lenses ([20], [21], [22]). Timolol maleate is present in the cationic form (the pKa value of the protonated timolol is 9.2 ([23])) in the loading solution (pH = 4.5) used in the drug soaking process. The interaction with the carboxylic groups of MAA in the polymeric network is expected to be ionic and/or through hydrogen bonds with the amino and hydroxyl groups in the molecular structure of timolol maleate. This suggests that solute interactions with polymer matrix are strong and the equilibrium partition deviated from ideal partitioning. As a consequence, the partition coefficient measured in the drug load direction will be different of that obtained in the timolol maleate release direction. Therefore, a new drug equilibrium coefficient was calculated from the back extraction experiments (dissolution experiments using the loaded discs by absorption) and the value of $K = 842.47 \pm 32.24$ was obtained, which was much higher than the coefficient obtained in the load direction, indicating a large drug/polymer network interaction.

The timolol maleate concentration profiles predicted from the mathematical approach, for different boundary conditions (Eq. (4) - Eq. (6)) and with the $K$ value obtained by back extraction of the drug, are presented in Figure 3.

The equilibrium coefficient effect in the drug concentration profiles predicted is evident from the comparison of Figures 3 and 1. Besides the case presented in Figure 3 a) (zero-sink condition and negligible mass transfer resistance in the release medium, represented by Eq. (4)), which is independent of the drug equilibrium established between the hydrogel and the external solution, the concentration profiles shapes' changed significantly because the value of $C_{AS}$ is conditioned by timolol maleate equilibrium. The magnitude of the drug concentration gradients inside the polymer becomes smaller because the value of $C_{AS}$ increases significantly due to the higher drug affinity with the hydrogel introduced by the new value of $K$ used in the predictions. As a consequence, the drug concentration profiles obtained are flatter when compared with the ones, presented in Figure 1, for a different value of $K$ calculated from the drug load experiments. The constant and uniform high drug concentration distribution achieved within the polymer after 12 hours, which is depicted in Figure 3 c), is also a consequence of the higher affinity of the timolol maleate with the polymeric matrix introduced in the predictions with $K = 842.47$. A significant fraction of the drug initially loaded in the delivery device remains linked with the polymer network.

Schematic representations of the drug concentration effect on the interface solid/liquid,
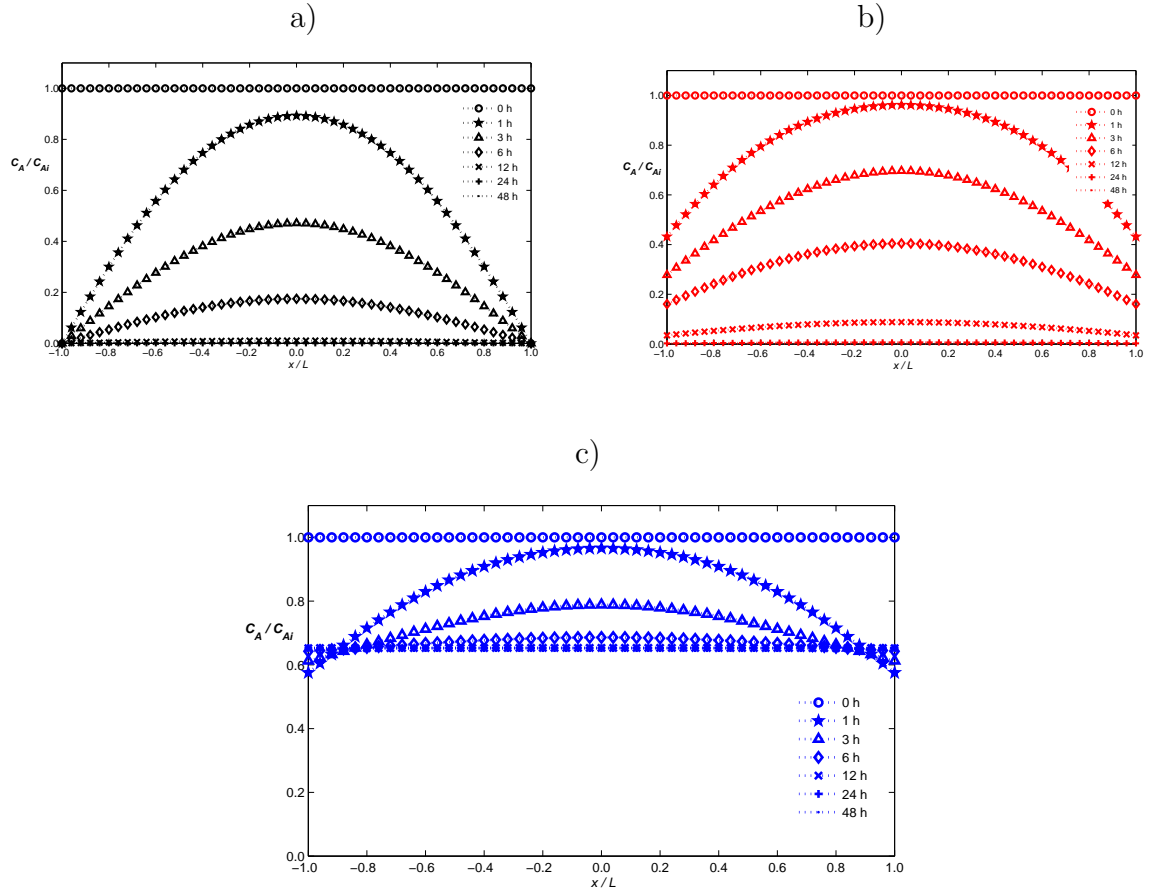
Figure 3: Timolol maleate concentration profiles developed within the polymeric matrix based on methacrylate hydrogel for different times of dissolution and predicted using different boundary conditions at the interface: a) Eq. (4), b) Eq. (5) and c) Eq. (6). The partition coefficient used in the predictions was obtained from drug load experiments ($K = 842.47$).

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caused by the different boundary conditions used on the delivery device's surface, are shown in Figure 4.
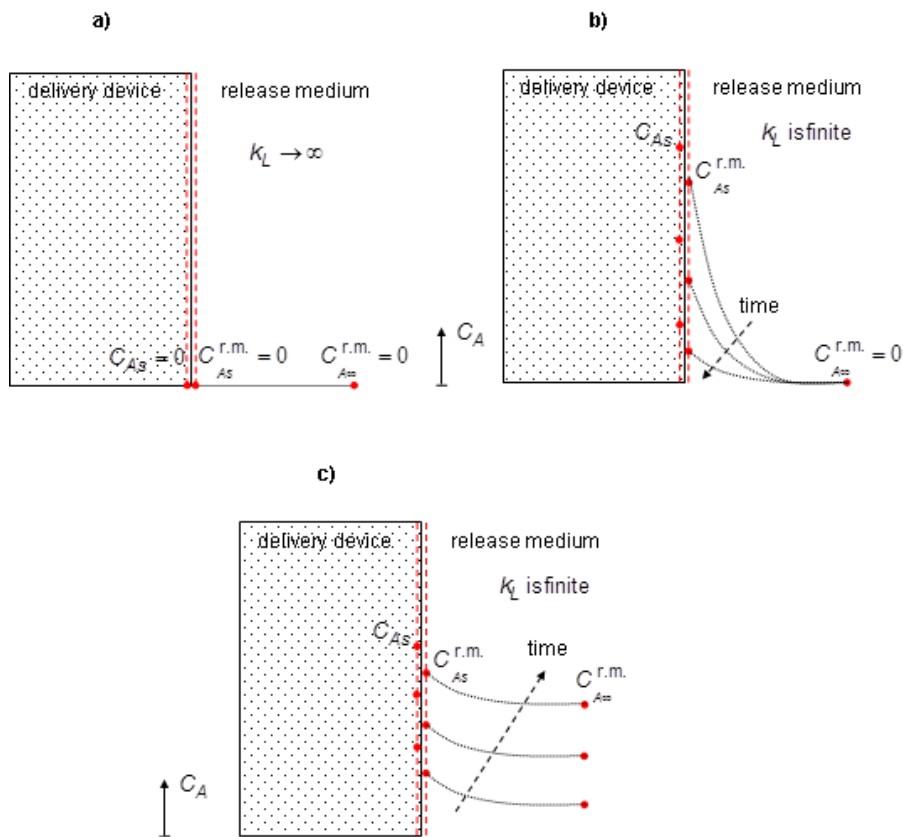


Figure 4: Schemes illustrating the effect of the boundary conditions used to obtain the predictions on the drug concentration on the delivery device's interface. Boundary conditions represented by: a) Eq. (4), b) Eq. (5) and c) Eq. (6).

The value of $C_{AS}$ is constant and equal to zero (see Figure 4 a)), when in the mathematical approach were considered that the drug concentration in the release medium during the dissolution process is negligible and there is no mass transfer resistance in the liquid. When Robin boundary conditions (mass flux equation) are used, the value of $C_{AS}$ is a time-dependent parameter, as is illustrated in Figures 4 b) and 4 c). If ideally the timolol maleate concentration in the bulk of the release medium is considered approximately zero throughout the dissolution process, the driving force $(C_{AS}^{\text{r.m.}} - C_{A\infty}^{\text{r.m.}})$ for mass transfer in the release medium decreases over time because $C_{AS}$ becomes smaller as the drug is released from the polymeric device. However, high driving forces are imposed by the mathematical approach as $C_{A\infty}^{\text{r.m.}}$ is maintained equal to zero during the whole release process. For a Robin boundary condition with $C_{A\infty}^{\text{r.m.}}$ variable, after an initial period (of about 1 hour),
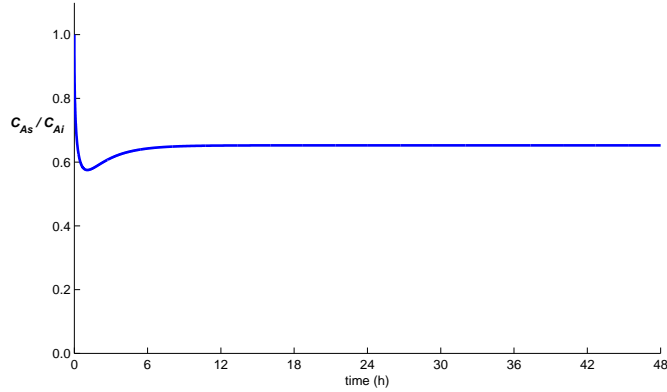
Figure 5: Dimensionless drug concentration on the polymeric matrix surface during the dissolution process predicted by the mathematical approach with the boundary condition represented by Eq. (6) ($K = 842.47$).

the value of $C_{AS}$ increases (see Figure 4 c)). Due to the initial burst release of timolol maleate the drug concentration in the release medium increases rapidly (see Figure 2) with a consequent rapid decrease in the driving force for mass transfer in the liquid. As the drug flux magnitude, used as a boundary condition, determines the flux crossing the polymeric device surface, the timolol maleate transferred by diffusion from the polymer's interior starts to accumulated near the periphery. As a result the value of $C_{AS}$ starts to increase as can be seen in Figure 5, where is represented the evolution of $C_{AS}$ predicted from the mathematical approach with the conditions illustrated in the scheme of Figure 4 c). This behavior was not detected in the predictions obtained from the mathematical approach with the conditions shown in the scheme of Figure 4 b), because it was considered that, ideally, the timolol maleate concentration in the release medium is maintained virtually zero during the dissolution process.

The timolol maleate release profiles predicted from the different mathematical approaches with the new scenario for drug equilibrium presented in Figure 6 reflect the significant changes observed in the drug diffusion within the polymer disc (see Figure 3).

Now, the predictions show that the conditions considered in the release medium constrain the dissolution profile indicating that this step has a significant contribution to the dissolution process. A distinct behavior is observed from the predictions obtained with Robin boundary condition for zero-sink and variable drug concentrations in the release medium. When $C_{A\infty}^{\text{r.m.}} = 0$ is considered all the drug inside the delivery device can be released because equilibrium between liquid and solid was never reached. However, the drug has a great affinity with the solid and the dissolution process is slower. Almost 30 hours
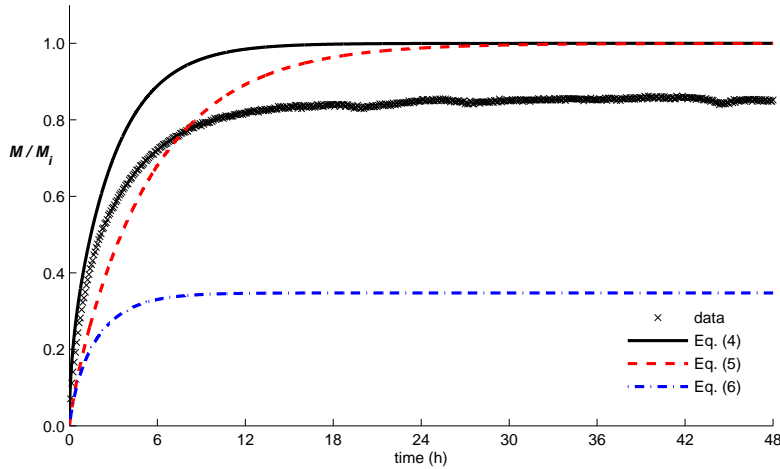
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Figure 6: Timolol maleate release profiles obtained from the dissolution experiment and predicted using the mathematical approach with different boundary conditions at the interface, represented by Eq. (4) - Eq. (6). The partition coefficient used in the predictions was obtained from drug back extraction experiments ($K = 842.47$).

is the time predicted for the entire drug to be released from the polymer disc. When the concentration $C_{A\infty}^{\text{r,m.}}$ used in the predictions is time-dependent (calculated with the amount of drug already released), the equilibrium is reached with a small fraction of drug released due to the high value of $K$. In this case, which is the most realistic mathematical approach, the released amount of timolol maleate is underpredicted, indicative of an overestimation of the partition coefficient used.

Frequently, besides the covalent cross-links established during polymerization in the presence of a cross-linking agent, secondary structures also contribute to the stabilization of the polymeric structure. In poly(HEMA) hydrogels, these forces may result from hydrophobic interactions between polymer chains (through the $\alpha$-methyl groups in HEMA structure) as explained in [24] or are attributed to hydrogen bonding as referred in [25]. When the secondary structures in the network polymeric chains are disrupted due to the carboxyl groups' ionization, the structure's stabilization is guaranteed by covalent cross-links. At a neutral pH, the cross-linking effect was revealed in the matrix hydratation during the swelling study performed in [26] with HEMA/MAA hydrogels prepared with different amounts of cross-linking agent.

The conditions used in the maleate timolol experiment presented in this study suggest that a ionized HEMA/MAA hydrogel prevails when immersed in the release medium and the covalent network developed during polymerization is the dominant effect in the

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polymeric structure's stabilization.

Several studies ([21], [27], [28]) indicate differences in the polymer network's structure when drug was added to the monomers solutions and it is present during inter and intrachain interactions promoted by the cross-linker agent during polymerization. These structural modifications in the hydrogel chains certainly interfere with the drug partition between the polymer network and the release medium, likewise the solute diffusion hinderance seems to be reduced because the timolol maleate diffusion coefficient is higher when the drug was occluded in the hydrogel, as referred in [7].

Hence, a new drug equilibrium coefficient was calculated from the dissolution experiment and a value of $K = 57.06$ was obtained, which is about six times greater than the coefficient in the load direction and is significantly smaller than the partition coefficient calculated during the drug back extraction experiments. This indicate a greater accessibility to drug sites inside the polymeric matrix with a consequent greater affinity with the release medium. It should be emphasized that in the drug back extraction experiments the timolol maleate was loaded to the release device after the hydrogel preparation and the covalent cross-links established during polymerization occurred in the absence of drug with structural modifications in the polymeric network.

Similar predictions were performed with $K = 57.06$ and the results are presented in Figures 7 and 8.

The drug concentration profiles obtained 1 hour after the polymer disc had been immersed in the release medium are similar in all the predictions performed, which shows that the conditions existing on the boundary of the delivery device are not significantly conditioned by the drug diffusion (see Figure 7). However, as the magnitude of the drug concentration gradients inside the polymer become smaller, the value of $C_{AS}$, dictated by the hydrodynamic conditions on the polymer disc's surface and the drug concentration in the release medium, become more important for the mass transfer diffusion process. As a consequence flatter drug concentration profiles are obtained when a higher value of $C_{AS}$ results from the boundary condition used in the mathematical approach.

Figure 8 shows that the predictions using the zero-sink condition at the release medium (Eq. (4) and Eq. (5)) during the dissolution process are not sensitive to the partition coefficient value. The condition of zero drug concentration imposed on the solution originates a driving force for mass transfer in the release medium which is so high that, in the predictions, the mass transfer process by drug diffusion in the polymeric matrix is maintained until the drug initially loaded to the delivery device is almost completely released. The negligible resistance of the timolol maleate convection in the release medium considered (Eq. (4)) has no effect on the global mass transfer process as the dissolution step is not the
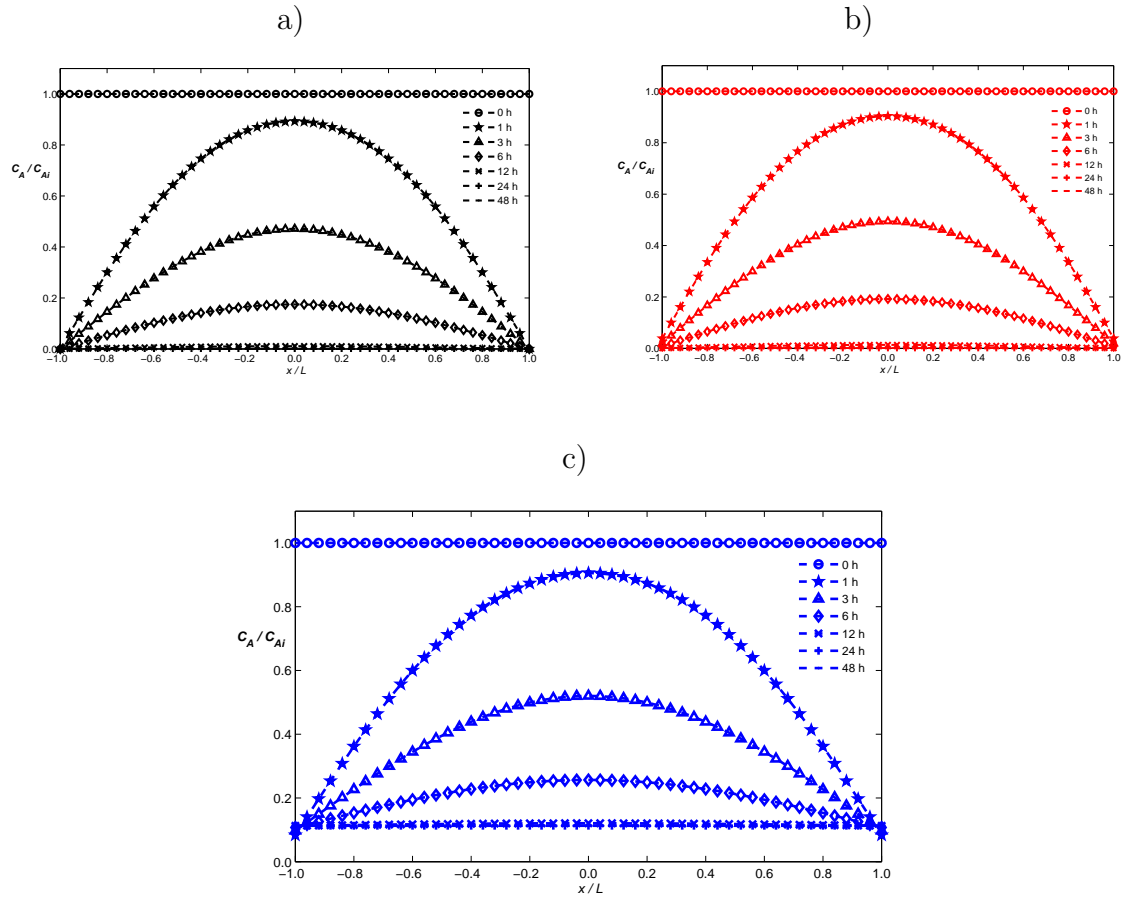
Figure 7: Timolol maleate concentration profiles developed within the polymeric matrix based on methacrylate hydrogel for different times of dissolution and predicted using different boundary conditions at the interface: a) Eq. (4), b) Eq. (5) and c) Eq. (6). The partition coefficient used in the predictions was obtained from drug load experiments ($K = 57.06$).
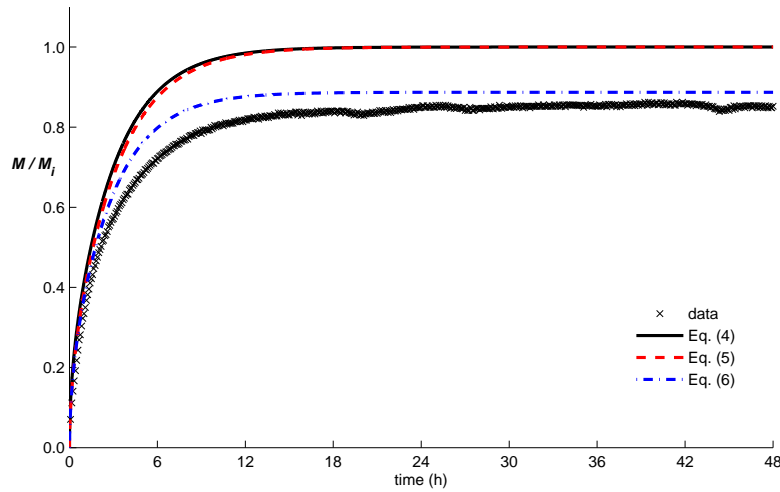
Figure 8: Timolol maleate release profiles obtained from the dissolution experiment and predicted using the mathematical approach with different boundary conditions at the interface, represented by Eq. (4) - Eq. (6), and using the drug partition coefficient measured from the drug release experiment ($K = 57.06$).

limiting step. When more realistic boundary conditions were used in the mathematical approach and a time-dependent value of $C_{A\infty}^{\mathrm{r,m.}}$ was assumed, the value of $K$, which establishes the relationship between $C_{AS}$ and $C_{AS}^{\mathrm{r,m.}}$, significantly influences mass transfer diffusion in the polymeric device. The value of $K$ calculated for drug release direction is affected by the interactions between the timolol maleate and the polymeric network. Therefore, the solute concentration on the solid surface, which is in equilibrium with the drug concentration in the release medium in contact with the polymeric matrix, is higher than for the situation where reversible equilibrium for solute partitioning was considered. This fact leads to lower local concentration gradients. As a result, after the initial period of drug burst, the dissolution process predicted starts slowing down due to the very small driving forces for timolol maleate mass transfer convection as the equilibrium is approaching. The amount of timolol maleate delivered to the release medium calculated is not so high and better predictions are obtained (Figure 8), because the value of $K$ used was obtained for conditions where the drug-polymer interactions are the same.

To facilitate the comparison of the partition coefficient value effect on the predicted drug release profiles, the predictions obtained with $K$ measured in the timolol maleate load direction, back extraction direction and in the dissolution experiment are presented in Figure 9. The drug flux across the interface was used as boundary condition with
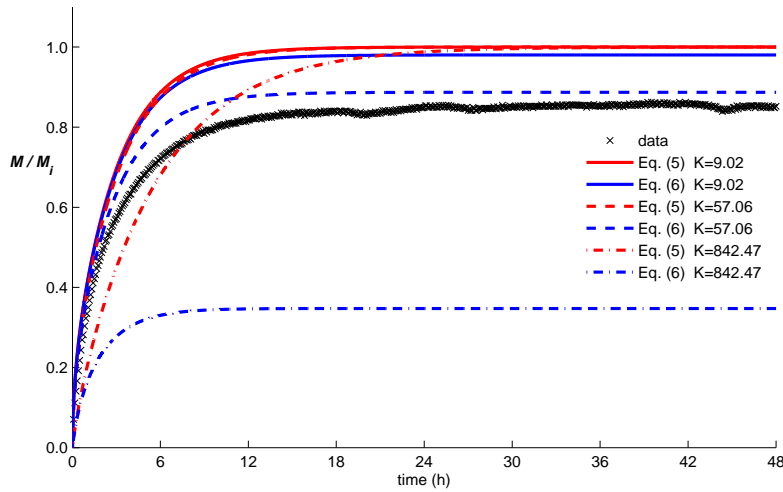
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Figure 9: Timolol maleate release profiles obtained from the dissolution experiment and predicted using the mathematical approach with Robin boundary conditions for zero-sink and variable $C_{A\infty}^{\mathrm{r,m.}}$ with $K = 9.02$ (measured in the drug load direction), $K = 842.47$ (measured in the drug extraction direction) and $K = 57.06$ (measured from the drug release experiment).

zero-sink and variable drug concentrations in the release medium. In fact, when the drug concentration in the solution is considered ideally zero during the dissolution process, theoretically all the timolol maleate initially loaded to the polymer disc could be released because the equilibrium between the drug dissolved in the release medium and within the solid is never reached. For that reason, in the drug release profiles illustrated in Figure 9 the $M/M_i$ ratio tends to 1.0 as the dissolution time increases irrespective of the value of $K$ used. However, for the highest value of $K$ measured in the timolol maleate back extraction experiments, the initial delivery rate of drug predicted for the dissolution process is lower and the drug concentration in the solution does not increase so rapidly. As a result, it takes about 30 hours to release the total amount of drug loaded into the polymer disc. When the two others values of $K$ were used in the predictions, about 12 hours was enough for all the drug loaded into the delivery device to be released, which indicates a faster dissolution process.

Conversely, when the boundary condition used assumes that the drug concentration in the solution increases with time and is calculated with the amount of timolol maleate already released, the equilibrium is reached gradually and the value of $K$ used in the predictions has a great importance. If the interactions between the solute and the solid are not considered the predicted amount of drug released from the delivery device almost

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Table 3: Model parameters obtained from nonlinear regression using the DDSolver add-in program and some popular tests to evaluate the adjustment of the data to the models.

| Model | Parameters | $R^2_{adjusted}$ | R | SSR | AIC | MSC |
|---|---|---|---|---|---|---|
| First-order | $k = 0.0001030$<br>$F_{max} = 0.8436$ | 0.9764 | 0.9918 | 0.0003733 | -883.9 | 3.671 |
| Weibull | $\alpha = 839.2$<br>$\beta = 0.7377$<br>$F_{max} = 0.8527$ | **0.9988** | **0.9994** | **0.00001868** | **-2610** | **6.664** |
| Logistic | $\alpha = -10.10$<br>$\beta = 2.690$<br>$F_{max} = 0.8794$ | 0.9928 | 0.9966 | 0.0001146 | -1564 | 4.849 |
| Gompertz | $\alpha = 952.2$<br>$\beta = 1.930$<br>$F_{max} = 0.9028$ | 0.9828 | 0.9919 | 0.0002729 | -1063 | 3.982 |
| Probit | $\alpha = -6.196$<br>$\beta = 1.656$<br>$F_{max} = 0.8659$ | 0.9939 | 0.9971 | 0.00009639 | -1664 | 5.023 |

corresponds to the initial load in the polymer disc. When significant interactions between the timolol maleate and the polymeric network are assumed only a small fraction (about 35%) of the drug is released.

### 3.2. Data versus kinetic models

The add-in program DDSolver was used to correlate data obtained in the dissolution experiment with the semi-empirical/empirical kinetic models presented in Table 1. As referred before, this program gives the optimized parameters estimations and also provides statistics in order to analyze the differences between data and predictions (Table 3). Analyzing the test values calculated to evaluate the adjustment of the data to the models shown in Table 3, these suggest that all the models tested present a good fit to data. However, the Weibull model shows the best correlation.

The dissolution data and the result of the regression analysis performed with the models tested are shown in Figure 10. In general, a good fitting between the data and the kinetic models' predictions is obtained. The first-order model slightly overpredicts the data during 8 hours after 4 hours of drug dissolution.
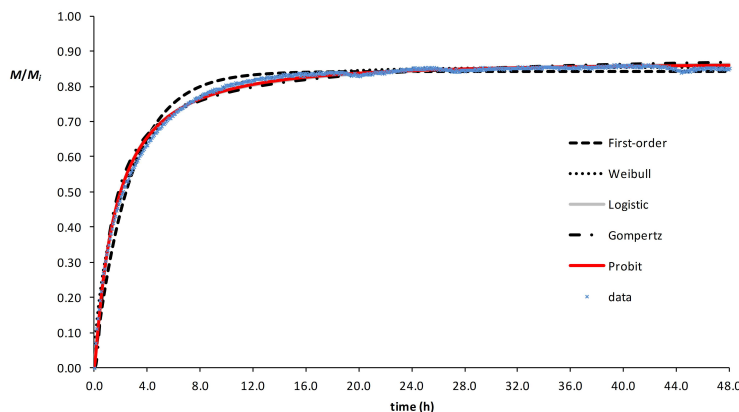
Figure 10: Timolol maleate release profile obtained from the dissolution experiment and predicted from first-order, Weibull, logistic, Gompertz and probit kinetic models. The DDSolver add-in program was used to correlate data.

The nonlinear regression needed to obtain optimized model parameters was easily implemented with the user-friendly supplement for Microsoft Excel, which was used to correlate data but without physical understanding of the complex drug mass transfer process through the delivery device and in the release medium.

## 4. Conclusions

The mathematical approach presented is based on diffusion equation with different boundary conditions on the external surface of the drug delivery device (a HEMA/MAA hydrogel disc). Zero-sink conditions with negligible mass transfer in the release medium and a finite mass transfer coefficient were applied as boundary conditions. This kind of boundary condition, although widely used in order to simplify the mathematical analysis and calculations, was inadequate for the description of the dissolution process presented because the predictions obtained overpredicted the data.

A more realistic Robin boundary condition was also used. In this condition, the drug concentration in the release medium is a time-dependent parameter which is calculated from the cumulative amount of drug dissolved. A numerical scheme for drug concentration calculation in the polymer device was implemented using Matlab language. The predictions obtained fitted the data well when the timolol maleate equilibrium partition coefficient and the timolol maleate diffusion coefficient in the polymer disc used were calculated from dissolution experiments.

Likewise the timolol maleate coefficient diffusion in the polymeric matrix, the drug partition coefficient is also an apparent quantity and a valuable parameter to obtain accu-

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rate predictions from available models. Three aspects should be analyzed and studied in order to better understand the partitioning of timolol maleate between the HEMA/MAA hydrogel and the release medium: chemical interactions, electrostatic effects and steric factors.

For different membrane compositions and other polymerization and release conditions new parameters must be obtained through extensive experimental determinations.

The experimental data was also analyzed using kinetic models available in the literature. A very good description of the data was obtained with the Weibull model, which had a correlation coefficient of 0.9988 and a very small ($1.868 \times 10^{-5}$) residual sum of squares. The logistic, Gompertz and probit models also adequately correlated the data. Within the models tested, the first-order model was the one that presented the most unfavorable evaluation parameters for the adjustment of data to the model.

Although the semi-empirical/empirical kinetic models available can be readily used to describe drug controlled release processes, the physical meaning of the model parameters is not clear and therefore the mass transfer insight is limited. However, it is a very useful tool for quantitative interpretation of data in routine quality control work and in similarity studies of dissolution profiles.

# AppendixA. Nomenclature

| Symbol | Definition |
|---|---|
| $A$ | area of the delivery system surface |
| AIC | Akaike information Criterion |
| $C_A$ | drug concentration in the delivery device |
| $C_{Ai}$ | initial drug concentration in the delivery device |
| $C_{AS}$ | drug concentration on the surface of the delivery device |
| $C_{A\infty}^*$ | drug concentration in the delivery device that equilibrates |
| | the bulk drug concentration in the release medium |
| $C_{A\infty}^{\text{r.m.}}$ | drug concentration in the bulk of the release medium |
| $C_{AS}^{\text{r.m.}}$ | drug concentration in the release medium contacting the delivery device surface |
| $D$ | drug diffusion coefficient |
| $F$ | fraction of drug released |
| $F_{max}$ | maximum fraction of drug released (at infinite time) |
| $K$ | drug partition coefficient |
| $k$ | parameter of the first order model |
| $k_L$ | mass transfer coefficient for the liquid phase |
| $\ell$ | semi-thickness of the delivery device |
| $M$ | amount of drug released at time t |
| $M_{initial}$ | amount of drug in the polymeric device |
| MSC | Model Selection Criterion |
| $\dot{m}_A\|_{x=\ell}$ | mass transfer rate at $x = \ell$ |
| $R$ | correlation coefficient |
| $R^2$ | coefficient of determination |
| $R_{adjusted}^2$ | adjusted coefficient of determination |
| SSR | sum of squares of residues |
| $t$ | time |
| $V$ | release medium volume |
| $x$ | mass diffusion direction (axial) |

# AppendixB. Greek Symbols

| Symbol | Definition |
|---|---|
| $\alpha$, $\beta$ | parameters of dissolution models |
| $\phi$ | standart normal distribution |

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