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Calculation of the plasma drug level with oral controlled release dosage forms. Effect of the dose frequency

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Abstract

Calculation has been made for determining the drug level-time history in the plasma compartment in the case of oral dosage forms with release controlled by diffusion. Some emphasis has been placed upon the frequency of multiple administration. A dimensionless number with the amount of drug as a fraction of the amount of drug initially in the dosage form was used. The case of aspirin was considered as the rate constant of elimination is rather high, leading to great interest for drug delivery with controlled release systems.

Keywords: Controlled release; Calculation; Plasma drug level; Multiple dose; Dose frequency; In vitro/in vivo

1. Introduction

There are two ways to improve the care of the sick: the development of new and better drugs, and the more effective and safer use of known drugs. It is well known that oral controlled-release dosage forms offer interesting advantages over oral conventional forms with immediate release: a more constant drug concentration in the blood compartment, which is associated with less adverse side-effects, a more constant and prolonged therapeutic effect and a better compliancy (Heilmann, 1983). Controlled release dosage forms are especially justified for drugs whose therapeutic index is very low, the median effective dose being close to the median lethal dose. Moreover, the main advantage is the possibility of once-daily dosing. This simplification in the therapy improves compliance and leads to a decrease in overall costs. These therapeutic systems have thus essentially been implemented in the treatment of hypertension, inflammatory processes, obstructive pulmonary diseases and Parkinson's diseases (Dominguez-Gil, 1993).

Oral dosage forms are tested by using the in vitro dissolution test. In vitro dissolution testing serves as an important tool for characterizing the biopharmaceutical quality of a product at different stages of drug development. It can be helpful in the evaluation and interpretation of possible risks (Siewert, 1993). These tests can also be used for determining the kinetics of release of the drug under given conditions of stirring, or pH (Vergnaud, 1993). Dissolution was originally conceived in 1925, but it took a few decades to show

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that the plasma peak and duration values were related to the dissolution rate of the drug with theophylline (Nelson, 1957); later on, aspirin dissolution rates were correlated with absorption rate (Levy, 1961); the importance of the rate of stirring of the dissolution liquid was established (Hamlin et al., 1962); the effect of particle size was explained, and a rank order in vitro/in vivo correlation was obtained (Aquiar et al., 1968).

The problem of correlating in vitro/in vivo results was especially studied through two workshops (Skelly et al., 1987, 1990). Both workshops concluded that the state of the science and technology at that time did not always permit meaningful correlations (Skelly and Shiu, 1993). Three levels of correlations were established: level A, when a unit to unit relationship can be established by comparing the in vitro curve to the input function resulting from deconvolution of the concentration-time curve in the plasma compartment; level B, when in vitro dissolution time is compared with the mean in vivo residence time; level C, when only a single pharmacokinetic parameter is compared with the mean in vitro dissolution time. Of course, the level A is preferred, as it is reflective of the entire curve. Requirements for establishing level A correlations have been defined and some of them must be considered: the correlation is appropriate only after single administration; the drug absorption must be a passive, windowless and non-saturable process, the intra- and inter-subject variability of kinetics must be ascertained beforehand.

Another way was followed for determining the concentration-time history of the drug in the plasma compartment by using a numerical model taking all the known facts into account (Ouriemchi et al., 1995). A three-step process was considered and studied: the kinetics of release of the drug out of the dosage form along the gastrointestinal tract; the stage of absorption in the blood compartment and the stage of elimination (Fig. 1). The kinetics of release of the drug have to be determined through in vitro tests, the release being controlled either by diffusion (Bidah et al., 1992) or erosion (Heller, 1984; Bidah and Vergnaud, 1990) or even simultaneously by the two ways (Feijen, 1984).

The main purpose of this study was to show that the drug level-time history in the plasma compartment can be calculated not only after a single but also after multiple administration. The case of aspirin was considered as its rate constant of elimination is rather high, and the process of drug transfer is essentially controlled by the rate of release out of the dosage form. The oral dosage form is spherical in shape, and the release of the drug is controlled by diffusion. The stages of absorption and elimination are described by two first-order reactions with a rate constant of absorption and elimination.

The other objective was to determine the effect of the dose frequency on the drug level-time history in the plasma compartment. The amount of drug in the plasma compartments at various times was expressed as a fraction of the amount of drug initially located in the dosage form, in order to find more general results which do not depend on the amount of drug in each dosage form. Comparison was also made with an immediate release dosage form. Moreover, the drug-time history was determined along the gastrointestinal tract, and during the stage of elimination. Finally, the time in the gastrointestinal tract was also taken into account.

2. Mathematical treatment of the problem

2.1. Assumptions

The following assumptions were made in order to describe the process.

(i) The process of drug transport is divided into three main stages: transport of drug through and out of the dosage form during the time in the

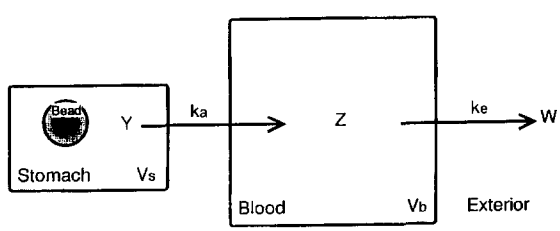

Fig. 1. Scheme of the compartments.

gastrointestinal tract; transport from the gastrointestine to the blood compartment with first-order kinetics; elimination from the blood with first-order kinetics.

(ii) The dosage form is spherical in shape, and the release is controlled by radial diffusion with a constant diffusivity independent of the pH.

(iii) The actual process is rather complex (Armand et al., 1987) with the diffusion of the liquid through the polymer enabling the dissolution of the drug and the diffusion of the drug through the liquid located in the dosage form. The process is simplified in the sense that only the diffusion of the drug is considered.

(iv) The effect of the volume of liquid in the gastrointestine on the rate of the drug transfer in the blood is very low, as proved by calculation.

(v) The partition factor for the drug between the dosage form and the gastrointestinal liquid is taken as 1. The effect of its value on the process is very low, as also proved by calculation.

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

(vii) The residence time of the dosage form along the gastrointestinal tract is considered.

2.2. Numerical treatment

As no mathematical treatment seems to be feasible for the problem, a numerical treatment was made.

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

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

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

The coefficient of mass transfer on the surface of the bead is so high that the concentration of drug on the surface $C_{r,t}$ is constantly proportional to the concentration of drug in the gastrointestinal liquid $C_{s,t}$:

$$C_{r,t} = K.C_{s,t} = K.\frac{Y_t}{V_s} \tag{2}$$

where K is the partition factor of the drug between the dosage form and the gastrointestinal liquid, Y_t is the amount of drug in the gastrointestinal liquid of volume V_s.

As shown in earlier studies (Vergnaud, 1993), the radius R of the bead is divided into N constant increments of space Δr and time in increments of time Δt, and each position is associated with an integer. From the mass balance evaluated within a spherical membrane of thickness Δr over the period of time Δt, the new concentration after this elapse of time can be expressed in terms of the previous concentrations through either an explicit method (Vergnaud, 1993) or the Crank-Nicolson method (Ouriemchi et al., 1995). This concentration can thus be evaluated at various places, e.g. the centre, within the bead, next to the surface of the bead, at any time.

The amount of drug remaining in the dosage form at time t, M'_t, is obtained by integrating the concentration of the drug at this time with respect to space:

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

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

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

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 next to the surface.

The amount of drug located in the gastrointestinal liquid at time t is thus given by:

$$\frac{dY}{dt} = -A.D.\frac{\partial C_{R,t}}{\partial r} - k_{a.}Y_t \tag{5}$$

with the constant of absorption k_a.

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

$$\frac{dZ}{dt} = k_{a.}Y_t - k_{e.}Z_t \tag{6}$$

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

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

The problem is resolved step by step in evaluating the amounts of drug extracted out of the dosage form, delivered in the gastrointestinal compartment Y, in the blood compartment Z and eliminated W, during each interval of time Δt (Ouriemchi et al., 1995).

3. Experimental

3.1. Dosage forms

The dosage forms were prepared by dispersing the drug in a polymer matrix. Sodium salicylate was the drug and Eudragit RL was the polymers, both in powder form. After pulverization of a small amount of ethanol, the mixture was pressed into spherical beads and dried. The radius was 0.16 cm, with 50% of drug in weight.

3.2. Conditions of release with in vitro tests

Experiments were performed with in vitro tests, by determining the kinetics of release of the drug. The process of release was found to be controlled by diffusion with the following characteristics: a constant diffusivity of 2.2×10^{-7} cm^2/s, and a very high coefficient of mass transfer on the surface. However it was difficult to measure precisely the partition factor, the value of 1 was selected.

3.3. Characteristics of the drug transfer in the compartments

The rate constants of absorption and elimination were (Vidal, 1994): $k_a = 2.772$/h and $k_e = 0.231$/h.

4. Results

Various parameters are of great interest in the case of oral dosage forms with controlled drug release, and they can be divided into three categories. The first group is associated with the patient, and the main parameter is the gastrointestinal-time history. The second group is concerned with the nature of the drug, and the rate constants of absorption and elimination as well as the plasmatic volume are its main characteristics. The third class of parameters characterizes the dosage form, with its size and the nature of the polymer playing the role of the matrix. These parameters are so important that they must be kept in mind when preparing the dosage form able to release the drug. Another parameter is of high importance for the care of the patient: the frequency at which the dosage form must be taken.

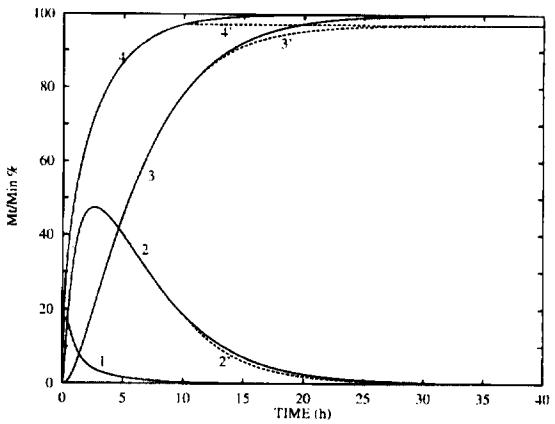

Fig. 2. Effect of the gastrointestinal tract time on the process of drug transfer, for the dosage form considered.

4.1. Effect of the gastrointestinal history

Along the gastrointestinal-time history for the dosage form, the dosage form is in contact with liquids of various pH ranging from 1.2 to 8. This pH-time history is of great interest when either the polymer or the drug is sensitive to the pH, leading to a change in the rate of drug release. Nevertheless, the main parameter is the time in the gastrointestinal tract.

The effect of the time in the gastrointestinal tract on the release of the drug out of the dosage form can be observed in Fig. 2 whose curves were obtained by calculation using the numerical model. The amount of drug transferred after time t, M_t, as a fraction of the amount of drug initially in the dosage form M_{in}, was expressed in terms of

time at various places: in the gastrointestine **(1)**; in the blood compartment **(2)**; eliminated **(3)**; and released out of the dosage form **(4)**. These curves were calculated for the dosage form, spherical in shape with a radius of 0.16 cm, and for two times in the gastrointestinal tract: infinite time, and 10 h (**2′**, **3′**, **4′**).

The following conclusions, about the effect of the time in the gastrointestinal tract are worth noting:

(i) The amount of drug located in the gastrointestine is rather low as shown in Fig. 2, curve **1′**, and it is difficult to appreciate the amount of drug which cannot be transferred in the gastrointestine after 10 h.

(ii) Better information is obtained with the curves **4** and **4′** expressing the kinetics of drug released out of the dosage form. As the process of release is controlled by diffusion with a very high coefficient of mass transfer on the surface of the dosage form, a vertical tangent is obtained at the origin of time. The rate of release decreases with time in an exponential way. The point of importance results from the time at which the process of release is stopped: in curve **4**, without speaking of an infinite time, a time of 20 h is necessary for nearly 100% of the drug in the dosage form to be released; in curve **4′**, it is clearly seen that around 2.8% of the drug remains in the dosage forms when these dosage forms leave the patient's body.

(iii) A slight modification in the plasma drug-time history is obtained when the dosage form leaves the patient's body, as shown with curves **2** and **2′**. Of course, after 10 h, a change in curves **2** and **2′** can be observed with a lower drug level resulting from the finite time in the gastrointestinal tract.

(iv) The two kinetics of elimination of the drug significantly differ from each other when the dosage form leaves the patient's body.

(v) As a result, the gastrointestinal tract time plays an important role in the preparation of a dosage form with controlled release.

(vi) The time in the gastrointestinal tract acts upon the drug amount time history in the blood compartment whatever the dose frequency. This effect cannot be seen for the dosage forms taken three times a day, but it is clearly apparent for the twice a day and once a day dosage forms. In these two cases, a decrease in the amount of drug in the blood compartment can be observed at the end of the gastrointestinal tract. This fact becomes especially sensitive for the once a day dosage form. It is thus responsible for a significant decrease in the amount of drug in the blood compartment.

4.2. Effect of the dose frequency on the drug level in the blood compartment

The amount of drug in the blood compartment as a fraction of the amount of drug initially in the dosage form was expressed as a function of time, for various values of the dose frequency: three times a day (Fig. 3), twice a day (Fig. 4) and once a day (Fig. 5), as was obtained from calculation. The amount of drug was also calculated for an immediate release dosage form, for the same values of the dose frequency.

These curves can lead to the following conclusions:

(i) It is possible to obtain the drug level in the blood compartment with a multidose treatment, for various dose frequencies.

(ii) In the case of the immediate release dosage from, undulating amount patterns of the drug are obtained in the blood, where high concentrations alternate with low concentrations producing a successive overdosing and underdosing of the

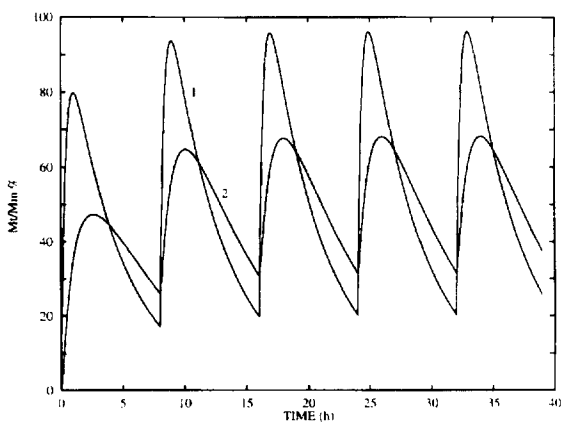

Fig. 3. Amount of drug in the blood compartment with the immediate release form **(1)** and the controlled drug release **(2)**. Dose frequency: three times a day.

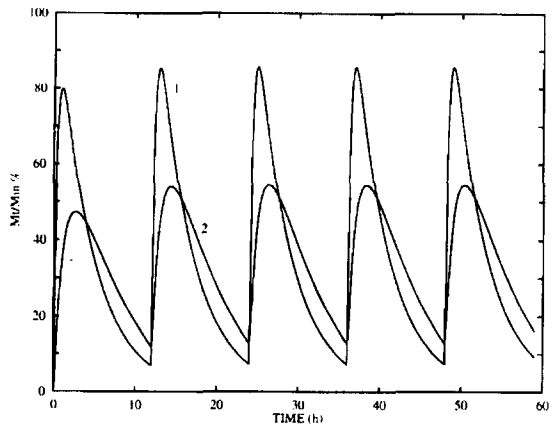

Fig. 4. Amount of drug in the blood compartment with the immediate release form (1) and the controlled drug release (2). Dose frequency: twice a day.

drug. The following statement holds: the lower the dose frequency, the greater the underdose.

(iii) A similar pattern is observed in the case of the controlled release dosage form. However, the maximum and minimum values of the amount of drug (or concentration) in the blood compartment are not so different as in the case of the immediate release dosage form. The ratio of the maximum and minimum value of the amount of drug can characterize this phenomenon, when it becomes constant after the third dose ().

(iv) The dose frequency notably affects the ratio of the maximum and minimum values of the

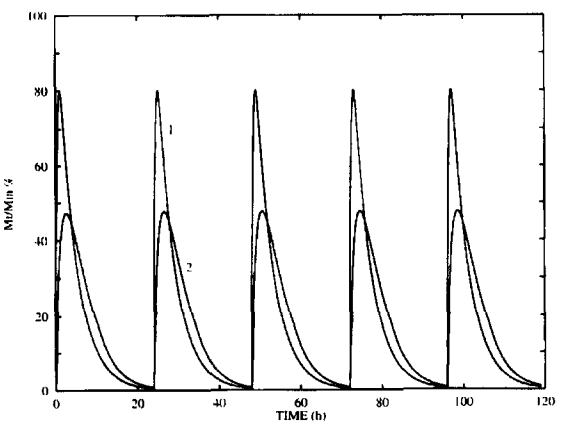

Fig. 5. Amount of drug in the blood compartment with the immediate release form (1) and the controlled drug release (2). Dose frequency: once a day.

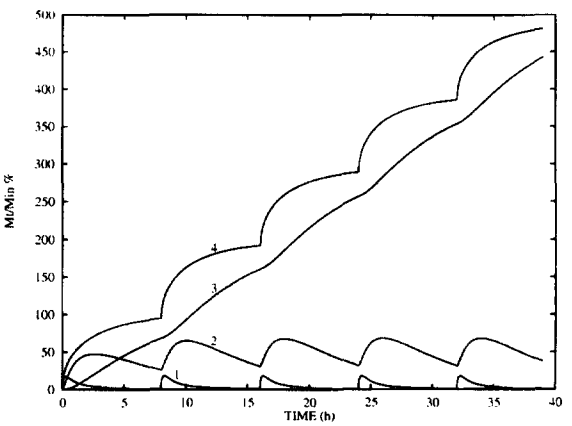

Fig. 6. Kinetics of the drug transferred through various compartments with the dosage frequency: three times a day — gastrointestine (1) — blood (2) — eliminated (3) — released out of the dosage form (4).

amount of drug, with the statement: the lower the dose frequency, the greater this ratio. Moreover the amount (and concentration) of drug in the blood is nearly zero over a period of time of 3–5 h for the once a day dose.

4.3. *Effect of the dose frequency on the whole process of drug transfer*

It may be of interest to acquire good knowledge of the whole process of drug transport through the patient's body. The amount of drug as a fraction of the amount initially in the dosage form can be calculated with the model in the various compartments: the gastrointestine (1), the blood compartment (2), eliminated (3), released out of the dosage form (4). The amount of drug was thus expressed as a function of time, for the various dose frequencies: three times a day (Fig. 6), twice a day (Fig. 7) and once a day (Fig. 8). A few conclusions of interest were drawn from these curves:

(i) The amount of drug remains rather low in the gastrointestine. Resulting from the delivery out of the dosage form and the absorption in the blood compartment, the amount of drug located in the gastrointestine passes through a maximum. This maximum is attained only a few minutes after the dose has been taken, as the coefficient of

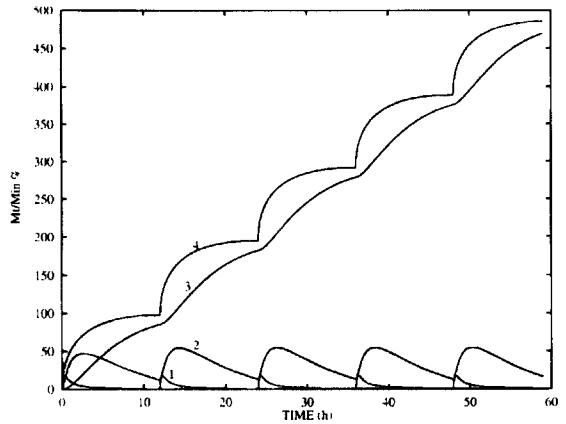

Fig. 7. Kinetics of the drug transferred through various compartments with the dosage frequency: twice a day — gastrointestine **(1)** — blood **(2)** — eliminated **(3)** — released out of the dosage form **(4)**.

mass transfer on the surface of the dosage form, h, is very high. Of course two main reasons exist for this low amount of drug in the gastrointestine: the rather low diffusivity of the drug through the dosage form, and the rather high rate constant of absorption. It must also be noticed that this amount of drug depends only a little on the volume of liquid surrounding the dosage form.

(ii) The amount of drug appearing in the blood compartment varies with time representing an undulating pattern, as already shown in Figs. 3–5.

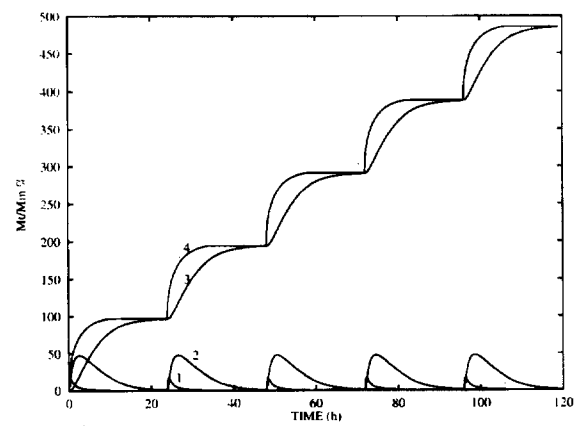

Fig. 8. Kinetics of the drug transferred through various compartments with the dosage frequency: once a day — gastrointestine **(1)** — blood **(2)** — eliminated **(3)** — released out of the dosage form **(4)**.

(iii) The kinetics of the drug eliminated (curves **3** in Figs. 6–8) are nearly flat for all dose frequencies, except in the case of the once a day dosing.

(iv) The kinetics of the drug released out of the dosage form (curves **4** in Figs. 6–8) for the various dose frequencies are informative. The effect of the dose frequency on the kinetics of drug released along the gastrointestinal tract appears very clearly. In the case of a dosage form made of beads with a radius of 0.16 cm, almost all the drug in the dosage form is delivered along the gastrointestinal tract. This is far from being the same for a bead of larger diameter. This last conclusion results from consideration of the dimensionless number $D.t/R^2$ intervening in the radial diffusional process: the greater the radius, the longer the time necessary for a given amount of drug to be released.

5. Conclusions

In the case of dosage forms with controlled release, the process of the drug transport through the various compartments of the patient's body is very complex, with the following steps: release of the drug out of the dosage form along the gastrointestinal tract, absorption in the blood compartment and elimination, without mentioning other additional facts which were not considered in this paper. However, numerical models were able to describe the process as far as it is known. Moreover, these models can be of help for determining precisely the effect of each parameter on the whole process and especially on the drug level-time history in the blood compartment.

In this paper, the effect of the dose frequency of a controlled release dosage form on the drug level in the blood was especially studied. The problem is very complex and it is difficult to draw clear conclusions. In fact, various important parameters intervene such as the time in the gastrointestinal tract, the diffusivity of the drug and the dimension of the dosage form. The first main parameter appears to be the time over which the dosage form passes through the gastrointestine. This time intervenes firstly in the dimensionless number $D.t/R^2$ characterizing the rate of release

of the drug out of the dosage form. The value of the radius of the bead has to be calculated for a given diffusivity of the polymer so that the amount of drug released after this time is as close as possible to the initial amount in the dosage form. As a result, the dose frequency of the dosage form depends essentially on the gastrointestinal time with the following statement: the longer the gastrointestine tract time, the lower the dose frequency.

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