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Modelling the plasma drug level with oral controlled release dosage forms with lipidic Gelucire

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Abstract

The plasma drug level is evaluated in the case of oral dosage forms with prolonged release when the matrix is made of lipidic Gelucire. From in vitro studies, the process of drug release follows a typical pattern: the liquid dissolves the drug in contact with it and thus, enters the dosage form, enabling the drug to diffuse out of the dosage form through the liquid located in it. The diffusivity of the drug increases with the concentration of the liquid in an exponential way. The kinetics of drug release out of the dosage forms fit the experimental results obtained with in vitro experiments perfectly. The plasma drug level is obtained with aspirin as the drug, by using a numerical model taking into account the kinetics of release of the drug out of the dosage form and the pharmacokinetic parameters. The effect of the dimensions of the dosage forms on the plasma drug level is considered.

Keywords: Controlled release; Modelling; In vitro/in vivo; Plasma drug level; Lipidic Gelucire

1. Introduction

Immediate release dosage forms where the drug is dispersed through a quickly soluble excipient are responsible for the drawback of high peaks and low troughs in the blood compartment; thus, the drug level in the plasma alternates between high peaks and low troughs with multiple doses during the cure (Heilmann, 1984). Prolonged release dosage forms are able to eliminate or at least to reduce this drawback.

Oral controlled release dosage forms are sometimes prepared by dispersing the drug in a polymer which plays the role of a matrix. The polymer may be erodible (Heller, 1984) or not. The process of drug release is controlled by diffusion and erosion with erodible polymers and by diffusion with non-erodible polymers. Gelucires have been sometimes used as matrices. Consisting of a mixture of polyglycide fatty esters, they are character-

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ized either by their melting temperature or their hydrophilic-lipidic balance (HLB), and they can cover a wide variety of properties (Gattefossé, 1983). For hydrophilic Gelucires with HLB next to 14, water can be absorbed and the process of drug release is controlled by diffusion and erosion (Bidah and Vergnaud, 1990). With lipidic Gelucires of HLP next to 1, the process of drug release was found in a first attempt to be controlled by diffusion with a constant diffusivity and a finite coefficient of convective transfer in the surrounding liquid (Bidah et al., 1992). In a deeper study (Aïnaoui et al., 1997), a more complex process was considered in order to obtain kinetics fitting perfectly well the experimental values. The process is thus, based on the two facts: (1) the liquid dissolves the grains of drug in contact with it and thus, enters the polymer taking the place of the drug, as no swelling is observed; and (2) the drug diffuses out of the dosage form through the water located in it and the diffusivity of the drug increases with the concentration of water located in the dosage form in an exponential way (Aïnaoui et al., 1997).

The first objective in this paper is to extend the numerical model describing the kinetics of release of the drug to the wider process of drug transport in the plasma compartment. Various studies have been performed in order to establish in vitro/in vivo correlations, without success in the case of dosage forms with controlled release (Skelly et al., 1990; Siewert, 1993; Skelly and Shiu, 1993). As shown in previous studies, another way was explored in modelling the process, i.e. by considering the kinetics of release of the drug out of the dosage form and the pharmacokinetic transports (Ouriemchi and Vergnaud, 1996). Thus, the following stages are considered: the kinetics of release of the drug out of the dosage form along the gastrointestinal tract, the kinetics of absorption in the plasma and the kinetics of elimination. The diffusivity of the drug does not depend on the pH of the liquid in this case, but the model could account for a pH-dependency.

The other purpose of this study is to determine the drug level in the plasma for various dimensions of these dosage forms. As the time necessary for the drug to be released varies with the $(\text{radius})^2$ of the spherical dosage forms and the finite gastrointestine residence time (Ouriemchi and Vergnaud, 1996) plays an important role with in vivo experiments, the dimension of the dosage form is a parameter of concern which must be optimized. Moreover, it is of interest to have an expression of the kinetics of release of drug out of the dosage form which fits perfectly well the experimental kinetics obtained with in vitro tests, for calculating precisely the drug level in the blood compartment. Two kinds of expression are considered: the one resulting from a mathematical treatment with a constant diffusivity (Crank, 1975; Vergnaud, 1993) and the other obtained with a numerical model based on a typical dependency of the diffusivity of the drug with the liquid concentration in the dosage form (Aïnaoui et al., 1997).

2. Theoretical

2.1. Assumptions

Some assumptions are made in order to make the process clear.

(1) The transports of liquid and drug are radial, the dosage form being spherical in shape.

(2) Initially, the drug is uniformly dispersed through the Gelucire matrix. The Gelucire is highly lipidic and does not absorb water.

(3) The liquid dissolves the drug in contact with it and occupies the place of the drug, progressing into the dosage form. The drug then diffuses out of the dosage form through the liquid located in this dosage form.

(4) The process of drug release is thus, controlled by either the progress of the liquid in the dosage form or the diffusion of the drug through the liquid located in the dosage form. The diffusivity of the drug varies with the concentration of this liquid in an exponential way, as often found (Bakhouya et al., 1996).

(5) As the volume of the dosage form does not vary during the process, the sum of the volumes of liquid and drug in the dosage form is constantly equal to the initial volume of the drug.

(6) The coefficient of convective transfer in the surrounding liquid next to the dosage form is finite, as always found (Hamlin et al., 1962; Bidah et al., 1992; Vergnaud, 1993).

(7) The drug released in the gastrointestinal (GI) tract is absorbed in the plasma volume and eliminated through two first order kinetics, with the rate constants of absorption and elimination.

(8) The amount of drug in the plasma volume at time t as a fraction of the initial amount in the dosage form is expressed as a function of time. The concentration of the drug in the plasma can thus, be evaluated when the plasma volume is known.

2.2. Mathematical treatment

The equation of radial diffusion with concentration-dependent diffusivity is:

$$\frac{\partial C_{r,t}}{\partial t} = \frac{1}{r^2}\,\frac{\partial}{\partial r}\left(D_t^{\mathrm{d}} r^2 \frac{\partial C_{r,t}}{\partial r}\right) \tag{1}$$

and the initial and boundary conditions are for the dosage form:

$$t = 0 \qquad 0 \le r \le R \qquad C_{r,0}^{\mathrm{d}} = C_{\mathrm{in}}^{\mathrm{d}} \qquad \text{drug} \tag{2}$$

$$t > 0 \qquad -D\left(\frac{\partial C}{\partial r}\right)_{R,t} = h(C_{R,t}^{\mathrm{d}} - C_{\mathrm{sur},t}^{\mathrm{d}}) \quad \text{drug} \tag{3}$$

The concentration in the surrounding liquid in the GI tract is difficult to determine, as the volume of liquid available is not known. The drug being absorbed in the plasma volume from the GI liquid with a first-order kinetics, this concentration in the GI volume is rather small. For calculation it is taken as zero in Eqs. (1)–(3).

The diffusivity of the drug varies with the concentration of liquid in the dosage form $C_{r,t}^{\mathrm{l}}$ at position r and time t:

$$D_t^{\mathrm{d}} = D_0^{\mathrm{d}}\ \exp(KC_{r,t}^{\mathrm{l}}) \tag{4}$$

and the concentration of liquid $C_{r,t}^{\mathrm{l}}$ in the dosage form is:

$$C_{r,t}^{\mathrm{l}} + C_{r,t}^{\mathrm{d}} = C_{\mathrm{in}}^{\mathrm{d}} \tag{5}$$

The rate of drug leaving the dosage form is thus given by:

$$F_t^{\mathrm{d}} = -AD_{R,t}^{\mathrm{d}}\left(\frac{\partial C}{\partial r}\right)_{R,t} = AhC_{R,t} \tag{6}$$

where A is the area of the dosage form of radius R and $\partial C/\partial r$ is the gradient of concentration at time t next to the surface.

The amount of drug located in the GI liquid at time t, Y_t, is:

$$\frac{\mathrm{d}Y}{\mathrm{d}t} = -AD\left(\frac{\partial C}{\partial r}\right)_{R,t} - k_{\mathrm{a}} Y_t \tag{7}$$

with the rate constant of absorption k_{a}.

The amount of drug located in the plasmatic compartment at time t is evaluated by:

$$\frac{\mathrm{d}Z}{\mathrm{d}t} = k_{\mathrm{a}} Y_t - k_{\mathrm{e}} Z_t \tag{8}$$

The amount of drug eliminated from the plasmatic volume is given by:

$$\frac{\mathrm{d}W}{\mathrm{d}t} = k_{\mathrm{e}} Z_t \tag{9}$$

2.3. Numerical analysis

The problem of drug transport is resolved step by step in evaluating the amounts of drug delivered in the gastrointestinal compartment Y_t, in the plasma compartment Z_t and eliminated W_t, during each internal of time (Ouriemchi and Vergnaud, 1996). In the same way, the amount of drug remaining in the dosage form at time t is obtained by integrating the concentration of drug with respect to space.

3. Experimental

3.1. Materials

The following components are used. Sodium salicylate (COPER) in powder form as the drug. Gelucire 50.02 (Gattefossé), a mixture of polyglycide fatty esters with controlled lipidic properties is the matrix. This Gelucire melts at 50°C (drop point: Mettler), and the HLB of 2 means that it is highly lipidic (Gattefossé, 1983).

3.2. Preparation of dosage forms

The Gelucire is heated to around 60°C and the small grains of sodium salicylate are dispersed in the viscous liquid strongly stirred in the ratio 50:50 by weight. Spherical beads of given dimensions are prepared from the paste weighed to the right amount.

3.3. In vitro tests in gastric liquid

Experiments are carried out in a closed flask at constant temperature (37°C) with 500 ml of liquid under a stirring at 250 rpm. The beads inserted in a Fiberglas basket are immersed into synthetic gastric liquid at pH 1.2. At intervals, a small sample (0.1 ml) is taken for analysis by using a UV spectrophotometer (Hitachi U 1000) calibrated at 207 μm (Aïnaoui et al., 1997).

3.4. In vivo calculation

In vivo calculation is made by using the numerical model and the data shown in Table 1.

4. Results

The results are expressed in two ways: one obtained with a single dose, the other with a multidose taken once a day. Three types of kinetics are calculated with the single dose: the kinetics of release of the drug out of the dosage form along the GI tract, the drug level in the plasma compartment, the kinetics of elimination out of the plasma compartment.

The effect of the dimensions of the spherical dosage form on the above kinetics is especially considered.

Table 1
Diffusion and pharmacokinetic parameters for aspirin

$D_d = 7.5 \times 10^{-8} \times \exp(3.9 \times C^l)$ (cm^2/s)
$h = 2.6 \times 10^{-5}$ (cm/s)
$k_a = 2.77$/h $k_e = 0.23$ 1/h

For diffusion parameters see Aïnaoui et al., 1997.
For pharmacokinetic parameters see Vidal, 1994.

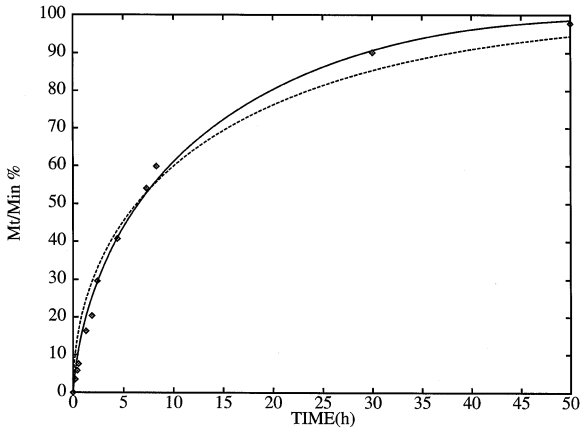

Fig. 1. Kinetics of release of drug with in vitro test, obtained: with experiment (◆): with the analytical expression and constant diffusivity (---): with the numerical model with concentration-dependent diffusivity (—). Radius, 0.402 cm.

4.1. Kinetics of drug release with in vitro tests

The kinetics of drug release from the form are obtained using in vitro test. Besides the experimental kinetics, two kinetics are shown in Fig. 1: the one obtained with the mathematical treatment made using a constant diffusivity, an infinite coefficient of convective transfer and a finite volume of liquid; the other obtained using the numerical model based on the concentration-dependent diffusivity.

The analytical expression is (Crank, 1975; Vergnaud, 1993):

$$\frac{M_t}{M_\infty} = 1 - \sum_{n=1}^{\infty} \frac{6\alpha(\alpha+1)}{9 + 9\alpha + q_n^2\alpha^2} \exp\left(-q_n^2 \frac{Dt}{R^2}\right) \quad (10)$$

where the q_n's are the non-zero roots of

$$\tan\ q_n = \frac{3q_n}{3 + \alpha q_n^2} \quad (11)$$

and α is the ratio of the amount of drug in the liquid and the dosage form at equilibrium. In this case, the volume of liquid is finite and the coefficient of convective transfer on the surface is infinite.

The numerical model is used for calculating the kinetics of release of the drug out of the dosage form, with the data shown in Table 1. The main characteristics of these data are: a finite coefficient

of convective transfer in the liquid next to the surface of the dosage form which is usual even with a stirred liquid (Hamlin et al., 1962; Vergnaud, 1993); and the diffusivity of the drug which varies with the concentration of the liquid located in the dosage form.

The kinetics calculated with the analytical expression (dot line) and the numerical model (full line) are compared with the experimental values (◆) in Fig. 1, leading to a few conclusions:

(1) As determined from the experiments, at the origin of time, the tangent for the kinetics is not vertical but oblique, meaning that the coefficient of convective transfer a the surface of the dosage form is finite (Vergnaud, 1993).

(2) For long periods of time, the kinetics obtained either by calculation with the analytical expression or by experiments strongly diverge. The most important fact to be noticed for a dosage form of radius 0.4 cm is that after 50 h, 2% drug remains in the dosage form while 6% is obtained with calculation using the analytical expression.

(3) Therefore, the kinetics calculated with the numerical model fit the kinetics obtained by experiments well.

4.2. In vivo kinetics of drug transfer with single dose

The drug level in the blood compartment with single dose is calculated by using the numerical model taking into account the following stages: the kinetics of release of drug out of the dosage form with either the constant diffusivity (dot line) or the concentration-dependent diffusivity (full line), the kinetics of absorption in the blood compartment and of elimination. The dimensionless number M_t/M_{in} expressing the amount of drug at time t in each compartment as a fraction of the amount of drug initially in the dosage form, is used in order to give more general results. The various kinetics are drawn for various dimensions of the spherical dosage forms, in Fig. 2 for a radius of 0.2 cm, in Fig. 3 with 0.25 cm and in Fig. 4 with 0.3 cm. In each figure, the following kinetics are shown: the kinetics of release of the drug out of the dosage form (curve 1) obtained either with the analytical solution in Eq. (10) (dot line) or with the numerical model and the concentration-dependent diffusivity (full line); the drug level-time history in the blood compartment (curve 2) obtained either with the analytical solution or with the model; the kinetics of drug eliminated out of the blood compartment in each case (dot and full line).

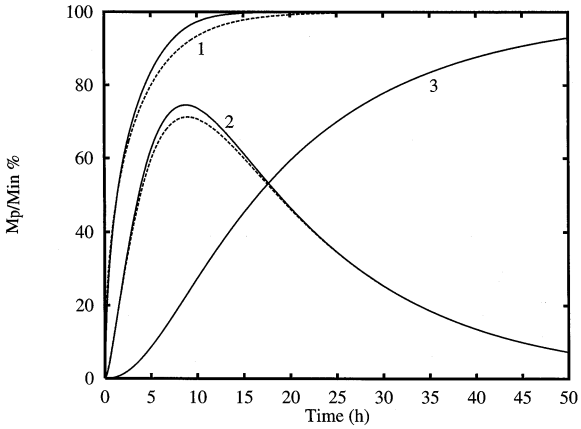

Fig. 2. Drug level-time history in the blood compartment calculated with the kinetics of release described by Eq. (10) (dot line) and by the numerical model (full line). Radius of the bead: 0.2 cm, single dose. (1) Kinetics of drug release out of the dosage form; (2) drug level in the plasma; and (3) kinetics of elimination.

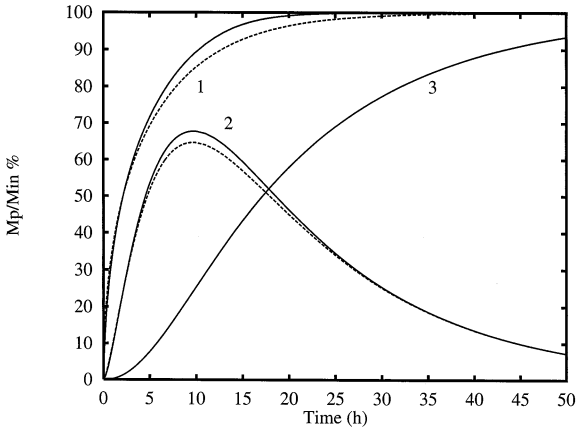

Fig. 3. Drug level-time history in the blood compartment calculated with the kinetics of release described by Eq. (10) (dot line) and by the numerical model (full line). Radius of the bead: 0.25 cm, single dose. (1) Kinetics of drug release out of the dosage form; (2) drug level in the plasma; and (3) kinetics of elimination.

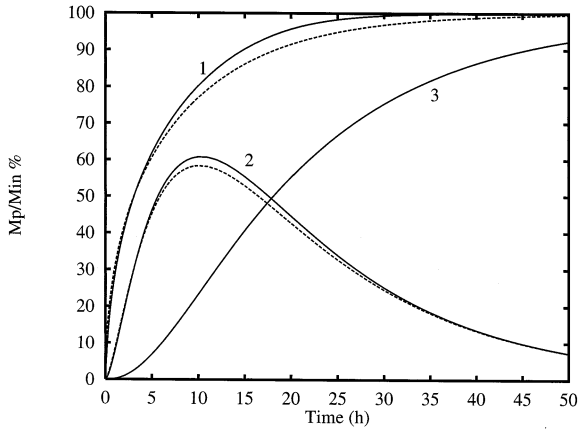

Fig. 4. Drug level-time history in the blood compartment calculated with the kinetics of release described by Eq. (10) (dot line) and by the numerical model (full line). Radius of the bead: 0.3 cm, single dose. (1) Kinetics of drug release out of the dosage form; (2) drug level in the plasma; and (3) kinetics of elimination.

A few conclusions can be drawn from these curves:

(1) The effect of the dimensions of the dosage forms on the various kinetics is illustrated by comparing the curves drawn in Figs. 2–4.

(2) The most important fact appears perhaps with the kinetics of release of the drug out of the dosage form. In Fig. 2 with the smaller dosage form, all the drug is released out of the dosage form before 24 h by using the two kinetics of release. In Fig. 3 with the dosage form of radius 0.25 cm, all the drug is released out of the dosage form before 24 h by using the kinetics of release with concentration-dependent diffusivity (full line), while about 2% remains in the dosage form with the constant diffusivity (dot line). In Fig. 4 with a radius of 0.3 cm, all the drug is released after 30 h when the concentration-dependent diffusivity is used, while 60 h are necessary with the constant diffusivity. This long period of time, 30 h for the release of the drug out of the dosage form along the gastrointestinal (GI) tract is a drawback, since the GI tract time is assumed to be 24 h or less (Ouriemchi and Vergnaud, 1996). This is the reason why the bead with a radius of 0.4 cm is not considered, leading to a much too long a time in the GI.

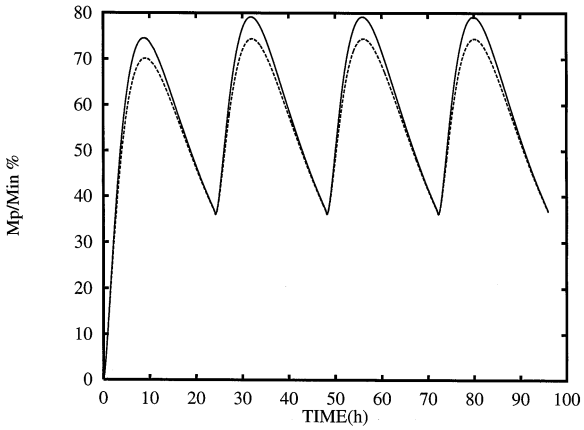

Fig. 5. Drug level-time history in the blood compartment calculated with the kinetics of release described by Eq. (10) (dot line) and by the numerical model (full line). Radius of the bead: 0.2 cm, multidoses once a day.

(3) Slight changes can be observed for the drug level in the plasma compartment by using either the constant or the concentration-dependent diffusivity.

4.3. Drug level in the blood compartment with multidoses

The drug level in the blood compartment is drawn for multidoses taken once a day for the various dosage forms: in Fig. 5 (radius 0.2 cm), in

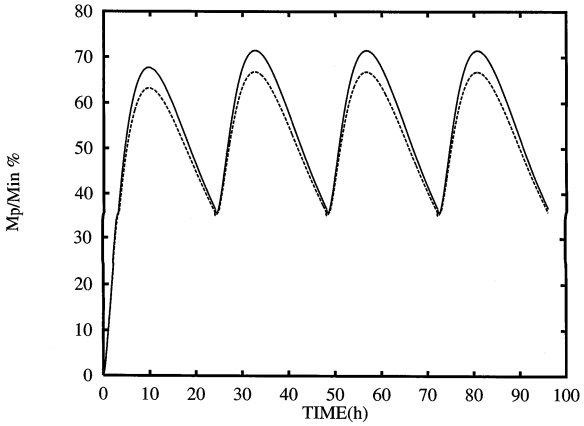

Fig. 6. Drug level-time history in the blood compartment calculated with the kinetics of release described by Eq. (10) (dot line) and by the numerical model (full line). Radius of the bead: 0.25 cm, multidoses once a day.

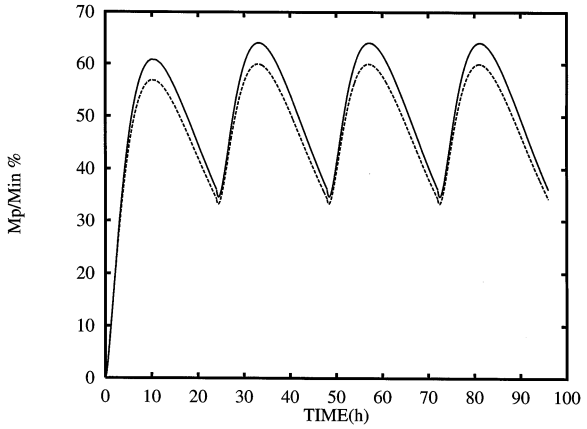

Fig. 7. Drug level-time history in the blood compartment calculated with the kinetics of release described by Eq. (10) (dot line) and by the numerical model (full line). Radius of the bead: 0.3 cm, multidoses once a day.

Fig. 6 (radius 0.25 cm) and in Fig. 7 (radius 0.3 cm). The plasma levels are calculated either with the constant diffusivity (dot line) or with the concentration-dependent diffusivity (full line).

For the various dosage forms, slight differences are observed between the two kinds of curves. Of course higher peaks are obtained with the concentration-dependent diffusivity and the troughs are about at the same level. The so-called steady state, the peaks and troughs are at constant levels, is attained after the second dose.

5. Conclusions

A new process of drug release out of the dosage form has been described, in the case of a lipidic Gelucire matrix. As the liquid does not diffuse through the lipidic matrix itself, the main way for the liquid to progress into the dosage form is to dissolve the grains of drug in contact with it, enabling the drug to diffuse through the liquid located in the dosage form. As shown from many studies, the diffusivity of the drug strongly varies with the concentration of the liquid and the exponential dependency is usual.

The main advantage of this process is that the kinetics of release calculated with the concentration-dependent diffusivity fits well the experimental kinetics obtained with in vitro tests. As it is necessary for predicting the drug level in the blood compartment to use this kinetics of release of the drug out of the dosage form, it is better to use the most accurate kinetics.

On the other hand, the drug level in the blood compartment is increased in a moderate manner by using the concentration-dependent diffusivity. The position of the peaks in single and multidoses is about the same.

However, especially at the end of the process of release, when the dosage form is at the end of the GI time, a negligible amount of drug remains in the dosage form of radius 0.3 cm with the concentration-dependent diffusivity and with the experimental data, while a significant amount of drug remains in the dosage form with the analytical solution. Thus, from an ethical point of view, a better way consists of using this new process with a concentration-dependent diffusivity.

Appendix A. Nomenclature

α	ratio of the amount of drug in the liquid and the dosage form at equilibrium, with in vitro test
A	area of the spherical dosage forms
$C_{r,t}$	concentration at radial abscissa r and time t
$C^{\mathrm{l}}_{r,t}$, $C^{\mathrm{d}}_{r,t}$	concentration of liquid and drug in the dosage form, respectively
$C^{\mathrm{d}}_{\mathrm{in}}$	initial drug concentration in the dosage form
D^{d}_{t}	diffusivity of the drug with the concentration of liquid (cm^2/s)
D^{d}_{0}	constant diffusivity when C^{l} is 0, in Eq. (4)
$D^{\mathrm{d}}_{R,t}$	diffusivity of the drug at time t at the radial abscissa R
h	coefficient of convective transfer of the drug in the liquid next to the surface (cm/s)
K	constant in Eq. (4)
k_{a}, k_{e}	rate constants of absorption and elimination of the drug
F^{d}_{t}	rate of drug release out of the dosage form at time t

M_t, M_∞	amount of drug released out of the dosage form after time t, after infinite time, respectively
M_{in}	amount of drug initially in the dosage form
r, R	radial abscissa, radius of the sphere, respectively
Y_t	amount of drug located at time t in the GI liquid
Z_t	amount of drug located at time t in the plasma volume
W_t	amount of drug eliminated at time t

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