ELSEVIER

International Journal of Pharmaceutics 113 (1995) 231–240

international journal of pharmaceutics

Modelling the process of controlled release of drug in in vitro and in vivo tests

E.M. Ouriemchi, J. Bouzon, J.M. Vergnaud *

Faculty of Sciences, University of Saint-Etienne, 23 Dr P. Michelon, Saint-Etienne 42023, France

Received 11 January 1994; modified version received 22 April 1994; accepted 1 June 1994

Abstract

Controlled release dosage forms offer advantages over conventional dosage forms, in a particular, a more constant and prolonged therapeutic effect. In vitro and in vivo testing is used to determine the release of the drug, and correlations are attempted between these results, leading often to major differences. The process of drug release from a drug-polymer device controlled by diffusion is established with either an in vitro or in vivo case. A numerical model taking all the known facts into account is built into these two cases. For the in vivo test, the parameters of interest are the diffusivity, the concentration of drug and dimension of the dosage form, the volume of liquid in the stomach, the volume of blood, and the rate constants of absorption and elimination. The results are obtained with the concentration-time histories of the drug in the stomach and in the blood.

Keywords: Controlled release; In vitro-in vivo testing; Drug-polymer device; Numerical model

1. Introduction

Controlled-release pharmaceutical dosage forms may offer advantages over conventional dosage forms with immediate release, such as a reduced dosing frequency, less adverse side effects, better pharmacological activity, and a more constant and prolonged therapeutic effect (Heilmann, 1983). The controlled release dosage form is especially justified when a lower drug concentration in blood decreases side-effects, and also when the compliancy of the patient is of concern.

Abbreviations/symbols: α_n, β_n, parameters shown in Eq. 4; C, CN, concentration of the drug in dosage form at time t and $(t+\Delta t)$, respectively; Δt, increment of time (s); D, diffusivity (cm^2/s) of the drug through the dosage form; n, integer, characterizing position; N, number of spherical slices; R, radius of the bead; Δr, thickness of each spherical slice; M, dimensionless number given in Eq. 5; k_a, rate constant of absorption (h^{-1}); k_e, rate constant of elimination (h^{-1}); K_b, partition factor of the drug between the stomach and the blood; K_p, partition factor of the drug between the polymer and gastric liquid; M_{in}, amount of drug initially located in the dosage form; M'_t, amount of drug located in the dosage form at time t; S, area of the dosage form; V_s, volume of gastric liquid in the stomach; V_b, volume of the blood; Y,YN, amount of the drug located in the stomach at time t and $(t+\Delta t)$, respectively; Z, amount of the drug located in the blood at time t; W, amount of the drug eliminated at time t.

* Corresponding author.

0378-5173/95/$09.50 © 1995 Elsevier Science B.V. All rights reserved
SSDI 0378-5173(94)00203-7

Generally, the dosage forms are tested by using the in vitro dissolution test. Alternative in vitro procedures such as the flow-through filter method and the rotating flask method are preferentially used, amongst others. This test is important for the following purposes: simply to test different lots in the development phase, to provide the necessary process control of release in the research phase, to determine the stability of the release, and to adapt the formulation to the purpose.

However, the in vitro process must be validated by establishing a correlation between the in vitro and in vivo tests (Skelly et al., 1990). Various studies have been performed in order to determine correlations between these two types of tests. The in vitro dissolution curve is compared to the input function resulting from deconvolution of the drug concentration-time history in the blood. Good correlation is obtained when these two types of curves are superimposed. Sometimes, the in vitro dissolution procedure of the dosage form is modified in order to correlate best with the deconvolution curve obtained with in vivo experiments. Studies have been carried out with thiamine hydrochloride encapsulated with Eudragit L (Aly and Megwa, 1989). Associations between in vitro and in vivo tests have been established by using moment and linear system analyses, as well as the mean residence time of the drug, and the effect of agitation in the in vitro test was found to be of importance (Nicklasson, 1990). Relations between drug liberation, estimated in vitro, and their behaviour in the human organism were attempted with theophylline retard preparations (Beerbaum et al., 1988). Studies were made with nylon-coated ion exchange resins containing sodium diclofenac (Garcia-Encina et al., 1993). In vitro/in vivo evaluation of a colonic release capsule of vasopressin was developed (Rao and Ritschel, 1992). In vitro and in vivo evaluation of an oral sustained-release floating dosage form of amoxycillin trihydrate with various hydrophilic polymers was investigated (Hilton and Deasy, 1992). Computer simulation of blood level profiles of drug liberated from two retard preparations was achieved with pentoxifylline (Koch, 1992). The dissolution behaviour of controlled-release tablets was studied in order to evaluate the correlation between in vivo and in vitro test by analyzing the in vivo results by deconvolution (Aoki et al., 1992). Very often, pharmacokinetic simulation revealed in vivo deviations from in vitro release, as shown for timolol in polymer matrices (Finne and Urtti, 1992). Attempts were made to determine the effect of the nature of the food in the stomach on the process. A new in vitro model to detect interactions between controlled release dosage forms and food was built and comparisons were made with in vivo data available from the literature (Junginger et al., 1990). Studies made in this in vitro food simulation test showed the absence of interactions with well-defined liquid food, and the in vivo behaviour was validated with the same materials (Verhoeven et al., 1989). The process of release of the drug from drug-polymer devices is rather complex, even with in vitro testing (Vergnaud, 1993). The process of release is more complex with the in vivo test for many reasons, and especially because the system is open, meaning that the drug follows the following typical pattern: (i) it diffuses out of the dosage form in the gastric liquid and the volume of liquid and agitation are of importance irrespective of the presence of food; (ii) it diffuses through the gastric membrane into the blood and this transport rate is evaluated by first-order kinetics and its rate constant of absorption; and (iii) it diffuses essentially into the kidney and this transport is defined by first-order kinetics and its rate constant of elimination.

The first purpose in this paper was to investigate the general process of controlled drug release from the dosage form either in the closed system of the in vitro test or in the open system of the in vivo test. In the in vitro test the drug is released in a synthetic gastric liquid of constant finite volume, while in the in vivo test the drug is released in the gastric liquid, and thus diffuses through the gastric membrane into the blood during the stage of absorption and then diffuses out of the blood circulation system during the stage of elimination. It is thus possible to build a numerical model taking into account all the known facts in either the in vitro or in vivo test.

Various parameters are thus introduced: those concerned with the dosage form itself with its dimension, drug concentration and diffusivity, the others necessitated by the process of absorption and desorption such as the volume of liquid in the stomach and the volume of blood, the rate constants of absorption and elimination corresponding with first-order systems.

The second objective was to calculate the concentration-time history, for a drug with given rate constants of absorption and elimination, in either the in vitro or in vivo test. The in vitro test is performed with the dosage form located in a constant finite volume of liquid, the system being closed so that the drug remains either in the synthetic gastric liquid or in the dosage form. With the in vivo test, the system is open in the sense that the drug is released firstly in the stomach out of the dosage form, is thus absorbed in the blood and then eliminated. The usual rate constants of absorption and elimination are used for this purpose.

2. Mathematical and numerical treatment of the problem

2.1. Assumptions

Some assumptions are made in order to define precisely the problem.

(i) The process of drug transport is divided into the following stages which are connected with each other: transport through and out of the dosage form, transport from the gastric liquid to the blood with the rate constant of absorption, transport from the blood to the surroundings with the rate constant of elimination.

(ii) The dosage form with controlled drug release is spherical in shape, and the radius remains constant during the process in the gastric liquid, and the transfer is radial.

(iii) The process of drug delivery from the dosage form in gastric liquid is simplified, by considering only the diffusion of the drug.

(iv) The drug diffuses out of the dosage form with constant diffusivity.

(v) The volume of gastric liquid is constant either in the stomach or in the flask with the in vitro test, during the process (in fact a change in this volume can be accounted for by the model with a slight modification).

(vi) With in vivo testing the rate constants of absorption k_a and of elimination k_e are constant.

(vii) The concentrations of the drug in the stomach and in the blood are uniform.

(viii) The stage of elimination is not perturbed by the presence of drug in the surrounding.

(ix) The presence of drug in the blood compartment may hinder the transfer of drug from the stomach to the blood. Conventional equations neglecting this fact and new equations considering this fact are used.

2.2. Numerical treatment for the transfer of drug in the dosage form

The concentration of the drug within the dosage form is calculated with a numerical model with finite differences, as no mathematical treatment seems to be feasible for this problem.

The equation of radial diffusion in the bead with constant diffusivity and constant dimensions is:

$$\frac{\partial C_{r,t}}{\partial t} = \frac{D}{r^2} \cdot \frac{\partial}{\partial r}\left(r^2 \cdot \frac{\partial C_{r,t}}{\partial r}\right) \tag{1}$$

and the coefficient of mass transfer on the surface of the bead is so high that the concentration of drug of the surface is constantly proportional to the concentration of drug in gastric liquid.

$$C_{R,t} = K_p \cdot C_s = K_p \frac{Y}{V_s} \tag{2}$$

where K_p is the partition factor between the dosage form and the gastric liquid, C_s and Y denote the concentration and the amount of drug in the stomach respectively, and V_s is the volume of gastric liquid.

As shown in earlier studies (Vergnaud, 1993), the radius is divided into N constant increments of space Δr and time in increments of time Δt, and each position is associated with an integer. The mass balance is evaluated within a spherical membrane of thickness Δr during the interval of

time $[t, t+\Delta t]$, and the new concentrations after this elapse of time are expressed in terms of the previous concentrations by using the Crank-Nicolson method. These relationships are given at three places: within the sphere, at the center, and on the surface.

Within the sphere, with $1 \le n \le N-1$:

$$-\alpha_n \cdot \mathrm{CN}_{n-1} + (1+\alpha_n+\beta_n) \cdot \mathrm{CN}_n - \beta_n \cdot \mathrm{CN}_{n+1} = \alpha_n \cdot C_{n-1} + (1-\alpha_n-\beta_n) \cdot C_n + \beta_n \cdot C_{n+1} \quad (3)$$

with the coefficients

$$\alpha_n = \frac{(n-0.5)^2}{2\left(n^2+\frac{1}{12}\right)M} \qquad \beta_n = \frac{(n+0.5)^2}{2\left(n^2+\frac{1}{12}\right)M} \quad (4)$$

and the dimensionless number M

$$M = \frac{(\Delta r)^2}{D \cdot \Delta t} \quad (5)$$

At the center of the sphere, with $n = 0$:

$$\left(1+\frac{3}{M}\right) \cdot CN_0 - \frac{3}{M} CN_1 = \left(1-\frac{3}{M}\right) \cdot C_0 + \frac{3}{M} C_1 \quad (6)$$

On the surface of the bead, with $n = N$:

Eq. 2, rewritten, evaluates the concentration of the drug on the surface of the bead:

$$CN_N = \frac{K_\mathrm{p}}{V_\mathrm{s}} YN \quad (7)$$

where YN is the value of the amount of drug in the stomach at time $t + \Delta t$.

Amount of drug remaining in the dosage form:

The amount of drug located in the dosage form at any time, M'_t, is obtained by integrating the concentration of the drug at this time with respect to space:

$$\frac{M'_t}{4\pi(\Delta r)^3} = \frac{C_0}{24} + \frac{C_{N-0.25}}{3}\left[N^3 - (N-0.5)^3\right] + \sum_{n=1}^{N-1}\left(n^2+\tfrac{1}{12}\right) \cdot C_n \quad (8)$$

Amount of drug located in the two compartments (stomach Y, and blood Z) and amount of drug eliminated to exterior (W) (Fig. 1):

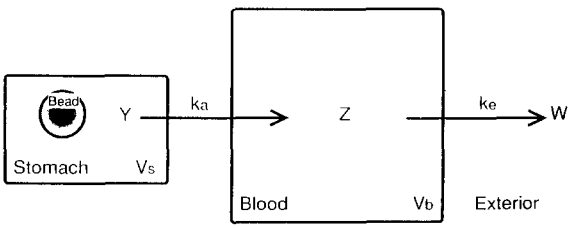

Fig. 1. Scheme for the in vivo test.

The flow of drug leaving the dosage form is given by:

$$F_\mathrm{form} = -S \cdot D \cdot \frac{\partial C_{R,t}}{\partial r} \quad (9)$$

where S is the surface of the dosage form, R its radius, and $\partial C_{R,t}/\partial r$ is the gradient of concentration next to the surface at time t.

The flow of drug passing from the stomach into the blood is often written in the simple form:

$$F_s = k_a \cdot Y \quad (10)$$

with the rate constant of absorption k_a.

This equation is not fully right, as the concentration of drug in the blood increases and hinders this transfer. More precisely, this equation must be rewritten as follows, with a partition factor of the drug between the blood and the stomach K_b:

$$F_s = k_a \cdot Y - \frac{k_\mathrm{a} V_\mathrm{s}}{K_\mathrm{b} V_\mathrm{b}} Z \quad (11)$$

When the ratio of the concentrations of the drug in the blood Z/V_b and the stomach Y/V_s is equal to the partition factor K_b, the flow of the drug from the stomach into the blood is zero.

The flow of drug eliminated out of the blood to the exterior is:

$$\frac{\mathrm{d}W}{\mathrm{d}t} = k_\mathrm{e} \cdot Z \quad (12)$$

The rate of increase in the amount of drug in the blood is:

$$\frac{\mathrm{d}Z}{\mathrm{d}t} = k_a \cdot Y - \left(\frac{k_\mathrm{a} V_\mathrm{s}}{K_\mathrm{b} V_\mathrm{b}} + k_\mathrm{e}\right) \cdot Z \quad (13)$$

The rate of increase in the amount of drug in the gastric liquid becomes:

$$\frac{\mathrm{d}Y}{\mathrm{d}t} = -S \cdot D \cdot \frac{\partial C_{R,t}}{\partial r} - k_\mathrm{a} \cdot Y + \frac{k_\mathrm{a} \cdot V_\mathrm{s}}{K_\mathrm{b} \cdot V_\mathrm{b}} Z \quad (14)$$

The set of differential equations, Eq. 12–14, is resolved step by step in evaluating the increases of the amounts of drug Y, Z and W during each interval of time $[t, t + \Delta t]$ by using the numerical Crank-Nicolson method. The flow of drug F_{form} in Eq. 9 is calculated at time t with a parabolic approximation on the grid-points N, $N-1$, $N-2$ of the dosage form. The new value YN thus obtained is introduced in Eq. 7, and the set of Eq. 3, 6 and 7 must be resolved, with the new concentrations CN_n, with $0 \leq n \leq N$, as unknowns. This problem has been resolved by using the L.U. method consisting of decomposing the matrix of the system into a product of two triangular matrices: lower and upper.

3. Experimental

3.1. Dosage forms

The dosage forms were prepared by dispersing the drug in a polymer matrix. The drug was sodium salicylate, and the polymer was Eudragit RL. As shown in an earlier study (Ouriemchi et al., 1994), the drug and polymer in powder form were intimately mixed; after pulverization of a small amount of ethanol, the mixture was pressed into a spherical bead and dried.

3.2. Conditions of release

Experiments were performed in a closed flask with a finite volume of liquid, with strong agitation.

3.3. Characteristics of the dosage forms

The radius was 0.32 cm. With 50% of drug in weight, the amount of drug was 60 mg. The diffusivity was constant: 2.2×10^{-7} cm^2/s (Ouriemchi et al., 1994). The coefficient of mass transfer on the surface was very high. The partition factor of the drug between the polymer and the synthetic gastric liquid was 60.7.

3.4. Characteristics of the compartments

The rate constants of absorption and elimination were (Vidal, 1991): $k_a = 2.772$/h and $k_e = 0.231$/h. The volume of blood was taken as 4 l. The volume of liquid in the stomach was taken as 0.1, 0.2 and 1 l, successively. Of course, the value of each parameter can be changed in the model, in order to determine the effect of this parameter on the process.

4. Results

Some emphasis is placed upon the comparison between in vitro and in vivo tests by using a numerical model taking into account all the known facts for each test.

This comparison is made either for a high rate of dissolution of the drug in the gastric liquid or for controlled release obtained with a dosage form, this dosage form being made of drug dispersed in a polymer and previously studied (Armand et al., 1987; Saber et al., 1988; Vergnaud 1993). In order to simplify the process, only the release of drug by diffusion out of the dosage form is considered, in spite of the fact that the process of drug release is controlled by the liquid diffusion into the polymer.

Many parameters appear in the whole process with the in vivo test, but only the effect of the volume of gastric liquid is studied as this volume intervenes in both the in vitro and in vivo tests.

Some results of interest are given with either the amount-time histories or concentration-time histories of the drug in the liquid gastric for the in vitro and in vivo tests and in the blood in the in vivo test.

4.1. High rate of dissolution of the drug in gastric liquid

The kinetics of the drug transferred either in the gastric liquid in the in vitro and in vivo tests or in the blood in the in vivo test are calculated and drawn in Fig. 2 with a low volume (0.11) and in Fig. 3 with a high volume (11) of gastric liquid. Moreover, the kinetics of the drug released from the dosage form and the kinetics of the drug eliminated out of the blood, are also drawn.

From these kinetics shown in Fig. 2 and 3, the following conclusions are worth noting:

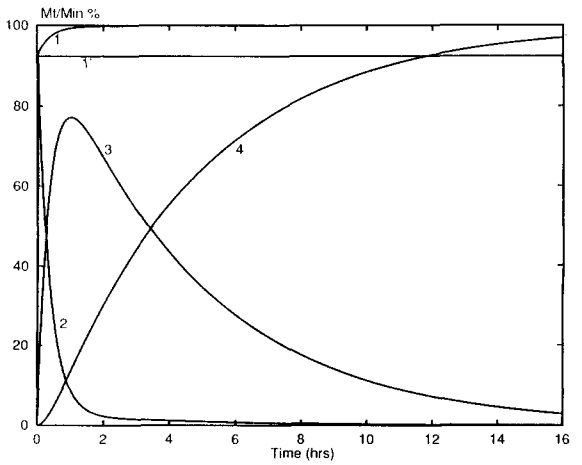

Fig. 2. Kinetics of drug transfer for a high rate of dissolution. $V_s = 0.11$, $D = 2.2$ cm^2/s, $k_a = 2.772$ h^{-1}, $k_e = 0.231$ h^{-1}, 1', release of drug in vitro; 1, release of drug in vivo; 2, amount of drug in the stomach; 3, amount of drug in blood; 4, amount of drug eliminated.

(i) Because of the partition factor of the drug in the polymer in contact with the gastric liquid, only a part of the drug is released out of the dosage form in the in vitro test. The amount of drug remaining in the dosage form is higher when the volume of gastric liquid is lower with the proportionality shown in Eq. 2.

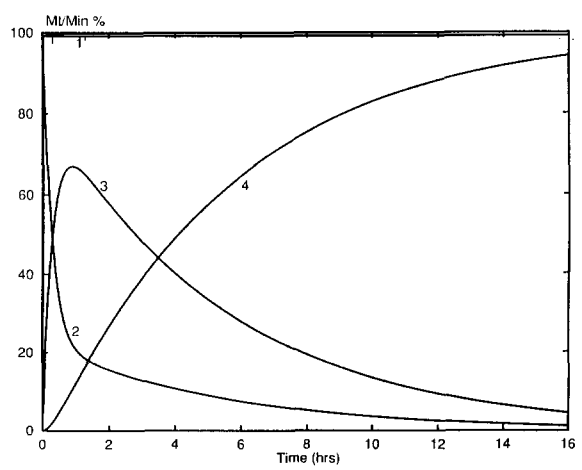

Fig. 3. Kinetics of drug transfer for a high rate of dissolution. $V_s = 11$, $D = 2.2$ cm^2/s, $k_a = 2.772$ h^{-1}, $k_e = 0.231$ h^{-1}. 1', release of drug in vitro; 1, release of drug in vivo; 2, amount of drug in the stomach; 3, amount of drug in blood; 4, amount of drug eliminated.

(ii) In spite of this partition factor, all the drug is extracted out of the dosage form in the in vivo test. This is due to the fact that the drug in the stomach is constantly transferred into the blood and eliminated.

(iii) The amount of drug located in the stomach with the in vivo test starts from the higher value and decreases exponentially with time. In the in vitro test the maximum concentration is reached very quickly and remains constant.

(iv) As usual, the amount of drug in the blood builds up quickly, passes through a high maximum and decreases slowly, exponentially with time.

(v) The amount of drug in blood at the maximum is a little lower when the volume of the gastric liquid is larger. However, an increase in the volume of gastric liquid by ten times is only responsible for a decrease by around 14% of this maximum in the blood.

(vi) The kinetics for elimination of the drug exhibit about the same shape in Fig. 2 and 3. However, these kinetics are faster when the volume of gastric liquid in the stomach is lower.

4.2. Low rate of release with dosage forms in the stomach

Three parameters are considered for comparison between the in vitro/in vivo tests: the volume of gastric liquid in the stomach, the value of the rate constant of absorption, and the rate of drug delivery from the dosage form.

4.2.1. Effect of the volume of gastric liquid in the stomach

Comparison is made for the drug delivery either with the in vitro or the in vivo test, with a dosage form made of the drug dispersed in a polymer, the diffusivity being 2.2×10^{-7} cm^2/s. At the same time, the effect of the volume of gastric liquid on the kinetics of transfer of the drug is also studied: the volumes of 0.11·(Fig. 4), and 11 (Fig. 5) for the gastric liquid are successively considered.

Some conclusions are drawn from these results:

(i) The kinetics of release of the drug in the in

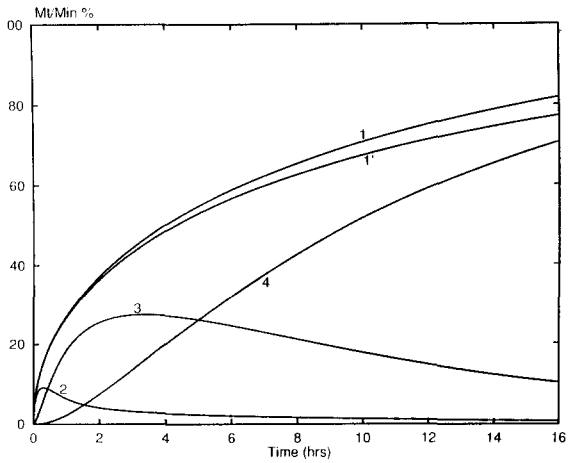

Fig. 4. Kinetics of drug transfer for a low rate of dissolution. $V_s = 0.11$, $D = 2.2 \times 10^{-7}$ cm^2/s, $k_a = 2.772$ h^{-1}, $k_e = 0.231$ h^{-1}. 1', release of drug in vitro; 1, release of drug in vivo; 2, amount of drug in the stomach; 3, amount of drug in blood; 4, amount of drug eliminated.

vitro test are about the same at the beginning for the various amounts of gastric liquid shown in Fig. 4 and 5; these kinetics become slightly different for times longer than 2 h, with the obvious statement: the higher the volume of gastric liquid, the faster the kinetics; the amount of drug released at equilibrium increases with the volume of liquid.

(ii) The kinetics for the drug delivery from the dosage form are about the same whatever the volumes of gastric liquid for the in vivo test. With a high volume of gastric liquid, the kinetics of drug delivery obtained with the in vitro and in vivo tests are about the same.

(iii) The kinetics of the drug appearing in the stomach largely depend on the volume of gastric liquid, in the case of the in vivo test. With low values of this volume, around 0.1 l, the amount of drug passes through a maximum and decreases rapidly. With a high value of this volume of 11, the maximum of the drug in the stomach is flat.

(iv) The kinetics of the drug appearing in the blood with the in vivo test depend on the volume of gastric liquid: the lower the volume of gastric liquid, the faster the kinetics.

(v) The kinetics of elimination of the drug have the same shape, and are faster when the volume of gastric liquid is lower.

4.2.2. *Effect of the rate constant of absorption*

The effect of the rate constant of absorption on the process of drug transport with the in vivo

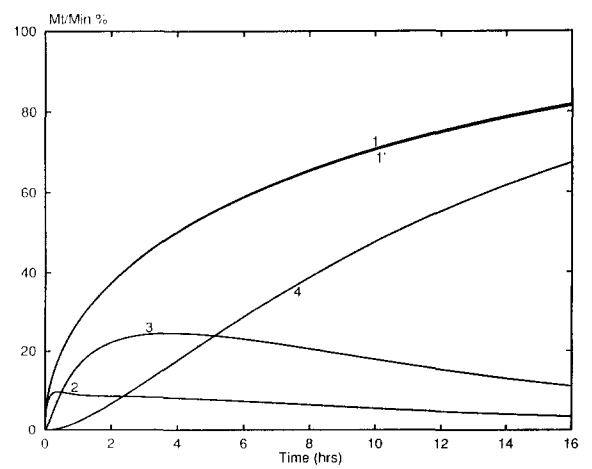

Fig. 5. Kinetics of drug transfer for a low rate of dissolution. $V_s = 11$, $D = 2.2 \times 10^{-7}$ cm^2/s, $k_a = 2.772$ h^{-1}, $k_e = 0.231$ h^{-1}. 1', release of drug in vitro; 1, release of drug in vivo; 2, amount of drug in the stomach; 3, amount of drug in blood; 4, amount of drug eliminated.

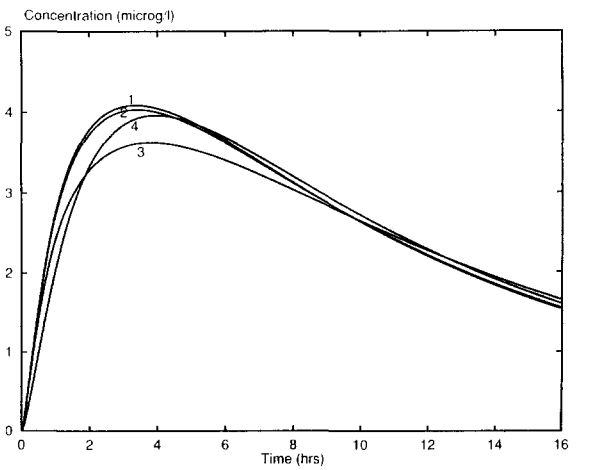

Fig. 6. Concentration-time histories of the drug in the blood, with a low rate of diffusion, the same bead and diffusivity (2.2×10^{-7} cm^2/s), and the same rate of constant of elimination (0.231 h^{-1}). 1 ($V_s = 0.11$, $k_a = 2.772$ h^{-1}); 2 ($V_s = 0.21$, $k_a = 2.772$ h^{-1}); 3 ($V_s = 1$ 1, $k_a = 2.772$ h^{-1}); 4 ($V_s = 0.21$, $k_a = 1.386$ h^{-1}).

test is demonstrated in Fig. 6 ($k_a = 2.772\ h^{-1}$) and ($k_a = 1.386\ h^{-1}$), where the kinetics are calculated with given conditions for the other parameters.

The following results are obtained:

(i) An increase in the rate constant of absorption is responsible for faster drug transport with the in vivo test.

(ii) The amount of drug in the stomach is considerably higher for the lower value of the rate constant of absorption.

(iii) The amount of drug in blood is about the same with each of the two rate constants. However, the maximum value is reached more rapidly for the higher rate constant.

(iv) The kinetics of elimination are about the same for the two values of the rate constant.

4.2.3. Effect of the rate of drug delivery out of the dosage form

The rate of delivery of the drug from the dosage form is expressed by the value of the diffusivity. As shown with the dimensionless number $D \cdot t/R^2$ appearing in the kinetics of diffusion through the dosage form, the time at which a given amount of drug is transferred is inversely proportional to the value of the diffusivity when the radius is constant.

Comparison between the curves in Fig. 6 ($D = 2.2 \times 10^{-7}\ cm^2/s$), and Fig. 7 ($D = 2.2 \times 10^{-6}\ cm^2/s$) with the same values of the other parameters (V_s, k_a and k_e) leads to the obvious statements:

(i) The greater the diffusivity, the faster the kinetics of drug delivery with the in vitro test.

(ii) In the case of the in vivo test, the amount of drug located in the stomach is considerably greater with the higher diffusivity.

(iii) The kinetics of the drug appearing in the blood largely depend on the value of the diffusivity. Moreover, the maximum is reached within a shorter time with the greater diffusivity.

(iv) The kinetics of elimination of drug are quite different with the various diffusivities. Of course, the greater the diffusivity, the faster the kinetics of drug elimination.

4.3. Concentrations of the drug in the various compartments

The amount-time histories of the drug in each compartment represent the process of the drug transport with the in vivo test. However, as the volumes of liquid in the stomach and blood compartment are quite different, it may be more informative to plot the concentration of the drug instead of the amount.

The concentration-time histories of the drug in the blood are illustrated in Fig. 7 for the higher diffusivities and in Fig. 6 for the lower value ($2.2 \times 10^{-7}\ cm^2/s$)..

The following conclusions are evident:

(i) The effect of the volume of gastric liquid with a high rate of drug delivery is described by the obvious statement: the lower the volume of gastric liquid, the greater the drug concentration in the gastrointestinal compartment. A very high diffusivity is also responsible for a greater concentration of drug in this compartment.

(ii) The case of rather low diffusivities is of great interest. The effect of the volume of gastric liquid is very well illustrated by the obvious statement: the larger the volume of gastric liquid, the lower the drug concentration in the gastrointesti-

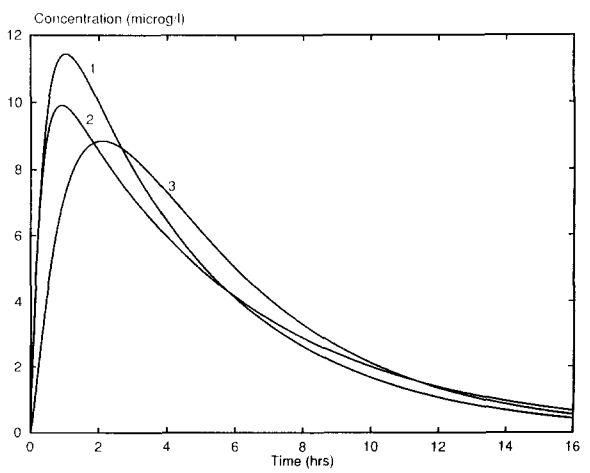

Fig. 7. Concentration-time histories of the drug in the blood, with a high rate of diffusion, with the same bead, and the same rate constants of absorption ($2.772\ h^{-1}$) and elimination ($0.231\ h^{-1}$). 1 ($V_s = 0.11$, $D = 2.2\ cm^2/s$); 2 ($V_s = 1\ 1$, $D = 2.2\ cm^2/s$); 3 ($V_s = 0.11$, $D = 2.2 \times 10^{-6}\ cm^2/s$).

nal compartment. The effect of the rate constant of absorption appears readily in Fig. 6 (curves 2 and 4).

(iii) The effect of the volume of gastric liquid on the concentration-time history of drug in the blood compartment is not of great importance. When the volume of gastric liquid is increased 10-fold, the drug concentration in the blood is only reduced by 14%. The shape of the kinetics is slightly changed, as shown in Fig. 7 for high rates of diffusion.

(iv) In the case of controlled drug delivery with a rather low diffusivity as shown in Fig. 6, the concentration-time histories for the drug are about the same, whatever the volume of gastric liquid in the stomach, and even when the rate constant of absorption is increased.

5. Conclusions

There is more than one difference between the in vitro and in vivo tests.

From a theoretical point of view, it can be said that with in vitro testing the system is closed, while the system is open with the in vivo test. In other words, with the in vitro test the drug is released in the synthetic gastric liquid located in a flask and remains in this flask. In contrast, with the in vivo test the drug follows a typical pattern: it is released in the gastric liquid in the stomach, is thus transferred into the blood and then eliminated, and the rate constants of absorption and elimination play an important role.

From a practical point of view, it is clear that the operational conditions for the in vitro tests are well defined and can be standardized. Some parameters appear to be of interest, such as the volume of the liquid in the stomach, the stirring and the nature of the liquid in the stomach which depends on the patient.

Many attempts were made in order to control the release of the drug in the stomach and even to deliver the drug with a constant rate. In fact, the problem of concern is to obtain a constant concentration in the blood, and the process is quite different and more difficult. This study has paved the way in a new direction for these studies.

The numerical model enabled one to draw all the stages of the process and to point out the importance of various parameters. Of course, the characteristics of the dosage form appear of interest, with the amount of drug and the rate of release with the diffusivity. However, other parameters such as the volume of liquid in the stomach must also be considered.

Finally, each drug is characterized by the two rate constants of absorption and elimination which play an important role for the transport of the drug, as well as the rate of release from the dosage form. It appears thus clearly that every drug would have to be placed in a typical dosage form in order to obtain a constant drug concentration in the blood over a long period of time.

References

Aly, S. and Megwa, S.A., In vitro/in vivo release of thiamine hydrochloride from microcapsules acrylic resin. *Pharm. Ind.*, 51 (1989) 1163–67.

Aoki, S., Uesugi, K., Tatsuishi, K., Ozawa, H. and Kayano, M., Evaluation of the correlation between in vivo and in vitro release of phenylpropanolamine HCl from controlled-release tablets *Int. J. Pharm.*, 85 (1992) 65–73.

Armand, J.Y., Magnard, F., Bouzon, J., Rollet, M., Taverdet, J.L. and Vergnaud, J.M., Modelling of the release of drug of gastric liquid from spheric galenic forms with Eudragit matrix. *Int. J. Pharm.*, 40 (1987) 33–41.

Beerbaum, H., Kulpe, K., Seidel, K.H., Zand, G., Nussbucker, B., Wilke, A., Rentsch, E., Wiesner, B. and Iwainsky, H., Theophyllin-Retardpraparate: beziehungen zwischen der Freisetzung in vitro und dem verhalten im menschlichen organismus. *Pharmazie,* 43 (1988) 325–9.

Finne, U. and Urtti, A., Pharmacokinetic simulation reveals in vivo deviations from in vitro release of timolol from polymer matrices, *Int. J. Pharm.*, 84 (1992) 217–22.

Garcia-Encina, G., Torres, D., Seijo, B. and Vila Jato, J.L., in vivo evaluation of nylon-coated diclofenac-resin complexes. *J. Controlled Release*, 23 (1993) 201–7.

Heilmann, K., *Therapeutic Systems*, Georg Thieme, Stuttgart, 1983, pp. 1–33.

Hilton, A.K. and Deasy, P.B., In vitro and in vivo evaluation of an oral sustained-release floating dosage form of amoxycillin trihydrate, *Int. J. Pharm.*, 86 (1992) 79–88.

Junginger, H.E., Verhoeven, J. and Peschier, L.J.C., A new in vitro model to detect interactions between controlled release dosage forms and food. *Acta Pharm. Technol.*, 36 (1990) 155–60.

Koch, H.P., Computersimulation von Blutspiegelprofilen: Wirkstoffliberation aus zwei Retardpraparaten und Computer-simulation der Ein-und Mehrdosen-Pharmakokinetik. *Pharmazie*, 47 (1992) 547–52.

Nicklasson, M., Association between in vitro and in vivo *Paperback APV*, 22 (1990) 155–173.

Ouriemchi, E.M., Bouzon, J. and Vergnaud, J.M., Oral dosage forms with a core and shell with the same polymer containing different drug concentrations *Int. J. Pharm.*, 102 (1994) 47–54.

Rao, S.S. and Ritschel, W.A., Development and in vitro/in vivo evaluation of a colonic release of vasopressin. *Int. J. Pharm.*, 86 (1992) 35–41.

Saber, M., Magnard, F., Bouzon, J. and Vergnaud, J.M., Modelling of matter transfers in drug-polymer device used as a galenic form. *J. Polym. Eng.*, 8 (1988) 295–314.

Skelly, J.P., Amidon, G., L., Barr, W.H., Benet, L.Z., Carter, J.E., Robinson, J.R., Shah, V.P. and Yacoubi, A., In vitro and in vivo testing and correlation for oral controlled/modified release dosage forms. Report of the 2nd workshop, Dec. 1988, Washington *J. Controlled Release*, 14 (1990) 95–106. *Int. J. Pharm.*, 63 (1990) 83–93.

Vergnaud, J.M., Drug delivery from dosage forms consisting of a drug dispersed in a non-erodible polymer. *Controlled Drug Release of Oral Dosage Forms.* Ellis Horwood, Chichester, 1993, pp. 199–259.

Verhoeven, J., Schutte, S.C., Peschier, L.J.C., Danhof, M., and Junginger, H.E., The design of a dry-coated controlled-release tablet for oxprenolol with microporous polypropylene powder, *J. Controlled Release*, 10 (1989) 205–17.

Vidal, Aspirine Bayer (1991) 115.