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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 and 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.

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 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 has 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 used not only in the development of new formulations, optimization of existing formulations but also 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 cannot 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

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Nomenclature

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
$C_{A\infty}^{r.m.}$	drug concentration in the bulk of the release medium
$C_{AS}^{r.m.}$	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
ℓ	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
$R^2_{adjusted}$	adjusted coefficient of determination
SSR	sum of squares of residues
t	time
V	release medium volume
x	mass diffusion direction (axial)

Greek symbols

α, β	parameters of dissolution models
ϕ	standard normal distribution

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 concerning 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 ± 0,14) during 48 h. The release medium temperature was maintained constant at 36 °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 through using a calibration curve (absorbance *versus* drug concentration) obtained previously. The release experiments were repeated 3 times in similar conditions 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

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

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 ℓ is the semi-thickness of the polymer. Eq. (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

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

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

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

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.