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Development of a mechanism and an accurate and simple mathematical model for the description of drug release: Application to a relevant example of acetazolamide-controlled release from a bio-inspired elastin-based hydrogel

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ABSTRACT

Transversality between mathematical modeling, pharmacology, and materials science is essential in order to achieve controlled-release systems with advanced properties. In this regard, the area of biomaterials provides a platform for the development of depots that are able to achieve controlled release of a drug, whereas pharmacology strives to find new therapeutic molecules and mathematical models have a connecting function, providing a rational understanding by modeling the parameters that influence the release observed. Herein we present a mechanism which, based on reasonable assumptions, explains the experimental data obtained very well. In addition, we have developed a simple and accurate "lumped" kinetics model to correctly fit the experimentally observed drug-release behavior. This lumped model allows us to have simple analytic solutions for the mass and rate of drug release as a function of time without limitations of time or mass of drug released, which represents an important step-forward in the area of *in vitro* drug delivery when compared to the current state of the art in mathematical modeling. As an example, we applied the mechanism and model to the release data for acetazolamide from a recombinant polymer. Both materials were selected because of a need to develop a suitable ophthalmic formulation for the treatment of glaucoma. The *in vitro* release model proposed herein provides a valuable predictive tool for ensuring product performance and batch-to-batch reproducibility, thus paving the way for the development of further pharmaceutical devices.

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1. Introduction

In the pharmaceutical industry, it is essential to understand the mass-transport mechanism involved in drug release and be able to quantitatively predict the kinetics of this process in order to successfully design new advanced delivery systems. In this regard, suitable mathematical models allow the effect of system-design parameters on drug-release kinetics to be estimated [1]. Accordingly, a great deal of research effort has been dedicated to the development of appropriate *in vitro* release models that can provide a predictive tool for ensuring product performance and batch-to-batch reproducibility [2–5]. It is also crucial to have a good understanding of drug-release kinetics *in vivo* to ensure effective and predictable product performance. However, in the early formulation-design stages, it is not practical to test each formulation *in vivo* due to the time required, expense and animal lives that this would involve.

In vitro release methods should be easy to apply and, ideally, should be predictive of *in vivo* release. Thus, if an *in vivo*/*in vitro* correlation (IVIVC) can be established, then the *in vitro* release profile obtained for different batches can be used to ensure product behavior *in vivo* for both quality-control purposes and bioequivalence studies [6].

In general, several factors intervene in the process of drug release from the hydrogel: 1) the solubility of the drug in the hydrogel, 2) diffusion of the drug through the membrane, and 3) the interface for transport to the receptor solution. Although several complex models (drug dissolution, diffusion and transfer to the fluid medium) have been applied to describe drug delivery from a hydrogel *via* a membrane to a receptor solution, the mathematical complexity of these models makes them inconvenient for practical use. As was pointed out nearly 40 years ago by Aris (1966) [7], and more recently by Levenspiel (2002) [8], what is really needed are simple models that can provide a good description of the system behavior.

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In light of the above, the aim of this contribution is to present a mechanism based on physically acceptable assumptions taking into account the characteristics of the experimental procedure used. In addition, we establish an accurate, robust and easy to apply mathematical model for the description of drug release from polymeric devices. Furthermore, as a proof of concept, we apply both (the mechanism and the model) to an illustrative example, namely the release behavior of acetazolamide (AZM) from a recombinant protein polymer-based hydrogel, in this case a tetrablock [9,10]. This tetrablock polymer belongs to a family of bioinspired protein-based polymers known as "elastin-like recombinamers" (ELRs) [11,12] and displays a set of features which have motivated its utilization as an example for applying the kinetic model developed herein. First of all, due to its recombinant nature, it is absolutely monodisperse, thus implying a greater robustness of the release data obtained as they will never be affected by this variable. Secondly, the similarity between the tetrablock recombinamer and natural elastin in terms of amino acid sequence results in a similarity in other properties, such as its biocompatibility and its inverse temperature transition behavior (ITT) [13,14], a concept similar to the LCST (lower critical solution temperature) notion commonly used in chemistry-related fields. Thus, the tetrablock chains remain soluble below a characteristic temperature known as the transition temperature (Tt) and assemble hydrophobically above this Tt, resulting in the formation of a hydrogel. Such thermo-gelling behavior in response to physiologically relevant stimuli, together with its biocompatibility, have positioned this recombinamer as a potential candidate for drug-delivery purposes, especially when injectable or topical administration is required. Thus, the tetrablock hydrogel can be applied either topically or injected to form a gel in a matter of seconds upon sensing body temperature. Although this tetrablock recombinamer has been physically characterized previously, its use in the field of drug delivery has not been explored yet. Herein we study the ability of this system to deliver AZM in a prolonged manner. AZM is a carbonic anhydrase inhibitor with weak diuretic activity and is used mainly in the management of glaucoma [15]. Other indications include epilepsy and high-altitude disorders. By inhibiting carbonic anhydrase in the eye, AZM decreases the formation of aqueous humor and therefore decreases intra-ocular pressure. It is used in the preoperative management of angle-closure glaucoma, or as an adjunct in the treatment of open-angle glaucoma. Topical administration is the most preferred route for ophthalmic medications due to enhanced patient comfort and minimization of potential systemic side-effects. However, this route has some limitations, such as the short precorneal residence time and poor bioavailability of most eye-drop solutions [16]. Several approaches to increase the ocular bioavailability of ophthalmic formulations have been investigated, with many of them exploring the inclusion of viscosifying agents in the formulation to achieve a lengthening of the pre-corneal contact time [17,18].

During the design stage of these and other formulations, or during experimental verification of their release behavior, it is desirable to develop and use simple but accurate mathematical models to describe the release kinetics [19]. Although these models are clearly based on transport (diffusion) equations, they are commonly known in the pharmaceutical or drug-delivery field as kinetic models, or kinetic expressions, as they describe the time-dependent behavior of drug release. Following this motivation, herein we present a mechanism that considers the fundamental step of diffusion in the hydrogel matrix and mass transfer at the membrane–solution interface. Although this mechanism does not have an analytical solution, thus meaning that a numerical procedure must be used, it describes the experimental data obtained very well. In addition, we have developed a kinetic model that can ensure effective and predictable product performance, a key parameter for transfer of the product to the pharmaceutical industry. As proof of concept, these models have been applied to a relevant example of controlled release, namely release of AZM from a tetrablock-based depot. The relevance of this system is based on the novel character of the tetrablock recombinamer and the need to develop advanced therapeutic approaches for the treatment of glaucoma.

2. Experimental

2.1. Materials

AZM was supplied by Parafarm (Buenos Aires, Argentina) and sodium chloride by Cicarelli Reagents (Rosario, Argentina). The tetrablock recombinamer was produced using recombinant techniques and purified as reported elsewhere [9,20]. Doubly distilled water was used throughout all experiments. All chemicals were of analytical grade and were used without further purification.

2.2. Characterization of the tetrablock recombinamer

2.2.1. DSC

DSC experiments were performed using a Mettler Toledo 822e instrument with liquid-nitrogen cooler. Both temperature and enthalpy were calibrated using a standard sample of indium. Tetrablock samples for the DSC measurements were prepared at 15% in an aqueous saline solution (NaCl 0.9%). A volume of 20 μL of the corresponding sample was placed inside a standard 40 μL aluminum pan and sealed hermetically.

The heating program for DSC measurements included an initial isothermal step (5 min at 0 °C to stabilize the temperature and state of the tetrablock), followed by heating from 0 °C to 60 °C at 5 °C/min.

2.2.2. Rheology tests

The mechanical properties of the hydrogels were determined using rheological tests in a controlled stress rheometer (AR2000ex, TA Instruments) equipped with a Peltier plate temperature control. A parallel plate geometry with a diameter of 20 mm and a sample volume of 350 μL in aqueous saline medium (NaCl 0.9%) was used, at a recombinamer concentration of 15 wt.%. Such concentration was chosen in base of previous work, in which it was established 15 wt.% as a suitable concentration to achieve gel formation [9]. Temperature ramp experiments were performed by heating the sample from 5 to 37 °C at a rate of 2.5 °C/min, at a constant strain of 0.5% and a frequency of 10 Hz.

2.2.3. Preparation of AZM-containing hydrogel

The liquid-like state of the tetrablock aqueous solution below its Tt makes mixing with the therapeutic agent efficient and extremely simple. Thus, the recombinamer was mixed at 15 wt.% with a 0.4 mg/mL solution of AZM in NaCl 0.9%. The resulting solution was kept at 4 °C overnight to allow complete dissolution of the elastomeric recombinamer.

2.2.4. In vitro release experiments

Release experiments were performed using the membrane model. Briefly, the solution was deposited into the release cell and maintained at 37 °C for 10 min to ensure hydrogel formation. Thereafter, a dialysis membrane with a cut-off of 10 kDa was placed between the hydrogel and the compartment of the receptor solution to avoid dissolution of the physical hydrogel. The delivery medium was added and, at predetermined time intervals, the solution (NaCl 0.9%) was completely removed from this compartment and new solution added. This study was conducted over 6 days.

The concentration of AZM in the release medium was determined by UV spectrophotometry at a maximum absorbance wavelength of 265 nm (UV2 Spectrometer Unicam, New York). All experiments were performed in triplicate.

To detect possible effects of the membrane on the release profile (drug-delivery rate), the compartment destined to be loaded with the hydrogel was loaded with a 0.4 mg/mL solution of AZM (without the hydrogel) and the release profile monitored as described previously.

The results were expressed as fraction of AZM released. The AZM release profile was analyzed considering the mechanism and using the lumped kinetics model developed in this paper.

3. Results and discussion

3.1. Mathematical development of the model

Upon administration, gel-forming solutions initially undergo a transient and dynamic gelation phase during which marked changes in their transport properties can occur over short length and time scales. Moreover, drug release may subsequently be substantially affected by surface or bulk erosion.

From a mathematical modeling point of view, controlled-release systems may be classified as diffusion-, chemically- or swelling-controlled processes [21]. One of the most widely used diffusion models is that based on the Higuchi equation [22], which was generalized by the model described by the Ritger–Peppas equation [23]. Unfortunately, these models have the drawback that they describe only part of the drug-release profile and are based on very restrictive assumptions.

The mechanism proposed by us to allow the entire drug-release profile to be accurately predicted is based on the moving boundary model, which considers that the transport steps of diffusion in the device and transport *via* the interface are faster than the advance of the front in the matrix. As such, a pseudo-steady state can be applied to the transfer steps.

Other important assumptions in our mechanism are:

a) Slab geometry of the device used;
b) Uniform drug concentration throughout the device at $t = 0$;
c) The drug diffuses in the matrix according to Fick's law;
d) A constant diffusion coefficient of the drug in the device matrix as a function of time; and
e) Negligible transport resistance in the dialysis membrane.

Based on these assumptions, the pseudo-steady state for the transport step is given by (see Fig. 1):

$$A * D \ \frac{(C_o \ - \ C_s)}{x} = A * kc * C_s \tag{1}$$

where D is the diffusion coefficient, kc is the interface mass-transfer coefficient and A the interface surface area. C_o, C_s and C_f are the drug concentration in the device matrix, at the interface and in the bulk receptor solution, respectively.

According to the experimental setup and procedure used, C_f is always zero (fresh receptor solution is added at each predetermined interval) and increases by a differential amount (sufficient to be detected and measured).

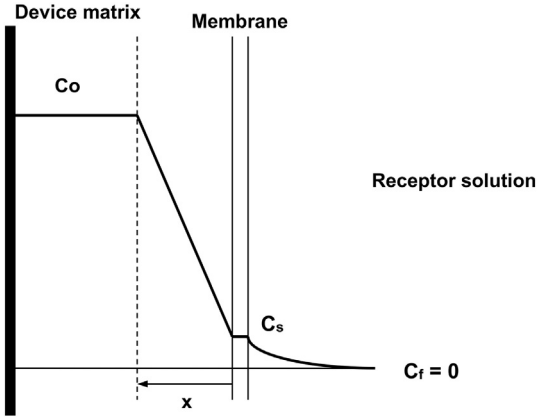

Fig. 1. Drug-concentration profile at $t > 0$.

Eq. (1) leads to:

$$C_{sp} = \frac{C_s}{C_o} = \frac{1}{1 \ + \ \frac{kc * x}{D}} \tag{2}$$

and advance of the front is given by the differential equation:

$$C_o * A * \frac{dx}{dt} = kc * A * C_s. \tag{3}$$

Taking into account Eq. (2), the rate of advance of the front is:

$$\frac{dx}{dt} = \frac{kc}{1 + \frac{kc * x}{D}}. \tag{4}$$

The mass balance for the cumulative amount of drug released at time t is given by:

$$\frac{dC_f}{dt} = \frac{A}{VL} \ kc * C_s \tag{5}$$

where VL is the volume of receptor solution added each time that a sample is taken.

The following equation is obtained upon dividing Eq. (5) by C_o:

$$\frac{dC_{fp}}{dt} = \frac{d\frac{C_f}{C_o}}{dt} = \frac{A}{VL} kc * C_{sp} \tag{6}$$

where C_{fp} is the fraction of the cumulative amount of drug released at time t with respect to the initial amount in the device.

The set of differential Eqs. (4) and (6), and the analytical relationship Eq. (2), was solved numerically using the program Polymath 6.1.

The initial boundary conditions are:

$$t = 0 \quad C_s = C_o \ \ (C_{sp} = 1) \quad x = 0$$

with:

$$VL = 2 \text{ cm}^3 \quad \text{and} \quad A = 0.636 \text{ cm}^2.$$

The only transfer step involved at the beginning of the process ($t = 0$) is that corresponding to interface mass transfer. As such, the value of the mass transfer coefficient can be estimated from (see Eq. (5)):

$$kc = \frac{VL}{A}\frac{dC_{fp}}{dt}|_{t=0} \tag{7}$$

Polymath 6.1 gave an excellent fit with the experimental data obtained (see Fig. 4). Moreover, this agreement was found with physically reasonable values for the mass-transfer coefficient at the interface of $kc = 5.7 \cdot 10^{-5}$ cm/s and a diffusion coefficient of $D = 7.2 \cdot 10^{-6}$ cm^2/s. The value of kc is very close to that estimated using Eq. (7).

Although the mechanistic theory based on real phenomena and physically realistic assumptions allows the fundamental coefficients that offer a great insight into the drug-release process to be determined, a numerical procedure must be used to obtain the mass and rate of drug release at any given time. Consequently, we proposed a lumped kinetic model that accounts for the different steps encountered in this process and provides simple and explicit analytical solutions.

A pseudo-second-order equation model has been tested and a lumped kinetics model was found to be suitable for this case [24].

Pseudo-second-order kinetic equation was found to consider all the transport and diffusion steps involved in drug release processes, besides

compiling with the reported need of developing models as simple as possible to provide a good description of the system behavior [7,8].

The pseudo-second-order kinetic expression for the process, in this case the drug-release rate, is:

$$\frac{dM_t}{dt} = k_2(M_\infty - M_t)^2. \quad (8)$$

Normalizing respect to M_∞ gives:

$$\frac{dM_{tp}}{dt} = \frac{d\frac{M_t}{M_\infty}}{dt} = k_2 * M_\infty (1 - M_{tp})^2 \quad (9)$$

where M_t and M_∞ are the cumulative amount of drug released at time t and at infinite time (amount of drug feasible to be released), respectively. The amount of drug remaining in the hydrogel is given by $(M_\infty - M_t)$.

Considering

$$k = M_\infty * k_2 \quad (10)$$

Eq. (9) becomes:

$$\frac{dM_{tp}}{dt} = k\ (1 - M_{tp})^2 \quad (11)$$

where M_{tp} is the cumulative fraction of drug released at time t, and k the kinetic parameter in $time^{-1}$. This equation is dimensionless with respect to the amount of drug released, whereas the kinetic parameter k depends on the amount of drug dosed in the hydrogel (M_∞).

Solving Eq. (11) with conditions:

at $t = 0$ $M_{tp} = 0$ and at $t = t$ $M_{tp} = M_{tp}$

Gives Eq. (12):

$$M_{tp} = \frac{k * t}{[1 + k * t]}. \quad (12)$$

Eq. (12) can be written in a more general form to fit the experimental results thus:

$$M_{tp} = \frac{a * t}{[1 + b * t]}. \quad (13)$$

Eq. (13) can be used to determine the time needed to release a given fraction of the drug:

$$t = \frac{M_{tp}}{a - b * M_{tp}} \quad (14)$$

as well as the rate of drug release as a function of time:

$$\frac{dM_{tp}}{dt} = \frac{a}{(1 + b * t)^2} \quad (15)$$

Eq. (13) can be also put in linear form as:

$$\frac{t}{M_{tp}} = \frac{1}{a} + \frac{b}{a} * t. \quad (16)$$

Using Eq. (16) and plotting a graph of (t / M_{tp}) versus time (t) gives a first estimate of the values of parameters "a" and "b".

This lumped model considers the different mass transport steps involved in drug release system. The model can be applied without limitations of time or mass of drug released. That is, it can be applied to fit the experimental data in the range $0 \le t \le \infty$ or $0 \le M_t \le M_\infty$. Furthermore, analysis using our proposed approach, yielded simple and explicit relations between mass and drug released rate with time.

3.2. Testing use of the tetrablock as a delivery vehicle for AZM

3.2.1. Thermo-gelling properties of the tetrablock-AZM device

The thermo-gelling properties of the tetrablock alone and in combination with AZM in saline solution (NaCl 0.9%) were evaluated in order to determine whether the presence of the drug in the tetrablock sample affects its thermo-gelling behavior. To this end, the corresponding samples were subjected to rheological tests comprising heating from 5 to 37 °C at a constant rate of 2.5 °C/min, and the parameters G′ and G″ were collected. G′ (also named as storage modulus or elastic modulus) is a measure of the ability of the material to store energy. In other words, it is a measure of elasticity of material. G″ (also named as loss modulus or viscous modulus) is a measure of the ability of the material to dissipate energy during the shearing process.

As shown in Fig. 2 a) and d), a sharp increase in G′ and G″ occurs for both samples in the temperature range 12–18 °C. Specifically, the crossover between G′ and G″, which is the most commonly used criterion for determining the gel point [25], occurs at 15.5 °C for both samples (tetrablock and tetrablock with AZM). At such point, the storage modulus becomes larger than the loss modulus which indicates that the fluid has transitioned from fluid flow like behavior to solid elastic behavior.

DSC scans were performed to confirm the absence of any influence of AZM on the ITT behavior of the tetrablock. As shown in Fig. 2c) and d), no difference between ITT variables, namely temperature (12.5 °C), and enthalpy (8.8 J/g) were found, thereby supporting the lack of interference between the drug and the recombinamer. Consequently, it was concluded that the presence of AZM in the hydrogel does not affect the thermo-gelling properties of the system. These findings point to the potential utility of the tetrablock recombinamer as a vehicle for achieving controlled AZM release. The liquid-to-gel transition behavior of this biomaterial potentially allows topical administration of the formulation as drops. Upon contact with the surface of the eye, the system would acquire a gel-like state immediately after administration, thereby enhancing the bioavailability of AZM.

3.2.2. AZM release from the tetrablock hydrogel

3.2.2.1. Experimental data for release of AZM from the tetrablock hydrogel in vitro. Once it had been demonstrated that the thermo-gelling properties of the tetrablock under physiological conditions were not affected by the presence of AZM, the next step was to evaluate the ability of this device to achieve sustained release of the therapeutic agent.

To this end, *in vitro* release tests were performed as described in the experimental section. An initial analysis of the release profile shows that AZM delivery is sustained over the period studied (150 h, approximately 6 days), with a visible absence of burst release at the initial timepoints (Fig. 3). Although the absence of burst release is a requirement in order to minimize undesirable peak concentrations of the drug exceeding the therapeutic dosage when applied *in vivo*, it is often difficult to achieve. As was expected, the release profile from the control cell (with AZM, but without recombinamer) did not display sustained release (Fig. 3, empty circles), thereby confirming the assumption of negligible transport resistance through the dialysis membrane (Section 3.1, assumption e)).

The prolonged-release profile of this system, together with the absence of burst release, suggests the potential application of this formulation in the area of ophthalmic formulations.

3.2.2.2. Modeling of in vitro AZM release from the tetrablock hydrogel. A multidisciplinary approach must be followed when designing a pharmaceutical formulation in order to both develop the polymer and the therapeutic agent and to take into account appropriate mathematical modeling. Such modeling must be able to correctly describe the system and predict the effects of different parameters on the release profile, and ultimately constitutes a key link in the development of pharmaceutical devices.

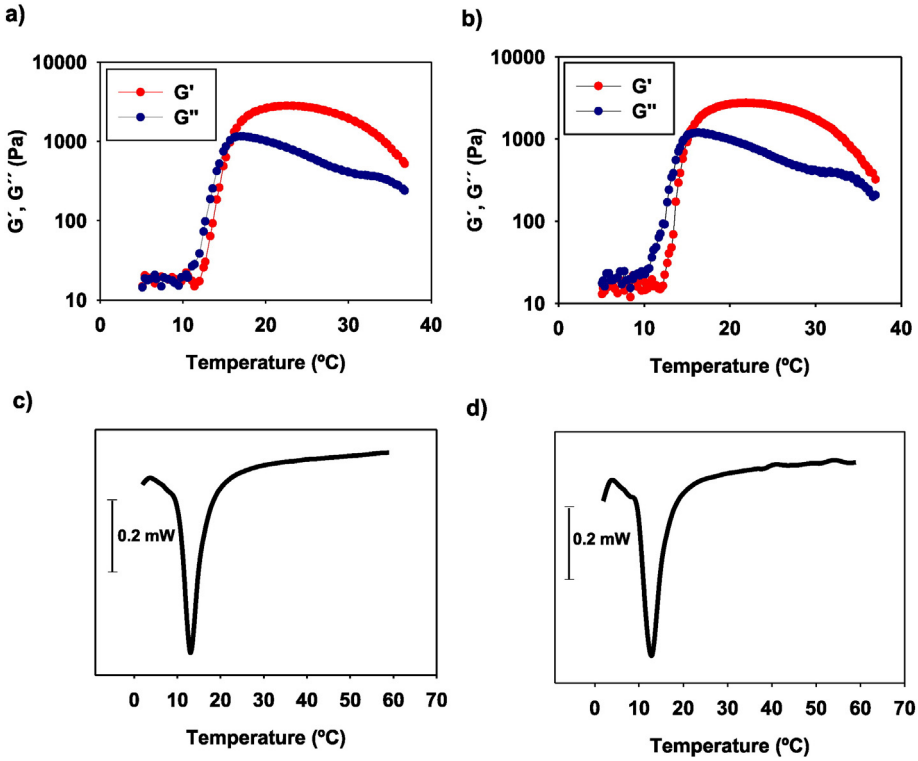

Fig. 2. Thermo-gelling properties of the tetrablock. a) Storage moduli (G′) and loss moduli (G″) for the tetrablock sample (15 wt.%) in NaCl 0.9% as a function of temperature. b) Storage moduli (G′) and loss moduli (G″) for the tetrablock sample (15 wt.%) in NaCl 0.9% with 0.4 mg/mL AZM as a function of temperature. c) DSC scans for the tetrablock sample (15 wt.%) in NaCl 0.9%. d) DSC scans for the tetrablock sample (15 wt.%) in NaCl 0.9% with 0.4 mg/mL AZM.

Considering the experimental procedure used, it is important to point out that the time period between two consecutive samples should be sufficient to accurately measure the change in M_{tp} but small enough to consider $dM_{tp}/dt \approx \Delta(M_{tp}/\Delta t)$. Under this condition, Eq. (15) will give us the maximum rate of the drug delivered ($time^{-1}$) when the amount of drug remaining in the hydrogel is $(M_\infty - M_t)$.

In order to calculate the fraction of drug released and the release rate at any particular time, Eqs. (13) and (15) can be applied to the whole range of M_{tp} $(0 \le (M_{tp}) \le 1)$.

The best procedure for obtaining the values of "*a*" and "*b*" is to carry out a non-linear regression analysis of the experimental data with the model presented herein using the values of "*a*" and "*b*" determined from the plot of Eq. (16) as a first estimate. A non-linear regression analysis with Polymath 6.1 gave the following values for the parameters "*a*" and "*b*":

$$a = 0.018381 \quad h^{-1} \quad \text{and} \quad b = 0.015014 \ h^{-1} \quad \text{with} \quad R^2 = 0.9900.$$

Therefore, the percentage amount of drug delivered as a function of time is given by (Eq. (13)):

$$(M_{tp}) = \frac{0.018381 * t}{[1 + 0.015014 * t]}. \tag{17}$$

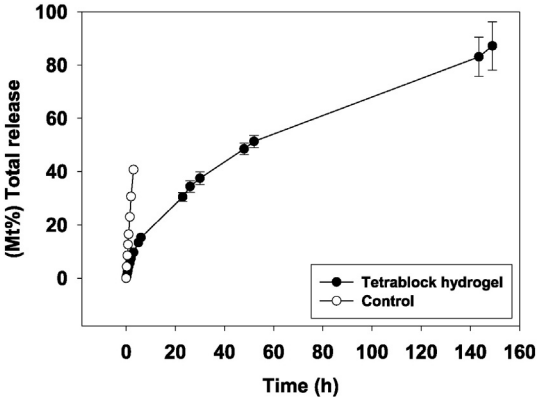

Fig. 3. Cumulative release of AZM from tetrablock hydrogel at 37 °C in NaCl 0.9% (black circles). The empty circles correspond to the negative control, which comprised placing an AZM solution in the release cell in the absence of hydrogel.

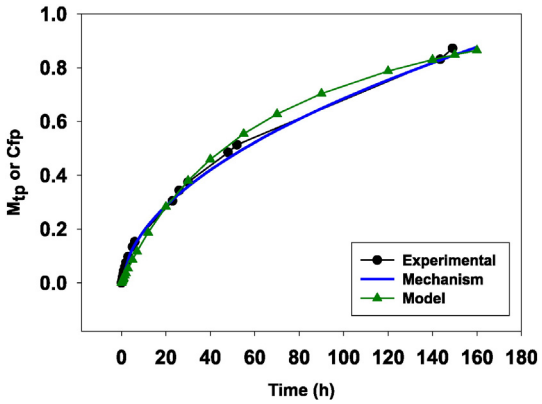

Fig. 4. Fraction of AZM released (*Mtp*). Squares: experimental data. Triangles: predicted values of AZM release from tetrablock hydrogel (*Mtp*) obtained by applying the non-linear regression resolution of the model developed in this contribution using the Polymath program. Circles: predicted values of AZM released from tetrablock hydrogel (*Cfp*) obtained by solving the mechanism proposed.

The values of (M_{tp}) as a function of time (t) estimated using the parameter values given by the non-linear regression analysis are plotted in Fig. 4.

Thus, the drug-release rate [$d(M_{tp})/dt$] as a function of time, according to the parameter values obtained by non-linear regression analysis and using Eq. (15), is:

$$\frac{d(M_{tp})}{dt} = \frac{0.018381}{[1 + 0.015014 * t]^2} \tag{18}$$

As can be seen, the ratio between parameters a and b is close to one, thereby supporting the experimental results, the internal consistency of the experimental methodology, and the suitability of the proposed model for fitting the results.

The main advantage of our model is that the solution of the kinetic gives a simple equation as function of time that lumped the different steps involved in the process, which is valid for $0 \le t \le \infty$ where $0 \le M_t \le M_\infty$. Also, the drug release rate can be easy found for any value of time ($t = 0$ to $t = \infty$), which is not possible to do with the Ritger–Peppas model because it cannot be applied to calculate the initial release rate neither to obtain M_∞ [26,27]. Note that our model is equivalent to the Ritger–Peppas model equation, but with a value of parameter "n" changing continuously from one at the beginning of the process to near zero at long time.

The reason for the increasing need to develop novel options for drug delivery to the eye is based on the need to progress from drug delivery discovered in earlier research into topically administered drugs. Although pharmaceutical research and development provides a route to achieve this objective, it is sometimes limited by available technology and regulatory constraints. The cost of the finished product must be bearable by the individuals and/or communities who will use the product, and it has to be economically viable for the manufacturer. The development of mathematical models that are able to accurately predict drug-release behavior constitutes a must in this context.

4. Conclusions

The development of mathematical models that are able to accurately predict drug-delivery profiles is a critical step in pharmaceutical product development. Herein we have presented a drug-release mechanism based on the moving-boundary model that is appropriate for the experimental procedure used. The mechanism takes into account drug diffusion in the hydrogel and transfer at the device–fluid interface. The shape of the complete release profile (up to 83% drug delivered) was modeled, giving an excellent fit with physically reasonable values for the diffusion and interface mass transfer coefficients. However, as a numerical method must be applied to solve the mechanism, it is not possible to derive explicit analytical solutions. We have also developed a second-order kinetic "lumped model" for the rate of drug release, and explicit analytical solutions for the fraction of drug release and rate of drug release as a function of time have been obtained. Although these equations fit the experimental data reasonably well, they are very simple and explicit analytical expressions that can be used to rapidly analyze experimental drug-release data to get a rough idea of the possible release mechanism. Furthermore, a simple internal consistency proof of the model and the experimental results has been developed using the ratio of parameters "a" and "b". Note that no limitations of time or of mass of drug released are required to apply the "lumped model". As such, complete drug delivery profile can be fitted, which represents an important achievement in the area of mathematical modeling.

As proof of concept, we have applied this model to a relevant experimental example in which release of AZM from a tetrablock hydrogel was evaluated. This tetrablock hydrogel represents a versatile and innovative system for the sustained local delivery of AZM, the duration of which lasted from hours to days. As such, the tetrablock hydrogel can offer better control of local drug levels, and less frequent and more convenient administration, thus leading to greater efficacy, reduced adverse events and better patient compliance. It can also provide advantages (e.g., efficiency and cost savings) to the provider and the health care system. The mechanism and second order drug release lumped kinetic model developed in this contribution fit the experimental data over the whole range of fraction of drug release ($0 \le M_{tp} \le 1$) very well, thus allowing us to be able to accurately predict the maximum drug-release rate at each time point due to the experimental procedure used. The encouraging results presented in this work pave the way for use of these novel platforms in the treatment of open-angle glaucoma and provide an accurate, robust and easy-to-apply mathematical model for the description of drug release from polymeric devices.

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