European Journal of Pharmaceutical Sciences 44 (2011) 288–298

Contents lists available at SciVerse ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

Mathematical modeling of drug delivery from one-layer and two-layer torus-shaped devices with external mass transfer resistance

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ARTICLE INFO

Article history:
Received 23 May 2011
Received in revised form 15 July 2011
Accepted 9 August 2011
Available online 16 August 2011

Keywords:
Vaginal ring
Pseudo-steady state approximation
Mass transfer resistance
Mathematical modeling
Moving front
Drug delivery

ABSTRACT

A mathematical modeling of controlled release of drug from one-layer and two-layer torus-shaped devices with external mass transfer resistance is presented. Analytical solutions based on the pseudo-steady state approximation are derived. The validity of the equations is established in two stages. In the first stage, the validity of the models derived for more complex systems is determined by comparison with profiles predicted by the simplest model, in asymptotic cases. In the second stage, the reliability and usefulness of the models are ascertained by comparison of the simulation results with vaginal rings experimental release data reported in the literature. In order to measures quantitatively the fit of the theoretical models to the experimental data, the pair-wise procedure is used. A good agreement between the prediction of the models and the experimental data is observed. The models are applicable only to torus-shaped systems in where the initial load of drug is higher than its solubility in the polymer.

1. Introduction

Drug delivery is an important aspect of medical treatment. The efficacy of many drugs is directly related to the way in which they are administered. Some therapies require that the drug be repeatedly administered to the patient over a long period of time. This presents certain drawbacks. For contraception, for example, daily oral intake of pills increases the risk of forgetting the intake. In addition, the hepatic first-pass reduces the bioavailability of the drug. Therefore, new routes of administration have been explored.

The administration of drug by the vagina has been described and the advantages of this via over oral administration have been noted (Cicinelli, 2008; Hussain and Ahsan, 2005). The vagina appears as an interesting route of drug administration for treatment not only local but also for systemic (Cicinelli, 2008; Hussain and Ahsan, 2005). Controlled release devices for vaginally drug delivery have been explored (Sitruk-Ware, 2006; Yoo and Lee, 2006). Among others, the intravaginal rings (IVRs) appear to be the most promising devices and have been used extensively. Several designs of ring have been developed, including matrix, reservoir and shell-type variants, each providing very different drug release profiles (Malcolm et al., 2002, 2003a; Woolfson et al., 1999, 2003). Despite a substantial body of work has been published to date on the development, implementation and clinical trials of IVRs (Johansson and Sitruk-Ware, 2004; Malcolm et al., 2003b; Roumen, 2008; Van Laarhoven et al., 2002), no attempt has been made to derive a model for predicting drug release rates.

In the past, different strategies have been used to model the drug release kinetic in systems with different geometric shapes (Arifin et al., 2006; Helbling et al., 2010a; Siepmann et al., 2008; Wu and Brazel, 2008). One of the most used has been the application of the approach of pseudo-steady state. The pseudo-steady state approximation (PSSA) was introduced first by Higuchi to derive an analytical solution for a rectangular slab under "sink condition" (Higuchi, 1961, 1963). Since then, this approach was used by many authors for the derivation of mathematical models. For example, Roseman and Higuchi (1970) and Tojo (1985) assumed PSSA in the modeling of a planar geometry device with the existence of a stagnant liquid layer. The same analysis but incorporating a finite external medium was carried out by Zhou and Wu, who derived an explicit analytical solution assuming PSSA (Zhou and Wu, 2002). Helbling et al. derived analytical solutions based on PSSA for the release of drug from erodible and non-erodible planar matrices, through a membrane, and taking into account the existence of a diffusion boundary layer and a finite release medium (Helbling et al., 2010b). In other systems, like cylinder or spheres, also PSSA was employed to develop the predicting equation to adjust the release data (Costa and Sousa Lobo, 2003; Roseman, 1972; Siepmann and Siepmann, 2008; Zhou and Wu, 2003).

In our previous work (Helbling et al., 2011), a mathematical model to predict the release of drug from torus-shaped one-layer

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doi:10.1016/j.ejps.2011.08.008

Nomenclature

a_{dis}	area of the interface of the dispersed-drug zone/depleted drug zone (cm^2)
a_{rel}	release area of the device (cm^2)
A	initial drug loading in the device (mg/cm^3)
$C_{a,1}$	dissolved-drug concentration in the external resistance layer at the matrix-external resistance layer interface (mg/cm^3)
$C_{a,2}$	dissolved-drug concentration in the external resistance layer at the membrane-external resistance layer interface (mg/cm^3)
C_{bl}	dissolved-drug concentration in the external resistance layer (mg/cm^3)
$C_{eq,1}$	dissolved-drug concentration in matrix at the matrix-external resistance layer interface (mg/cm^3)
$C_{eq,2}$	dissolved-drug concentration in matrix at the matrix-membrane interface (mg/cm^3)
C_m	dissolved-drug concentration in the membrane (mg/cm^3)
$C_{m,1}$	dissolved-drug concentration in the membrane at the matrix-membrane interface (mg/cm^3)
$C_{m,2}$	dissolved-drug concentration in the membrane at the membrane-external resistance layer interface (mg/cm^3)
C_s	maximum drug solubility in the polymeric matrix (mg/cm^3)
C_t	dissolved-drug concentration in the matrix (mg/cm^3)
D_a	drug diffusion coefficient in the external resistance layer (cm^2/s)
D_m	drug diffusion coefficient in the membrane (cm^2/s)
D_p	drug diffusion coefficient in the polymeric matrix (cm^2/s)
h_a	thickness of the external resistance layer (cm)
h_m	thickness of the membrane (cm)
K_1	drug partition coefficient at the matrix-external resistance layer interface (dimensionless)
K_2	drug partition coefficient at the matrix-membrane interface (dimensionless)
K_3	drug partition coefficient at the membrane-external resistance layer interface (dimensionless)
m	cumulative amount of drug released (mg)
Q	cumulative amount of drug released per unit area of the device (mg/cm^2)
r	spatial coordinates (cm)
R_e	distance from the rotation axis to the external surface of the matrix (cm)
R_g	distance from the rotation axis to the center of the generating circle (cm)
R_0	radius of the generating circle (cm)
$S(t)$	position of the dissolution–diffusion moving front (cm)
t	time (s)
V_s	volume of the torus-shaped matrix (cm^3)

Greek letters

$\delta(t)$	position of the dissolution–diffusion moving front (dimensionless)

devices with initial drug loading higher than the maximum solubility of drug in the polymer, assuming PSSA and taking into account the specific characteristic of the torus-shaped geometry on the release process was developed. This model showed to be efficient in the prediction of the profiles of drug released. Based on these results, the need for a model that includes other effects such as the presence of resistance to mass transfer is a fact.

The purpose of the present study was to extend the analysis previously done by developing a model that takes into account the presence of external mass transfer resistance. Also, a model that predicts the release profiles from a torus-shaped two-layer device is derived. The new models were derived based on PSSA and can cover a wider range of situations.

2. Model development

The mathematical model is developed for a torus-shaped device containing solid drug particles. The device is schematically illustrated in Fig. 1. When the torus-shaped device is placed in the release medium, the liquid takes contact with the device over its entire surface. As the liquid contacts the device, the solid drug particles dissolve in and then diffuse out of the matrix. The discrete crystals in the layer closer to the matrix surface are the first to elute. When this layer becomes "exhausted", the solid drugs in the next layer begin to be depleted. So, a drug depletion zone is created. The thickness of this zone increases with time and as more solid drugs elute out of the device, thus leading to the inward advancement of the interface of the dispersed-drug zone/depleted drug zone, phenomenon commonly referred to as "dissolution–diffusion moving front". Because the liquid comes in contact with the device over its entire surface at the same time, the formation of the depletion zone and therefore the inward advancement of the interface of the dispersed-drug zone/depleted drug zone takes place in all radial directions at the same time (considering a radial direction as the direction of the radius of the generating circle for a particular value of φ) (Helbling et al., 2011). This means that the same phenomenon of "dissolution–diffusion moving front" takes place for all value of φ (from 0 to 2π) and also for any value of ω (from 0 to 2π) (Helbling et al., 2011). So, it is sufficient to find the way in which the front moves in a single radial direction and then extrapolated it to the entire device, since the front moves in the same form in all the radial directions. Therefore, for the mathematical analysis only the half section of the area of the generating circle in the radial direction $\varphi = 0$ ($R_g < r < R_e$) and in a particular value of ω (the value of ω is irrelevant because the same phenomenon occurs for all ω) is considered. The analysis can be then extrapolated to the entire device (Helbling et al., 2011). The parameters present in Fig. 1 are defined below.

The general assumptions of the model to be mathematically formulated are the following: (i) The system is a torus-shaped device. (ii) The device is considered as an isotropic medium. (iii) The device is composed by a polymeric matrix that contains solid drug particles dispersed in its interior. (iv) The initial distribution of the drug in the polymeric matrix is homogeneous. (v) The initial drug loading in the matrix is higher than the maximum drug solubility in the polymer. (vi) For simplicity, all the drug particles have the same size and a spherical form. (vii) The polymeric matrix is inert, unswellable and non-erodible. (viii) For a one-layer device, the system consists only of a polymeric matrix. In the case of a two-layer device, the system consists of the polymeric matrix coated with a second empty layer that resembles a membrane. (ix) The initial drug loading in the membrane is zero. (x) The membrane is inert, unswellable and non-erodible. (xi) The membrane can be made up of the same polymer as the matrix or of a different one. (xii) When the "dissolution–diffusion moving front" begins to move, the dissolved drug profile is attained instantaneously