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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.

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.