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Prediction of In-vivo Blood Level with Controlled-release Dosage Forms. Effect of the Gastrointestinal Tract Time

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Abstract

The process of in-vivo drug transfer is very complex in the case of oral dosage forms with controlled release. A numerical model taking all the known facts into account, including the release of the drug controlled by diffusion through the dosage form along the gastrointestinal tract, the kinetics of absorption in the blood compartment and the kinetics of elimination was constructed.

Various parameters intervene in an important manner for a given drug: the size of the dosage form which is associated with the rate of release of the drug, and the dose frequency in multidosing.

Some emphasis is placed upon the gastrointestinal tract time which appears to be the main and first parameter to be considered in preparing a dosage form.

In place of conventional dosage forms with immediate release, therapeutic systems with controlled release of the drug can achieve major advances in improving and rationalizing the administration of therapeutic agents. In these therapeutic systems the important specification is not the total dose given but the rate and duration of drug administration. The systems can thus enhance the therapeutic ratio and regimens of various existing agents, and they also permit treatment with active substances which are not of use in conventional dosage forms because of their toxicity or short half-lives (Heilman 1984). The importance of dosage form is often undervalued, and this has sometimes led to formulations with low therapeutic efficiency.

Oral dosage forms are most suitable for the patient, make out-patient treatment possible, and avoid the cost and inconvenience associated with intravenous administration. Oral dosage forms are usually tested by using the in-vitro dissolution test, which is the tool for characterizing the biopharmaceutical quality of the drug at various stages of the development and thus evaluating the possible risks (Siewert 1993), and also for determining the kinetics of drug release under given conditions of pH and stirring (Bidah & Vergnaud 1990). Various results have thus been obtained, and a few of them are summarized. Aspirin dissolution rates have been correlated with the rate of absorption of the drug (Levy 1961); the effect of the particle size has been explained (Aquiar et al 1968; Dominguez-Gil 1993) the importance of the rate of stirring of the dissolution liquid has been established (Hamlin et al 1962).

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Another main interest of the in-vitro dissolution test appears with the establishment of in-vitro/in-vivo correlations. The problem of correlating in-vitro/in-vivo data has been examined in different ways and has been the subject of much discussion (Hüttenrauch & Speiser 1985; Süverkrüp 1986; Skelly & Shiu 1993). Two workshops (Skelly et al 1987, 1990) devoted to these studies have concluded that the state of technology and science at that time did not always permit meaningful correlations. Three levels of correlations have been established, and level A offers the greatest scope; this consists of a 1 : 1 relationship established by comparing the in-vitro curve with the input function resulting from deconvolution of the concentration–time curve in the plasma compartment. Some requirements for establishing level A correlations are worth noting; drug absorption must be passive, windowless and follow a non-saturable process; the drug absorption must be limited by the release out of dosage form; this correlation is appropriate only after single administration.

Another way for evaluating the amount–time history of the drug in the plasma compartment has been shown by using a numerical model taking all the known facts into account (Nia et al 1995; Ouriemchi et al 1995). The whole process of drug administration is divided into three main steps: the kinetics of release of the drug from the dosage form along the gastrointestinal tract; the absorption into the blood compartment, and the elimination. In-vitro tests are of help for determining the kinetics of release of the drug from the dosage forms in liquids of various pH. For dosage forms where the drug is dispersed through a polymer matrix, the process of release is controlled either by diffusion (Bidah et al 1992) or by erosion (Heller 1984; Bidah & Vergnaud 1990).

The main objective in this paper is to determine the role played by various parameters in the process of drug transport through the body by using oral dosage forms with release controlled by diffusion. Some emphasis is placed

upon three parameters which appear of great interest for controlled-release dosage forms: the gastrointestinal residence time, the dose frequency, the size of the dosage forms. By extending the capability of the numerical model (Ouriemchi et al 1995) over multidosage with given frequencies, it is thus possible to obtain the kinetics of the drug in the blood compartment, as well as the kinetics of drug eliminated and the kinetics of drug released out of the dosage form. Two dose frequencies were selected for three sizes of the dosage form. A dimensionless number was used in various cases, by considering the amount of a drug at a given time and place as a fraction of the total amount of drug initially located in the dosage form. Aspirin was chosen for the drug because of its high rate of elimination which makes the prolonged release of interest.

Materials and Methods

Mathematical treatment

Assumptions. The process of drug transport was divided into three steps: transport through and out of the dosage form along the gastrointestinal tract; absorption in the blood compartment with first-order kinetics; elimination from the blood with first-order kinetics.

The dosage form was assumed to be spherical in shape, with the release controlled by radial diffusion with a diffusivity which does not depend on the drug concentration and the pH of the liquid. The coefficient of mass transfer on the surface of the dosage form is very high (Bidah & Vergnaud 1990).

In spite of the fact that the process of release is rather complex (Armand et al 1987; Vergnaud 1993), the process was simplified and only the diffusion of the drug was considered.

The effect of the volume of liquid in the gastrointestinal tract on the rate of the drug transfer in the blood was very low, as shown by calculation.

The partition factor of the drug between the dosage form and the gastrointestinal liquid was assumed to be unity. The effect of its value on the process is very low, in the same way as the volume of liquid in the gastrointestinal tract.

The gastrointestinal residence time of the dosage form was considered, and two extreme values were selected as 10 and 24 h (Abrahamsson et al 1993).

The distribution by radial diffusion in the dosage form, is given by:

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

where $C_{r,t}$ is the drug concentration at abscissa r and time t, and D is the diffusivity constant.

As the coefficient of mass transfer on the bead surface is very high, the drug concentration on this surface $C_{R,t}$ is constantly proportional to the drug concentration in the gastrointestinal liquid $C_{s,t}$:

$$C_{R,t} = KC_{s,t} = K . \frac{Y_t}{V_s} \quad (2)$$

where K is the partition factor, and Y_t is the amount of drug in the gastrointestinal liquid of volumes V_s.

The principle of the method consists of dividing the bead into N spherical membranes of constant thickness Δr, and the time into increments Δt. The centre of each membrane is associated with an integer n. The mass balance is evaluated within a spherical membrane during the increment of time Δt, leading to a relationship between the new concentration after elapse of time Δt and the previous concentrations at the same and adjacent places (Vergnaud 1993). The drug concentration can thus be evaluated at various places and any time.

The amount of drug remaining in the dosage form at time t, M_t, is obtained by integrating the drug concentration at this time with respect to space:

$$\frac{M'_t}{4\pi(\Delta r)^3} = \frac{C_{o,t}}{24} + \sum_{n=1}^{N-1}(n^2 + \tfrac{1}{12})C_{n,t} + \frac{(3C_N + C_{N-1})}{12}[N^3 - (N - 0.5)^3] \quad (3)$$

and the amount of drug released is obtained by subtracting M'_t from the initial amount in the dosage form.

The flow of drug leaving the dosage form is expressed by Fick's law:

$$F_{d.form} = -A.D.\frac{\partial C_{R,t}}{\partial r} \quad (4)$$

where A is the area of the dosage form of radius R, and $\partial C_{R,t}/\partial r$ is the gradient of concentration at time t on the surface.

The amount of drug in the gastrointestinal tract is given by:

$$\frac{dY}{dt} = -AD\frac{\partial C_{R,t}}{\partial r} - k_a Y_t \quad (5)$$

where k_a is the rate constant of absorption and Y_t is the amount of drug in the gastrointestinal tract.

The amount of drug in the blood compartment Z is given by:

$$\frac{dZ}{dt} = k_a Y_t - k_e Z_t \quad (6)$$

where k_e is the rate constant of elimination and Z_t is the amount of drug in the blood compartment at time t.

The rate of amount of drug eliminated at time t is given by:

$$\frac{dW}{dt} = k_e Z_t \quad (7)$$

where W_t is the amount of drug eliminated after time t.

The problem is resolved step by step by calculating after each increment of time the amount of drug extracted out of the dosage form, delivered to the gastrointestinal tract Y, in the blood compartment Z and eliminated W.

Experimental procedure

Preparation of dosage forms. Sodium salicylate as the model drug and Eudragit RL, in powder form, were intimately mixed. After pulverization in a small amount of methanol, the mixture was pressed into spherical beads and dried. Dosage forms of different sizes were prepared with 50 wt % drug.

Kinetics of release with in-vitro test. The kinetics of release of the drug was determined in-vitro. The process is controlled by diffusion with a constant diffusivity ($D = 2{\cdot}2 \times 10^{-7}\,cm^2\,s^{-1}$). A very high coefficient of mass transfer on the surface was obtained (Vergnaud 1993). The value of 1 is taken for the partition factor, i.e. that the concentration of the drug at equilibrium is the same in the liquid located in the dosage form and in the liquid surrounding this dosage form. In fact, the effect of the value of the partition factor on the kinetics is very low.

Characteristics of the drug transport in the compartments. The rate constants of absorption k_a and elimination k_e were taken as 2·77 and $0{\cdot}23\,h^{-1}$, respectively (Vidal Dictionary 1994).

Results and Discussion

Kinetics of drug distribution

The kinetics of the drug transferred in the various compartments were calculated for beads of radius 0·16, 0·231 and 0·32 cm for gastrointestinal residence times of 10 and 24 h (Figs 1–3).

The effect of the gastrointestinal residence time. With the small radius of 0·16 cm, a residence time of 24 h is long enough for the percent release of drug to reach near 100, while a residence time of 10 h allows a percent release of around 97. With the radius of 0·231 cm, the effect of the residence time on the process is more important, since 24 h enables only 98·2% drug release. The effect of the residence time is still more important with the larger dosage form of radius 0·32 cm, and only around 91% drug is released after a residence time of 24 h.

The effect of the radius of the dosage forms. In a process controlled by diffusion, a dimensionless number exists Dt/R^2 showing that the time necessary for a given amount

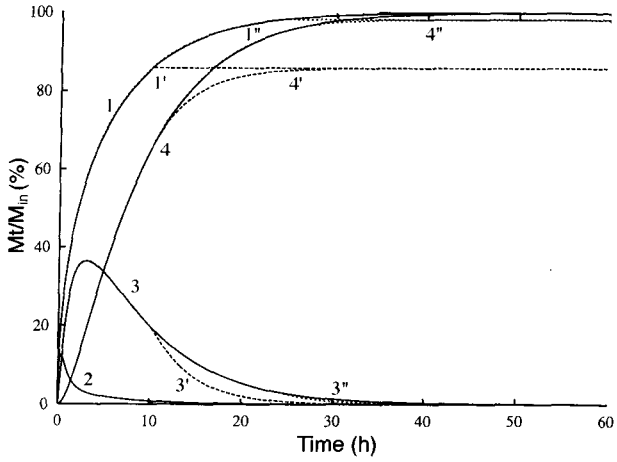

FIG. 2. Kinetics of drug transfer in various compartments with a bead of radius of 0·231 cm. Drug release (1, 1′, 1″); gastrointestinal tract (2, 2′, 2″); blood compartment (3, 3′, 3″); eliminated (4, 4′, 4″). 1, 2, 3, 4: Kinetics with an infinite gastrointestinal tract. 1′, 2′, 3′, 4′: Kinetics with a finite gastrointestinal tract. 1″, 2″, 3″, 4″: Kinetics with a finite gastrointestinal tract residence time of 24 h.

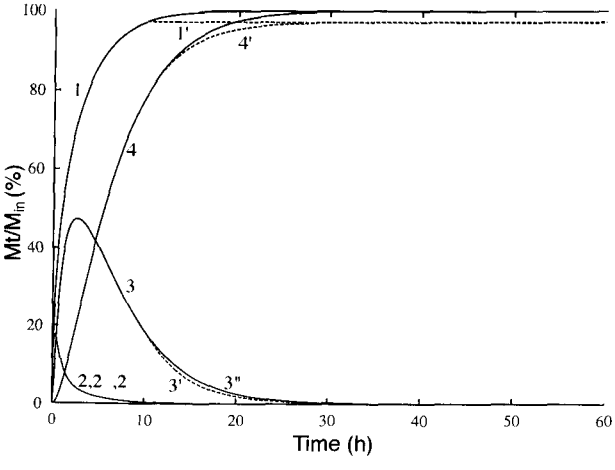

FIG. 1. Kinetics of drug transfer in various compartments with a bead of radius 0.16 cm. Drug release (1, 1′, 1″); gastrointestinal tract (2, 2′, 2″); blood compartment (3, 3′, 3″); eliminated (4, 4′, 4″) released. 1, 2, 3, 4: Kinetics with an infinite gastrointestinal tract residence time. 1′, 2′, 3′, 4′: Kinetics with a finite gastrointestinal tract residence time of 10 h. 1″, 2″, 3″, 4″: Kinetics with a finite gastrointestinal tract residence time of 24 h.

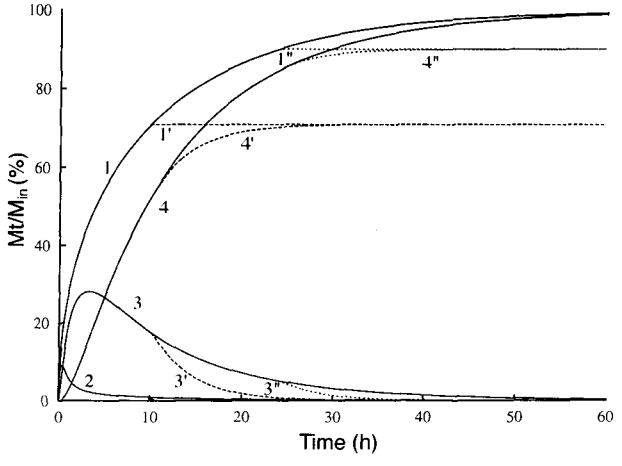

FIG. 3. Kinetics of drug transfer in various compartments with a bead of radius of 0.32 cm. Drug release (1, 1′, 1″); gastrointestinal tract (2, 2′, 2″); blood compartment (3, 3′, 3″); eliminated (4, 4′, 4″). 1, 2, 3, 4: Kinetics with an infinite gastrointestinal tract residence time. 1′, 2′, 3′, 4′: Kinetics with a finite gastrointestinal tract residence time of 10 h. 1″, 2″, 3″, 4″: Kinetics with a finite gastrointestinal tract residence time of 24 h.

to be released is proportional to the square of the radius of the dosage form (Vergnaud 1993).

The amount of drug in the gastrointestinal tract. The amount increases rapidly, passes through a maximum and decreases more slowly. The smaller the bead, the shorter the period of time over which the drug is located in the gastrointestine. In the same way, the larger the bead, the lower the maximum of the amount of drug. The effect of the residence time appears especially for the two largest beads with a time of 10 h, provoking an abrupt decrease in the amount of drug at this time.

Drug appearing in the blood. The kinetics follow the typical pattern with a rather flat maximum. The gastrointestinal residence time plays an important role on this kinetics. For instance, in Fig. 1 with the smaller bead, a decrease in the amount of drug is observed after 10 h with a residence time of 10 h. This effect of the residence time is enhanced (Figs 2, 3) when using larger beads. For instance for the bead of radius 0·32 cm (Fig. 3), a drastic decrease in the amount of drug is observed with the tract time of 10 h, and is sustained with the residence time of 24 h.

Elimination. The kinetics of drug eliminated are also affected by the residence time. The effect is enhanced by using larger beads.

Multiple dosing

The amount of drug delivered to the blood compartment as a fraction of the amount of drug initially located in the dosage form was calculated as a function of time following various dose frequencies: 3 times a day (Fig. 4) twice a day (Fig. 5) and once a day (Fig. 6). The dosage form of radius 0·16 cm was considered. Fig. 7 illustrates the plasma drug level–time courses for an immediate dosage form delivered to the patient with those dose frequencies.

The effect of the dose frequency clearly appears in Figs 4–6. At all frequencies, the amount of drug alternates between maximum and minimum values. These values are of great importance, as the drug level should be placed around the optimal drug level without causing overdosing and underdosing.

With the controlled-release dosage form, the range through which the drug amount varies is narrow with the 3 times a day dosing, but it becomes larger when the dose frequency is lower.

The effect of the gastrointestinal residence time is low in the case of the small dosage form of radius 0·16 cm. However it is clear that the shorter the residence time, the larger the range through which the amount of drug varies.

With the immediate-release dosage form, the plasma drug level–time curves are quite different from the corresponding curves obtained with the controlled-release dosage form. Because of the immediate release, the effect of the residence time is negligible.

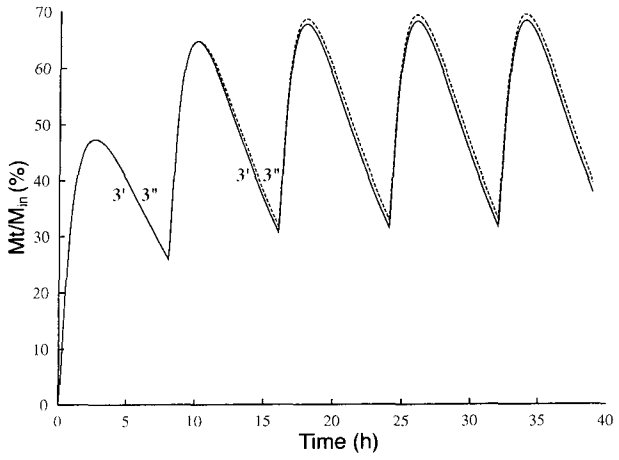

FIG. 4. Controlled-release dosage form. Drug level–time curves in the blood compartment with 3 times a day dosing. Effect of the gastrointestinal tract residence time: (3′) 10 h–(3″) 24 h.

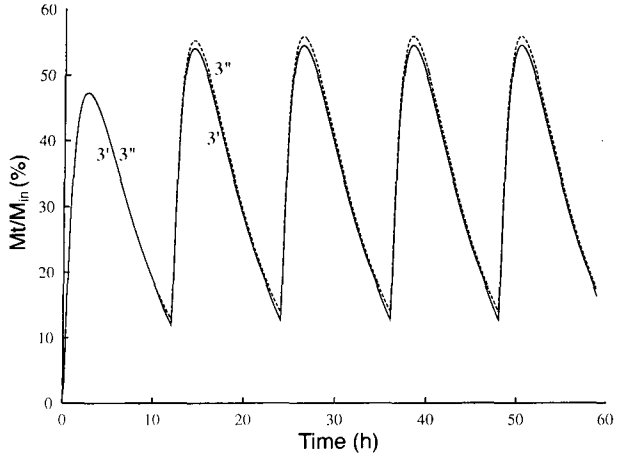

FIG. 5. Controlled-release dosage form. Drug level–time history in the blood compartment with twice a day dosing. Effect of the gastrointestinal tract residence time: (3′) 10 h–(3″) 24 h.

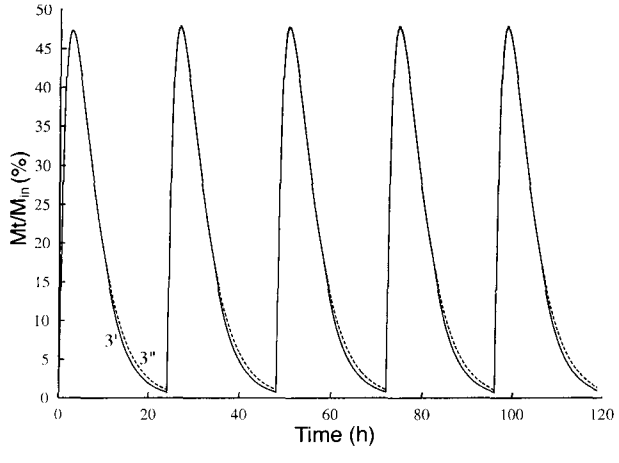

FIG. 6. Controlled-release dosage form. Drug level–time history in the blood compartment with once a day dosing. Effect of the gastrointestinal tract residence time: (3′) 10 h–(3″) 24 h.

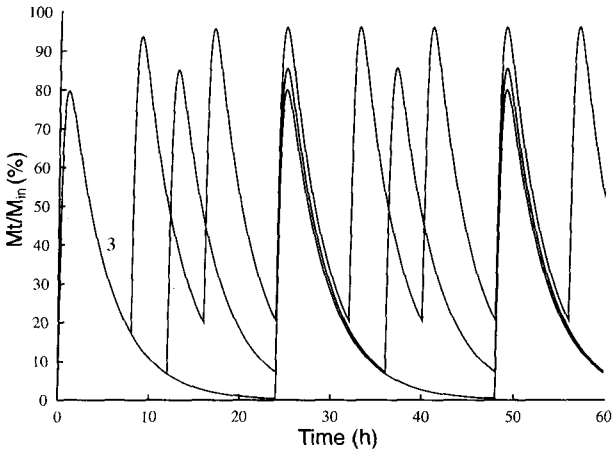

FIG. 7. Immediate-release dosage form. Drug level–time histories in the blood compartment with the three frequencies: three times, twice, once a day, for various gastrointestinal tract residence times (10, 24 h).

With the immediate-release dosage form, the plasma drug level alternates from high values to low values. For each dose frequency, the maximum of the drug level is considerably higher for the immediate-release dosage form than for the controlled-release dosage form, and the minimum is considerably lower. For instance, comparison between the two drug levels drawn in Figs 4 and 7 for the 3 times a day dosing shows that the drug level ranges from 30 to 68 for the controlled-release dosage form and from 20 to 96 for the immediate-release dosage forms.

The process of the drug transfer through the various compartments of the patient's body can be described by a numerical model in the case of oral controlled-release dosage forms. The simple case when the drug is absorbed in the blood compartment through a simple first-order kinetics and with the same rate constant along the gastrointestinal tract is considered in this paper.

However, the process already is rather complex. Three parameters intervene in an important way: the gastrointestinal residence time, the size of the dosage form, and the dose frequency. The time necessary for the dosage form to pass through the gastrointestinal tract is the first and the main parameter to be considered. From the knowledge of this time, the dosage form can be built and the size of the dosage form can be determined. It is clear that the dose frequency is responsible for a drug level in the blood compartment alternating between a high and low value, and the lower the dose frequency, the wider the range through which the drug level varies. For instance for a once a day dose and the dosage form considered in the paper, an underdosing is observed for a period of time around 24 h.

Moreover the gastrointestinal tract time has an effect on the evaluation of the size of the dosage form. The dimensionless number Dt/R^2 for a spherical dosage form is thus useful for evaluating the radius of the dosage form. Upon putting the residence time as the time in this ratio, the radius can be determined for a given diffusivity. It must be kept in mind that this radius is the selected value for which a given amount, Mt/M_{in}, of the drug initially in the dosage form, is delivered along the gastrointestinal tract.

A larger dosage form is able to release the drug over a wider period of time, provoking a narrower range of the drug level in the blood compartment, but it is also associated with a larger amount of drug remaining in the dosage form at the end of the gastrointestinal tract.

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