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Research paper

Calculation of the dimensions of dosage forms with release controlled by diffusion for in vivo use

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Abstract

Using numerical models and data obtained from in vitro experiments, the dimensions of diffusion controlled release dosage forms to achieve desired in vivo levels are predicted. Monolithic polymer-drug devices are considered, the release of the drug being controlled by transient diffusion with constant diffusivity. The dimensions of the devices are calculated for various shapes (e.g. spheres, parallelepipeds, cylinders), so that 85% of the drug is released within 6 or 24 h, respectively. Caffeine, diltiazem HCl, and theophylline are studied in ethylcellulose (EC), plasticized with dibutyl sebacate (DBS) or acetyltributyl citrate (ATBC), respectively. The dosage forms are to be administered orally once a day. The resulting drug levels in the plasma are calculated using a numerical model that takes into account: the kinetics of drug release and the pharmacokinetic data of these dosage forms and drugs. Plasma levels resulting from immediate release dosage forms are also calculated, serving as reference.

Keywords: Controlled release; Diffusion; Modelling; Oral dosage forms; Plasma drug level; Shape

c	Concentration of drug in the dosage form
D	Diffusivity
h	Mass transfer coefficient in the boundary layer
H	Height of the cylinder
k_a, k_e	Rate constants of absorption and elimination, respectively
L_1, L_2, L_3	Dimensions of the rectangular parallelepipedic dosage forms
M_t, M_∞	Amount of drug released from the dosage form at time t, and infinite time, respectively
M_{inf}	Amount of drug released at infinite time, in figures
n, m, p	Integers varying from 0 or 1 to ∞ in series of Eqs. (2), (5), (8), and (9)
q_n	Root of the Bessel function of the first kind and order 0
R	Radius of the spherical dosage forms
t	Time
W	Amount of drug eliminated from the plasma at time t
x, y, z	Axes of the rectangular parallelepiped
Y, Z	Amount of drug at time t in the GI tract and in the plasma, respectively.
β_n	Root of Eq. (6), given in Tables [16,17].

1. Introduction

There are two ways to improve the care of the sick: (1) the development of new and better drugs, and (2) the more effective and safer use of drugs that already exist. Drug delivery systems could be significantly improved by the simultaneous development of two areas of knowledge, namely, the drug pharmacokinetics and the technology of delivering drugs more effectively [1].

Conventional dosage forms most often lead to an immediate release of the drug within the gastrointestinal tract. As many drugs are absorbed into the blood compartment following first-order kinetics, the drug concentrations in the plasma increase rapidly (resulting in high plasma peaks), and the drug concentrations in the gastrointestine (GI) decrease quickly. In addition, due to the first-order kinetics of elimination of many drugs from the blood compartment, the plasma drug level decreases rapidly with time. For drugs with high rate constants of absorption and high rate constants of elimination, the resulting peak of drug concentration is very high, and the trough is very low, so that the optimal therapeutic level may be only briefly present. Dosage forms with controlled drug release are able to slow down the solution process in the GI tract. They are thus capable to prolong the pharmacodynamic effects of the drugs and hence to reduce the necessary dosing

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interval. Monolithic devices have been prepared by dispersing the drug molecularly in a polymer. The entire process of drug release may be rather complex as the GI liquid enters the polymer, dissolves the drug, and enables the drug to diffuse out of the dosage form through the liquid located in it [2]. However, most often the kinetics of drug release is of greater importance and the only one considered.

The drug level-time history in the serum is of greater concern for curing the patient. As the drug release can be readily determined by in vitro tests, and moreover, in vivo investigations necessitate rather complex experimental studies with healthy volunteers, correlation of in vitro and in vivo results is of great interest. Attempts were made in order to establish in vitro/in vivo correlations by two workshops [3,4]. It was concluded that the state of science and technology at that time did not always permit meaningful correlations for controlled release dosage forms [5,6]. More detailed studies on the correlation of in vitro drug dissolution kinetics and in vivo bioavailability showed that the problem of the drug transport along the GI tract is rather complex [7]. Among the facts examined, it must be pointed out that the permeability of the GI membrane may vary from place to place, meaning that the rate constant of absorption of the drug may depend on the position along the GI tract. This fact is important as dosage forms with immediate or controlled release deliver the drug to different parts of the GI tract. Another way was paved for evaluating the concentration-time history of the drug in the plasma by using a numerical model taking into account all the known facts, e.g., the kinetics of drug release obtained by in vitro tests and the stages of absorption into and elimination out of the serum compartment with the pharmacokinetic parameters [8], and some emphasis was placed on the dose frequency [9] and the GI tract residence time [10].

The pharmacokinetics may be complex for some drugs, either because of the first-pass metabolism, or because of a change in the rate constant of absorption along the GI tract and in the rate constant of elimination with the drug concentration. For instance, with diltiazem HCl [11], the AUC increased more than two-fold after doubling the dose. For theophylline, it was shown that the elimination followed first-order kinetics at least up to 10.4 mg/kg [12]. However, in humans 1-demethylation of theophylline appears to be the potentially saturable metabolic pathway, leading to nonlinear pharmacokinetics at increasing doses. Sustained release preparations with theophylline have poor bioavailability [13]. Caffeine kinetics were also found to be nonlinear [14].

The first objective of this study is to predict the characteristics of controlled release dosage forms (e.g. the dimensions and shape for a given polymer matrix), so that they are able to release a given percentage of the drug over a given period of time. The accuracy of these calculations has been confirmed by comparing the kinetics of drug release obtained either by experiments or calculation. Good agreement was found [15]. The required dimensions of the devices are calculated, so that 85% of the drug is released within either 6 or 24 h, for various shapes, e.g. spheres, cylinders and parallelepipeds. Three drugs are considered, theophylline in spherical dosage forms, caffeine in cylinders, and diltiazem HCl in parallelepipeds. Simple assumptions are made by neglecting the first-pass metabolism, and by considering that the rate constant of absorption does not vary along the GI tract and that the rate constant of elimination does not depend on the drug concentration. It should be emphasized that, provided that they are known, these facts can be taken into account by the numerical model.

The other purpose of this study is to assess the plasma drug level for these various dosage forms with different drugs by using the numerical model. Assuming that the dosage forms can be kept in the GI tract over a period of time exceeding the usual GI tract residence time by various ways, no limitation of time is imposed for the dosage form in the GI. The drug level obtained from immediate release dosage forms is also calculated. The plasma drug profiles from immediate and controlled release dosage forms (with various drugs and different shapes) are compared.

2. Theoretical development

2.1. Assumptions

1. The process of drug release is controlled by Fickian diffusion with constant diffusivity, as shown from in vitro tests.
2. The dosage forms are either spherical, cylindrical or parallelepipedic in shape.
3. The process is controlled by diffusion out of the dosage form along the GI tract, by absorption into and elimination out of the plasma compartment.
4. Each drug is characterized by its pharmacokinetic parameters, e.g. the rate constants of absorption and elimination.
5. The rate constant of absorption remains constant along the GI tract [7].
6. The possible first-pass metabolism is neglected. In fact, it could be considered if it was known.
7. The rate constant of elimination is constant, and does not depend on the plasma drug concentration.

2.2. Mathematical treatment

The following stages are considered (Fig. 1):

(1a) Diffusion of the drug out of the parallelepipedic dosage forms.

The equation of diffusion in tri-dimensions along the three perpendicular axes x, y, z, is, with constant diffusivity

$$\frac{\partial C}{\partial t} = D \times \left[\frac{\partial^2 C}{\partial x^2} + \frac{\partial^2 C}{\partial y^2} + \frac{\partial^2 C}{\partial z^2} \right] \quad (1)$$

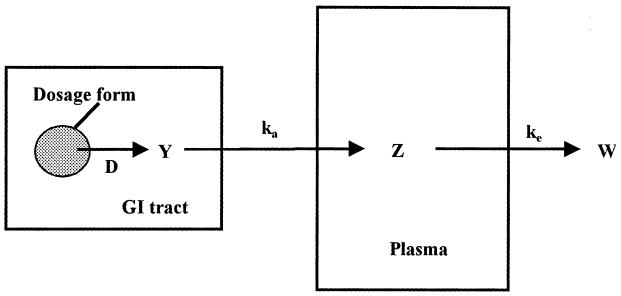

Fig. 1. Scheme of the process considered in the new model for plasma drug level evaluation.

The kinetics of drug release, with a very high coefficient of mass transfer in the boundary layer at the surface of the dosage form is [16]

$$\frac{M_\infty - M_t}{M_\infty} =$$

$$\frac{512}{\pi^6} \times \sum_{n=0}^{\infty} \frac{1}{(2n+1)^2} \exp\left(-\frac{(2n+1)^2 \times \pi^2 \times D \times t}{L_1^2}\right)$$

$$\times \sum_{p=0}^{\infty} \frac{1}{(2p+1)^2} \exp\left(-\frac{(2p+1)^2 \times \pi^2 \times D \times t}{L_2^2}\right)$$

$$\times \sum_{m=0}^{\infty} \frac{1}{(2m+1)^2} \exp\left(-\frac{(2m+1)^2 \times \pi^2 \times D \times t}{L_3^2}\right) \quad (2)$$

where M_t and M_∞ are the amounts of drug released at time t, and at infinite time, respectively; L_1, L_2, L_3 are the three lengths of the parallelepiped, and n, p and m are integers.

(1b) Diffusion of the drug out of the spherical dosage forms.

The equation of radial diffusion with constant diffusivity is

$$\frac{\partial C}{\partial t} = \frac{D}{r^2} \times \frac{\partial}{\partial r}\left[r^2 \times \frac{\partial C}{\partial r}\right] \quad (3)$$

The boundary condition expresses that the rate at which the drug leaves the device is always equal to the rate at which the drug is brought to the surface by internal diffusion. The constant of proportionality is called mass transfer coefficient in the boundary layer, h.

$$-D \times \left(\frac{\partial C}{\partial r}\right)_R = h \times (C_s - C_\infty) \quad (4)$$

where C_s is the actual drug concentration on the surface at time t, and C_∞ is the corresponding concentration which is at equilibrium with the liquid.

The solution is given by [17]

$$\frac{M_\infty - M_t}{M_\infty} = \sum_{n=1}^{\infty} \frac{6 \times S^2}{\beta_n^2 \times (\beta_n^2 + S^2 - S)} \times \exp\left(-\frac{\beta_n^2}{R^2} \times D \times t\right) \quad (5)$$

where the $\beta_n s$ are the roots of

$$\beta \times \cot\beta = 1 - S \quad (6)$$

with the dimensionless number

$$S = \frac{h \times R}{D} \quad (7)$$

The values of β_n are given in tables for various values of S [16,17].

When the value of the mass transfer coefficient in the boundary layer is very high, so that h × R/D is around 100 or larger, Eq. (5) reduces to

$$\frac{M_\infty - M_t}{M_\infty} = \frac{6}{\pi^2} \times \sum_{n=1}^{\infty} \frac{1}{n^2} \times \exp\left(-\frac{n^2 \times \pi^2}{R^2} \times D \times t\right) \quad (8)$$

(1c) Diffusion of the drug out of the cylindrical dosage forms.

The equation for a cylinder of finite length is given by the product of two series, associated either with the radial or with the longitudinal transfer [16]

$$\frac{M_\infty - M_t}{M_\infty} = \frac{32}{\pi^2} \times \sum_{n=1}^{\infty} \frac{1}{q_n^2} \times \exp\left(-\frac{q_n^2}{R^2} \times D \times t\right) \times \sum_{p=0}^{\infty} \frac{1}{(2p+1)^2} \times \exp\left(-\frac{(2p+1)^2 \times \pi^2}{H^2} \times D \times t\right) \quad (9)$$

where R is the radius and H the length of the cylinder.

The $q_n s$ are the roots of the Bessel function $J_0(q)$ of the first kind of order zero, approximate values being given in various books [16,17].

(2) Amount of drug in the GI compartment.

The amount of drug in the GI compartment, Y, is evaluated using the following relation

$$\frac{dY}{dt} = \frac{dM}{dt} - k_a \times Y \quad (10)$$

where $\frac{dM}{dt}$ represents the rate at which the drug is released from the dosage form, and k_a denotes the rate constant of absorption.

(3) Amount of drug in the plasma, Z.

The following equation is used

$$\frac{dZ}{dt} = k_a \times Y - k_e \times Z \quad (11)$$

with k_e being the rate constant of elimination.

(4) Amount of drug eliminated, W.

$$\frac{dW}{dt} = k_e \times Z \quad (12)$$

As drug release from the dosage form is controlled by diffusion, there is no analytical solution of this set of differential equations. The problem is resolved, step by step, with a numerical model.

3. Materials and methods

3.1. Materials

The following chemicals were obtained from commercial suppliers and used as received: acetyltributyl citrate (ATBC; Citroflex A-4, Morflex Chemical Co., Greensboro, NC), caffeine (Merck, Darmstadt, Germany), dibutyl sebacate (DBS, Merck-Schuchardt, Hohenbrunn, Germany), diltiazem HCl (Gödecke, Freiburg, Germany), ethyl cellulose (Ethocel Standard 10 Premium, Dow Chemical Company, Midland, MI), theophylline (Knoll Deutschland GmbH, Ludwigshafen, Germany).

3.2. Experimental methods

3.2.1. Film preparation

Drug containing films have been prepared by solvent casting. The drug (0.5–2% w/w, referred to the mass of the film), plasticizer (10 or 20% w/w, referred to the mass of the polymer) and polymer were dissolved in 100 ml isopropanol and then poured into teflon molds (15 cm × 15 cm). The subsequent drying process was as follows: 3 days at room temperature, 3 days at 35°C and 4 days at 50°C. Thus, the quantity of residual solvent was minimized [18]. The films were then cut into pieces of 7 × 14 cm. The thickness of each piece was measured at 50 homogeneously distributed points using a foil thickness gauge (Model 497, Erichsen, Hemer, Germany).

3.2.2. Microparticle preparation

Microparticles were prepared by grinding the dried, drug-loaded films (thickness: approximately 50 μm) in a ball mill (Retsch Schwingmühle, Typ MM 2000, amplitude: 50 min^{-1}, for 5 min) (Retsch GmbH & KG, Haan, Germany), under cooling with liquid nitrogen, and subsequent sieving (50, 100, and 150 μm meshsize). A light microscope (Axioskop, Zeiss, Jena, Germany) was used to measure the diameter of the particles (assuming spherical geometry, based on visual observation).

3.2.3. In vitro release experiments

Release experiments ($n = 3$) were conducted in 0.1 M pH 7.4 phosphate buffer (USP XXIV), at 37°C in a horizontal shaker (GFL 3033, Gesellschaft für Labortechnik, Burgwedel, Germany) at 100 rpm. Films of approximately 12 g dry weight were released within 1000 ml medium in plastic boxes. To assure a constant surface area exposed to the buffer solution, the films were fixed within the plastic boxes. Glass flasks (filled with 32 ml phosphate buffer) were used for the release of the microparticles (300 mg). At predetermined time intervals, 5 ml (films) or 2 ml (microparticles) samples were withdrawn and replaced with fresh medium. The drug concentration was analyzed spectrophotometrically (Shimadzu UV-2101 PC UV-VIS scanning spectrophotometer, Columbia, USA), at the following wavelengths: theophylline, $\lambda = 271$ nm; caffeine, $\lambda = 273$ nm and diltiazem HCl, $\lambda = 236$ nm.

The parameters of diffusion obtained by in vitro tests are shown in Table 1. The pharmacokinetic parameters (Table 2) were taken from the literature [19].

4. Results and discussion

Two kinds of results are considered: (1) in vitro data showing the accuracy of the kinetics of release obtained by calculation [15], and (2) in vivo data showing the drug level in various compartments, obtained by calculation with dosage forms made of the polymer-drug systems shown in Table 1 and whose dimensions are shown in Table 3. Moreover, the drug level in the plasma is evaluated for multiple dosing, administering the device once a day. Comparison can be made between three dosage forms, with (1) immediate release, (2) controlled release, 85% of the drug being released within 6 h, and (3) controlled release, 85% of the drug being released within 24 h.

4.1. Drug release kinetics out of the dosage forms

As shown in Fig. 2, curve 1, good agreement is observed between the kinetics of drug release obtained either by calculation using Eq. (8) or by in vitro experiments, confirming the good agreement already shown in previous studies [15] (for $R = 52$ μm, the following particle size distribution was found experimentally: 0% <20 μm, 2%

Table 1
Experimentally determined parameters of diffusion for different drug-polymer-plasticizer combinations

Drug	Polymer, plasticizer	Diffusivity 10^{10} cm^2/s	Mass transfer coefficient, h 10^5 cm/s
Caffeine	Ethyl cellulose 10, ATBC 20%	8.2	0.5
Theophylline	Ethyl cellulose 10, ATBC 20%	5.0	1.8
Diltiazem HCl	Ethyl cellulose 10, DBS 10%	2.5	0.3

Table 2
Pharmacokinetic parameters of the drugs [19] used for the theoretical simulations of the resulting plasma levels and elimination kinetics

Drug	k_a (h^{-1})	k_e (h^{-1})
Caffeine	3.03	0.17
Theophylline	0.41	0.14
Diltiazem HCl	0.96	0.23

20–30 μm, 8% 30–40 μm, 39% 40–50 μm, 33% 50–60 μm, 16% 60–70 μm, 3% 70–80 μm, 0% >80 μm). As the dimensionless number S is very high (around 700), Eq. (8) assuming an infinite value for the mass transfer coefficient in the boundary layer can be used [16].

The process of drug release is controlled by diffusion with constant diffusivity, the initial amount of drug in the dosage form being released at infinite time. The dimensions of the dosage forms shown in Table 3 are calculated, so that 85% of the drug is released within either 6 or 24 h.

The curves in Fig. 2 can lead to a few comments:

1. Typical kinetics of release controlled by diffusion with constant diffusivity are obtained.
2. The rate of release at the beginning is very high, with an almost vertical tangent, associated with the very high value of the mass transfer coefficient in the boundary layer.
3. The rate of release decreases with time.
4. Of course, the curves 2 and 3 are quite different, since 85% of drug is delivered within either 6 or 24 h.

4.2. Assessment of the amount of drug within various compartments

The amount of drug within various compartments at different times (expressed as a fraction of the amount of drug released from the dosage form at infinite time, M_t/M_∞) is illustrated for the three drugs in dosage forms of various shapes: (1) theophylline in spheres (Fig. 3), (2) caffeine in cylinders (Fig. 5), and (3) diltiazem HCl in parallelepipeds (Fig. 7). The curves resulting from immediate release dosage forms are also given. The notation is as follows:

1, 2, 3: drug release kinetics from the dosage forms
$1'$, $2'$, $3'$: drug plasma levels
$1''$, $2''$, $3''$: elimination kinetics of the drugs

1, $1'$, and $1''$ refer to the immediate release dosage forms, 2, $2'$, and $2''$ denote the controlled release dosage forms with 85% of the drug being released within 6 h, whereas 3, $3'$, and $3''$ represent the kinetics resulting from controlled

Table 3
Calculated dimensions (μm) of various dosage forms required to achieve desired drug release rates

Drug	Dosage form	L_1 (or H)	L_2	L_3	R
85% drug delivered within 6 h					
Caffeine	Cylinder	185			112
Theophylline	Sphere				87
Diltiazem HCl	Parallelepiped	96	96	192	
85% drug delivered within 24 h					
Caffeine	Cylinder	320			250
Theophylline	Sphere				174
Diltiazem HCl	Parallelepiped	192	192	384	

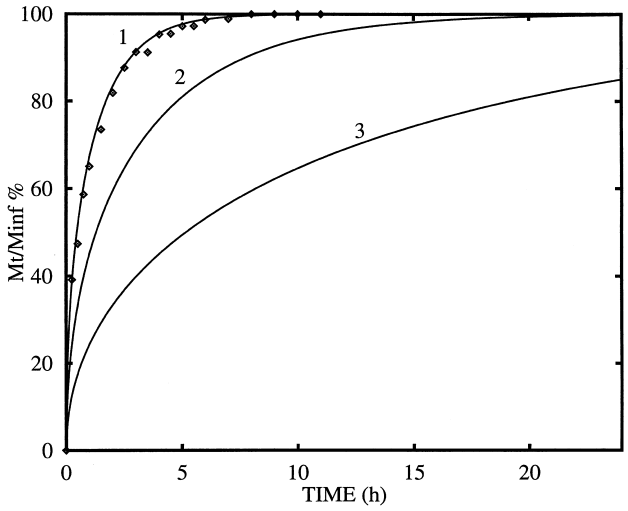

Fig. 2. Release kinetics of theophylline from spherical dosage forms with different radii: (1) $R = 52$ μm, (2) $R = 87$ μm, and (3) $R = 174$ μm; diamonds: experimental values, curves: theoretical values; $D = 5 \times 10^{-10}$ cm^2/s.

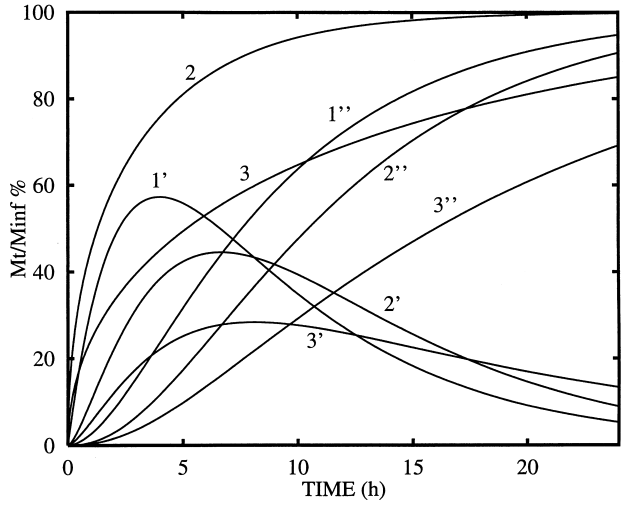

Fig. 3. Relative amount of theophylline (M_t/M_{inf} %) vs. time, for different dosage forms: immediate release (1, $1'$, $1''$); controlled release from spherical dosage forms with: $R = 87$ μm (2, $2'$, $2''$); $R = 174$ μm (3, $3'$, $3''$). 1, 2, 3: Kinetics of drug release out of the dosage form, $1'$ $2'$, $3'$: plasma drug level, $1''$, $2''$, $3''$: kinetics of drug elimination out of the plasma; $D = 5 \times 10^{-10}$ cm^2/s, $k_a = 0.41/h$, $k_e = 0.14/h$ (curve 1 superimposes on the y-axis and the horizontal line at 100%).

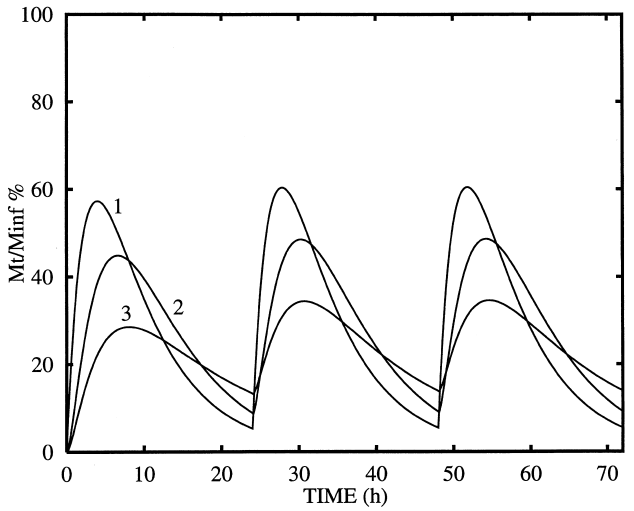

Fig. 4. Theophylline level (M_t/M_{inf} %) vs. time in the plasma for various dosage forms taken once a day: immediate release (1), controlled release from spherical dosage forms with $R = 87$ μm (2); $R = 174$ μm (3); $D = 5 \times 10^{-10}$ cm^2/s, $k_a = 0.41/h$, $k_e = 0.14/h$.

release dosage forms with 85% of the drug being released within 24 h.

The following conclusions are worth noting from the curves in Figs. 3, 5 and 7:

1. The kinetics of drug release out of the dosage forms are quite different (1, 2, 3). The kinetics associated with the immediate release is not shown, as it superimposed on the M_t/M_∞ %-axis and the horizontal line at 100%.
2. The plasma drug levels ($1'$, $2'$, $3'$) are also quite different. A rather high peak is obtained with the immediate release dosage forms, while flatter levels are displayed with their controlled release counterparts, especially with those releasing 85% drug within 24 h.
3. The kinetics of drug elimination are also typical, the amount of drug eliminated decreasing from the immediate release dosage forms to the other two controlled release dosage forms.
4. The effect of the nature of the drug on the plasma level and on the kinetics of elimination can also be appreciated [20], in spite of the different shapes of the dosage forms. Of course, a high value of the rate constant of absorption is responsible for a fast rate of drug delivery into the plasma. Thus, the peak is higher and attained at a shorter time with caffeine, which has the highest rate constant of absorption. Theophylline, for which the rates constants of absorption and elimination are lower, displays a flatter plasma drug level with a lower peak.
5. It appears that it is necessary to design a controlled release dosage form with appropriate shape and dimensions for each drug, in order to obtain a desired plasma drug level.
6. Of course, the interest of keeping the controlled release dosage forms within the GI tract for a period of time longer than the usual GI tract transit time, is clearly apparent.

4.3. Assessment of the plasma drug level from oral dosage forms administered once a day

It is possible to evaluate the plasma drug level with multiple doses using the numerical model described above. These plasma drug levels are calculated for the three drugs in different dosage forms: theophylline (Fig. 4), caffeine (Fig. 6), and diltiazem HCl (Fig. 8).

The notation is as follows: drug profiles associated with immediate release (curve 1), controlled release with 85% of the drug being released within 6 h (curve 2), and controlled release with 85% of the drug being released within 24 h (curve 3).

The following conclusions can be drawn:

1. The advantages of controlled release systems over their immediate release counterparts are clear for every drug. The dosage forms with controlled release are responsible for more constant plasma drug levels with lower peaks and higher troughs.
2. The effect of the nature of the drug is also clearly apparent when comparing the plasma drug levels in Figs. 4, 6 and 8. The drug with a high rate constant of absorption and a high rate constant of elimination is associated with high peaks and low troughs. This is the case for caffeine, and it is difficult to find a dosage form with controlled release leading to flat plasma drug levels.

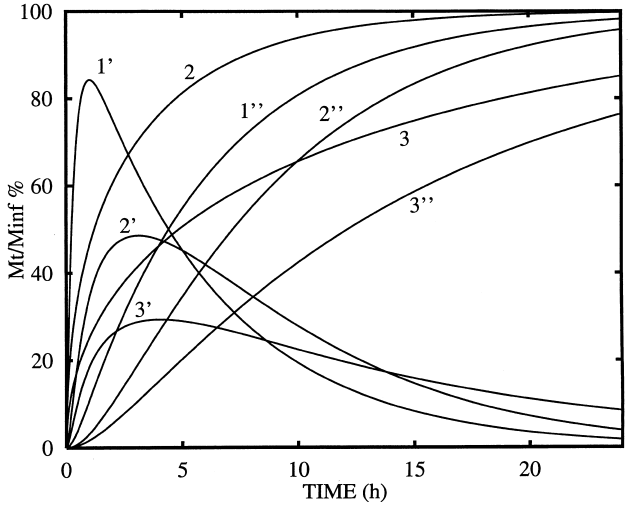

Fig. 5. Relative amount of caffeine (M_t/M_{inf} %) vs. time for different dosage forms: immediate release (1, $1'$, $1''$), controlled release from cylindrical dosage forms in shape with $R = 112$ μm, $H = 185$ μm (2, $2'$, $2''$), $R = 250$ μm, $H = 320$ μm (3, $3'$, $3''$). 1, 2, 3: Kinetics of drug release out of the dosage form, $1'$, $2'$, $3'$: plasma drug level, $1''$, $2''$, $3''$: kinetics of drug elimination out of the plasma; $D = 8.2 \times 10^{-10}$ cm^2/s, $k_a = 3.03/h$, $k_e = 0.17/h$ (curve 1 superimposes on the y-axis and the horizontal line at 100%).

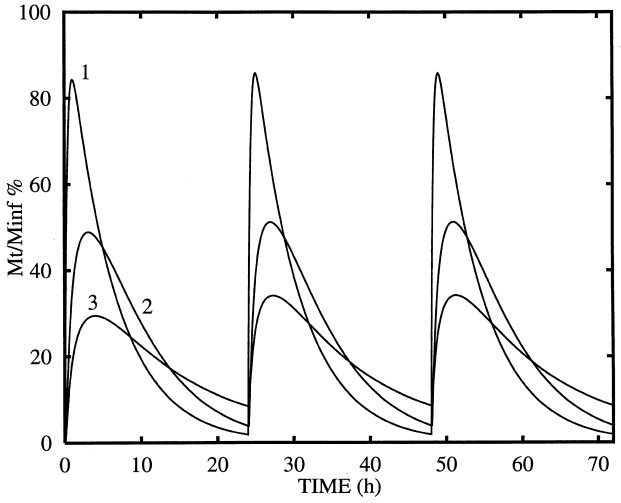

Fig. 6. Caffeine level (M_t/M_{inf} %) vs. time in the plasma for various dosage forms taken once a day: immediate release (1), controlled release from cylindrical dosage forms with $R = 112$ μm, $H = 185$ μm (2), $R = 250$ μm, $H = 320$ μm (3); $D = 8.2 \times 10^{-10}$ cm^2/s, $k_a = 3.03/h$, $k_e = 0.17/h$.

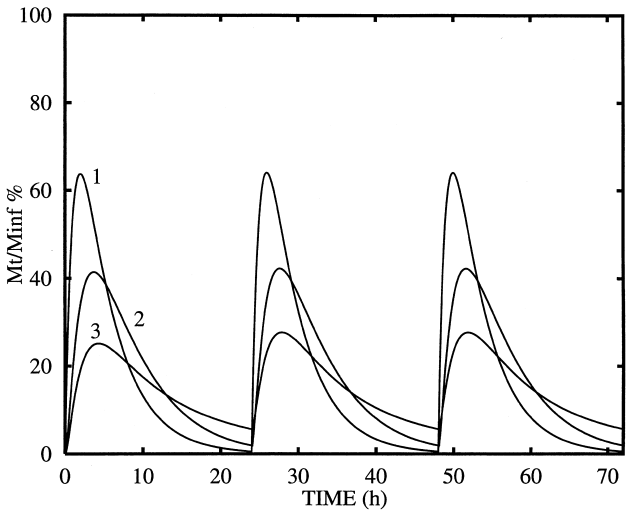

Fig. 8. Diltiazem HCl level (M_t/M_{inf} %) vs. time in the plasma for various dosage forms taken once a day: immediate release (1), controlled release from parallelepipedical dosage forms with $96 \times 96 \times 192$ μm (2), $192 \times 192 \times 384$ μm (3); $D = 2.5 \times x10^{-10}$ cm^2/s, $k_a = 0.96/h$, $k_e = 0.23/h$.

5. Conclusions

From these results, it stands to reason that it is possible to determine the dimensions of controlled release dosage forms with a given shape (e.g. sphere, cylinder or parallelepiped) to achieve desired release profiles. The dimensions of dosage forms of various shapes have been calculated so that 85% of the drug is released within either 6 or 24 h, respectively. In addition, the amount of drug located in various compartments of the human body can be assessed using a numerical model, when the pharmacokinetic parameters of the drug are known. The resulting plasma drug levels from various dosage forms (administered once a day) have been evaluated.

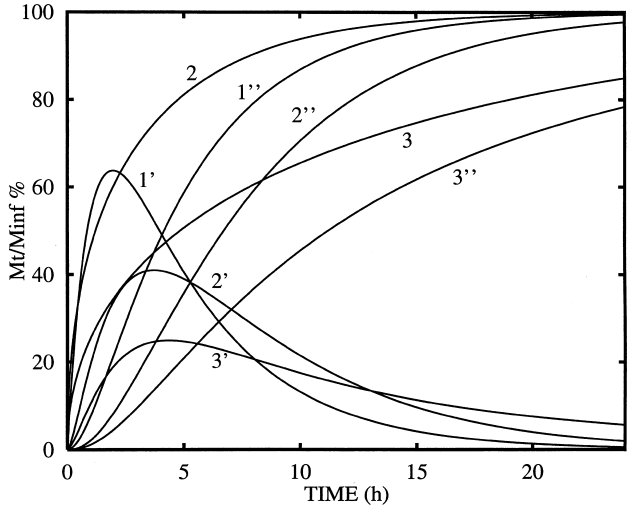

Fig. 7. Relative amount of diltiazem HCl (M_t/M_{inf} %) vs. time for different dosage forms: immediate release (1, 1′, 1″), controlled release from parallelepipedical dosage forms with $96 \times 96 \times 192$ μm (2, 2′, 2″), $192 \times 192 \times 384$ μm (3, 3′, 3″). 1, 2, 3: Kinetics of drug release out of the dosage form, 1′, 2′, 3′: plasma drug level, 1″, 2″, 3″: kinetics of drug elimination out of the plasma; $D = 2.5 \times 10^{-10}$ cm^2/s, $k_a = 0.96/h$, $k_e = 0.23/h$ (curve 1 superimposes on the y-axis and the horizontal line at 100%).

The effect of the nature of the drug on the release kinetics and on the plasma drug level appears to be of great concern. A drug such as caffeine with a high rate constant of absorption and a high rate constant of elimination is associated with a fluctuating plasma drug level with high peaks and low troughs.

The interest of keeping dosage forms within the patients GI tract over periods of time longer than the usual GI tract transit time seems worth noting. The dosage form releasing 85% of drug within 24 h leads to more constant plasma drug levels.

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