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Calculation of the antibiotic level in the plasma with an oral erosion-controlled dosage form

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Abstract

The drug level-time history in the plasma compartment was determined either from experiments or calculation for oral dosage forms with immediate release and ciprofloxacine as the drug. Calculation was also made for determining these profiles with oral dosage forms whose release is controlled by erosion. Comparison was made for the plasma drug level obtained with these two oral dosage forms for single dose, and multiple dose taken once, twice and three times a day.

1. Introduction

With a conventional oral dosage form made of a drug dispersed in a soluble excipient, the drug is very rapidly liberated in the gastrointestine and quickly builds up to a high concentration in the blood, which then falls exponentially with time, until the next dose. There is an undulating concentration pattern of the drug in the blood, as well as in the tissues, depending on the values of the rate constants of absorption and elimination. Thus, high concentrations alternate with low concentrations, and the optimal therapeutic level is only briefly present (Heilman, 1984).

In order to eliminate this drawback, oral dosage forms with controlled release have been considered. Most of them are prepared by dispersing the drug through a polymer playing the role of a matrix in a monolithic device. The process of drug release is thus controlled by a rather complex process: diffusion of the liquid into the polymer, dissolution of the drug and diffusion of the drug out of the form through the liquid located into the polymer (Vergnaud, 1993). The polymer generally swells, and the polymer matrix may be eroded or not; and the release of the drug is thus controlled either by diffusion or by erosion (Heller, 1984), but in fact the mechanism of erosion follows the process of diffusion (Feijen, 1984; Sebert et al., 1994).

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These dosage forms with controlled release are studied and tested by using in vitro tests with synthetic gastric liquid at 37°C. They are also evaluated using in vivo tests with healthy volunteers achieved under standard conditions (Skelly et al., 1990). As in vivo tests are more complex and consume longer time than in vitro tests, various attempts have been made in order to establish correlations between the kinetics of release obtained with in vitro tests and the drug level obtained with in vivo experiments (Skelly et al., 1987; Skelly et al., 1990). Two workshops managed by the Food and Drug Administration concluded that meaningful correlations were not obtained at that time (Skelly and Shiu, 1993).

Another way was paved for predicting the drug level-time history in the plasma compartment by calculation with a numerical model, taking all the known facts into account (Nia et al., 1995). In this numerical model, the following three stages were considered: the kinetics of release of the drug out of the dosage form along the gastrointestinal tract controlled by diffusion; the stage of absorption in the plasma compartment and the stage of elimination, these last two stages being described by first-order kinetics. Another example was given for the use of this model by considering oral dosage forms whose release was controlled by diffusion with a constant diffusivity, and the effect of the dose frequency on the drug level in the plasma volume was especially studied with multidose (Ouriemchi and Vergnaud, 1996). In this method, the kinetics of release of the drug was previously determined through in vitro tests.

The first purpose in this study was to develop a numerical model by considering a dosage form whose drug release is controlled by erosion. With erosion, the drugs are released with kinetics which are quite different from those obtained by diffusion, (Bidah et al., 1992; Bidah and Vergnaud, 1990). This model has been tested in the case of an immediate release oral dosage form for which in vivo data were available (Breilh, unpublished results).

The other objective was to determine the drug level-time histories in the blood volume either for the immediate release dosage form or for an erosion-controlled release dosage form. Comparison between these curves with their peaks and troughs was made for various dose frequencies, namely, once a day, twice and three times a day. The antibiotic ciprofloxacine (Goldman et al., 1990; Terp and Rybak, 1987) was thus selected for this purpose, as well as its metabolite desethylciprofloxacine. Both these drugs have the same pharmacokinetics parameters (Breilh, unpublished results).

2. Theoretical

The process of drug transport was divided into three successive stages: the release of the drug out of the dosage form controlled by erosion, the absorption in the plasma compartment and the elimination.

2.1. Assumptions

The following assumptions are made:

(1) Two oral dosage forms are considered: the one with immediate release of the drug; the other with a release controlled by erosion of the polymer matrix.
(2) The rate constants of absorption and elimination are determined from in vivo data (Breilh et al., unpublished results).
(3) The mean apparent volume of distribution was obtained from in vivo data (Breilh et al., unpublished results). It was kept constant for the multidose treatment, as shown in earlier studies (Le Bel et al., 1986)

2.2. Release of the drug out of the dosage form

The rate of release of the drug out of a dosage form controlled by erosion is constantly proportional to the actual area of the surface of the dosage form.

$$\frac{\mathrm{d(volume)}}{\mathrm{d}t} = k(\mathrm{area}) \tag{1}$$

In the case of a dosage form, spherical in shape, the Eq. (1) reduced to (Vergnaud, 1993; Bidah and Vergnaud, 1990):

$$\left(1-\frac{M_t}{M_{in}}\right)^{1/3}=1-K_{er}\cdot t \qquad (2)$$

where M_{in} is the amount of drug initially in the dosage form, and M_t is the amount of drug released after time t. k_{er} is the rate constant of erosion, which takes into account the rate of erosion of the bead and its radius.

The amount of drug located in the gastro-intestinal compartment at time t, Y_t, is thus given by:

$$\frac{dY}{dt}=R_{er_t}-k_a\cdot Y_t \qquad (3)$$

where R_{er_t} represents the rate at which the drug is released out of the dosage form at time t.

2.3. Absorption of the drug in the plasma compartment

The amount of drug located in the plasma compartment at time t, Z_t, is:

$$\frac{dZ}{dt}=k_a\cdot Y_t-k_e\cdot Z_t \qquad (4)$$

where k_a and k_e represents the rate constants of absorption and elimination.

2.4. Elimination of the drug

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

$$\frac{dW}{dt}=k_e\cdot Z_t \qquad (5)$$

The problem was resolved step by step in evaluating the amounts of drug released by the dosage form, delivered in the gastrointestinal compartment Y, in the plasma compartment Z and eliminated, during each interval of time Δt.

3. Experimental

The drug, the dosage form, the in vitro and in vivo tests are described in succession.

3.1. Drug

The drug was ciprofloxacine which gives a metabolite, the desethylciprofloxacine. Its pharmacokinetic parameters are (Breilh et al., unpublished results)

$k_a = 1.29/h \qquad k_e = 0.12/h \qquad V_p = 210\,l$

where k_a and k_e are the rate constants of absorption and elimination, and Vp is the apparent plasma volume.

3.2. Oral dosage forms

The dosage form with immediate release was Ciflox 500 mg (Bayer) with 500 mg of ciprofloxacine.

The dosage form with controlled release was prepared by mixing and pressing the mixture of ciprofloxacine (500 mg) and the polymer hydroxypropylmethylcellulose.

3.3. In vitro tests

The dosage form with controlled release swells in gastric liquid, and the kinetics of release of the drug can be adequately described by the Eqs. (1) and (2) which are associated with the process of erosion. The kinetics of erosion with a rate constant of erosion of 0.081/h was thus found and used for calculation.

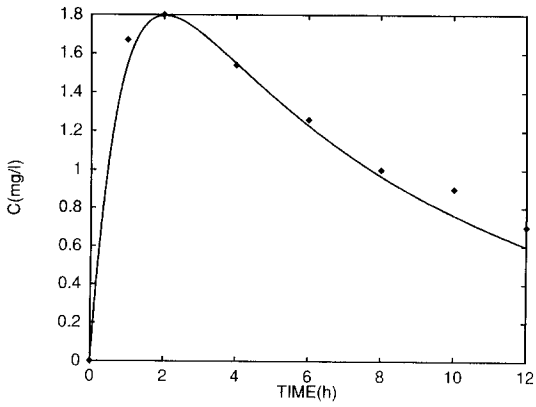

Fig. 1. Drug level-time history of ciprofloxacine in the plasma volume, obtained by calculation (——) and experiment (◆).

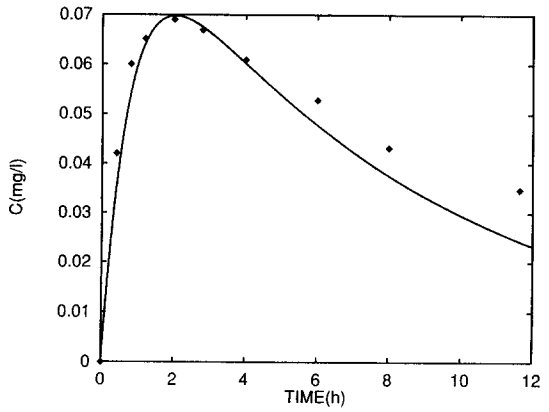

Fig. 2. Drug level-time history of desethylciprofloxacine in the plasma volume, obtained by calculation (——) and experiment (◆).

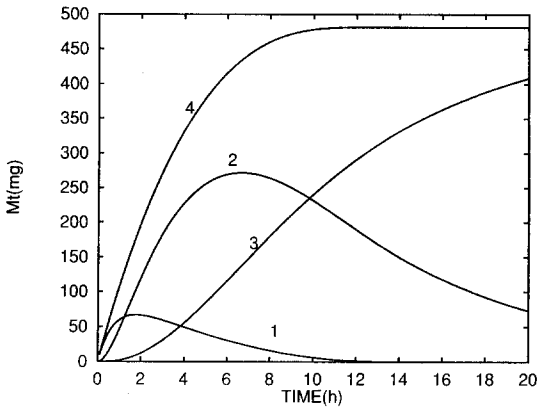

Fig. 3. Amount of drug in various compartments at various times, for ciprofloxacine: (1) gastrointestine; (2) plasma; (3) eliminated; (4) released.

3.4. *In vivo tests*

Ciprofloxacine and its metabolite were analysed by HPLC with a UV detector.

The method and procedure were fully described elsewhere (Breilh et al., unpublished results).

4. Results

The following results were obtained and considered:

(1) The drug level in the blood compartment obtained with an immediate release dosage form.
(2) The drug level in the blood compartment evaluated with a dosage form whose drug release was controlled by erosion, either for a single dose or for multiple dose with different regimens.
(3) Comparison was made between the drug level-time histories in the blood compartment obtained either with immediate release or controlled release dosage forms.

4.1. *Single dose with the immediate release dosage form*

The drug level (mg/l)-time histories in the blood compartment obtained by calculation with the help of the numerical model and by experiments are drawn in Fig. 1 for ciprofloxacine. The amount of ciprofloxacine found by experiments in the blood compartment was of 481.3 mg for an amount of 500 mg initially located in the dosage form. The amount of desethylciprofloxacine as a metabolite was of 18.7 mg in the blood compartment (Breith, unpublished results).

The drug level-time histories in the blood compartment were also drawn for the desethylciprofloxacine in Fig. 2.

The curves shown in Figs. 1 and 2 lead to the following comments:

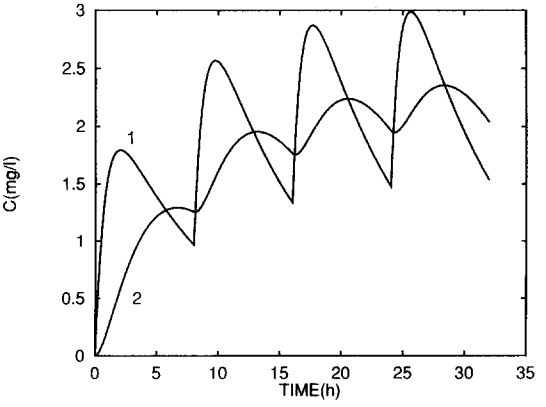

Fig. 4. Drug level-time histories in the plasma compartment for ciprofloxacine, obtained with dosage forms: (1) with immediate release; (2) with controlled release by erosion. Dosage forms taken 3 times a day.

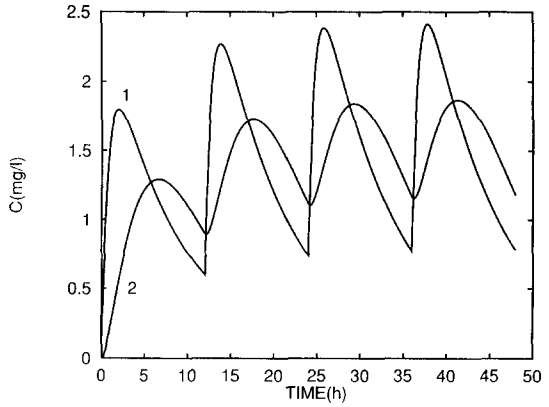

Fig. 5. Drug level-time histories in the plasma compartment for ciprofloxacine, obtained with dosage forms: (1) with immediate release; (2) with controlled release by erosion. Dosage forms taken 2 times a day.

(1) Good correlation could be appreciated between the drug level-time histories obtained either by calculation or experiments, for the immediate release dosage form.
(2) This correlation between experiments and calculation was acceptable for ciprofloxacine as well as for the metabolite desethylciprofloxacine.
(3) The rate constants of absorption and elimination are the same for ciprofloxacine and its metabolite.
(4) A peak is reached for the drug level at 1.8 mg/l after around 2 h, as shown in experiments (Breilh et al., unpublished results). It must be said that these data are in good agrement with those of a previous study (Crump et al., 1983) and differ from the others obtained elsewhere (Le Bel et al., 1986).

4.2. Single dose with the dosage form whose release is controlled by erosion

With a single dose and the erosion-controlled dosage form, it was possible by using the numerical model to calculate the amount of drug-time histories: in the gastrointestinal compartment, in the plasma compartment, eliminated out of the blood compartment, and released from the dosage form.

These amounts of drug-time histories were drawn in Fig. 3, leading to a few conclusions:

(i) The amount of drug located in the gastrointestine was rather low, as already shown for dosage forms whose release was controlled by diffusion (Ouriemchi and Vergnaud, 1996). The curve started with an oblique tangent at time O, passed through a peak at around 1.77 h. After a time of around 11–12 h the amount of drug was negligible.

(ii) The rate constant of erosion 0.12/h was associated in Eq. (2) with the time of 8 h 20 min necessary for the whole release of the drug from the dosage form.

(iii) The amount of drug located in the blood compartment passed through a peak at around 6.6 h. This time of 6.6 h compared with the time of 2 h shown in Fig. 1 showed the effect of the controlled released with regard to the immediate release.

(iv) The kinetics of elimination of the drug out of the blood compartment followed the typical pattern. The rate increased between 1 and 5 h, became about constant up to 13 h, thus decreasing slowly.

4.3. Multiple doses with the two dosage forms: with immediate release, with erosion-controlled release

The drug level-time histories in the blood compartment calculated with the help of the model were drawn in Figs. 4–6 for ciprofloxacine taken orally with these two types of dosage forms.

These two dosage forms were taken at given frequencies: three times a day (Fig. 4), twice a day (Fig. 5) and once a day (Fig. 6). Moreover, the same curves were drawn in Fig. 7 for desethylciprofloxacine for the two dosage forms taken once a day. Some conclusions were worth noting:

(i) The main advantage of the controlled release dosage form over its immediate release counterpart clearly appeared in these figures. The immediate release dosage form was responsible for a process whereby the drug level in the blood compartment alternated between high peaks and deep troughs. (Le Bel et al., 1986). On the contrary, the controlled release dosage form was associated with lower peaks and higher troughs.

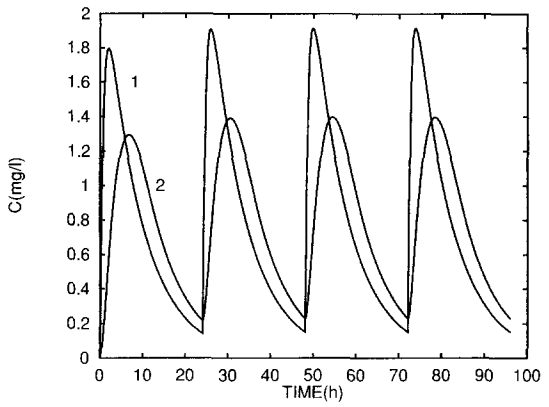

Fig. 6. Drug level-time histories in the plasma compartment for ciprofloxacine, obtained with dosage forms: (1) with immediate release; (2) with controlled release by erosion. Dosage forms taken once a day.

(ii) The values of the peaks and troughs increased progressively from dose to dose and the curves became reproducible after a given number of doses. This number of doses was found to depend on the dose frequency: it was of 4 for three times a day dosing, of 3 for twice a day dosing and 2 for the once a day dose.

(iii) The effect of the dose frequency also appeared effective by comparing the curves in Figs. 4–6. As already shown for diffusion-controlled dosage forms (Ouriemchi and Vergnaud, 1996), increasing the dose frequency, namely from once a day to three times a day, was associated with lower peaks and higher troughs, and thus with a more constant drug level.

(iv) Of course at the beginning of the cure, after the first dose, there was a timelag for the controlled release dosage form.

(v) The drug level-time histories were the same for the metabolite as for ciprofloxacine, as shown in Figs. 6 and 7. The amount of the metabolite found from experiments at 18.7 mg was kept at the same level for the following dosage forms. It must be said that the numerical model could take into account any other change in the process.

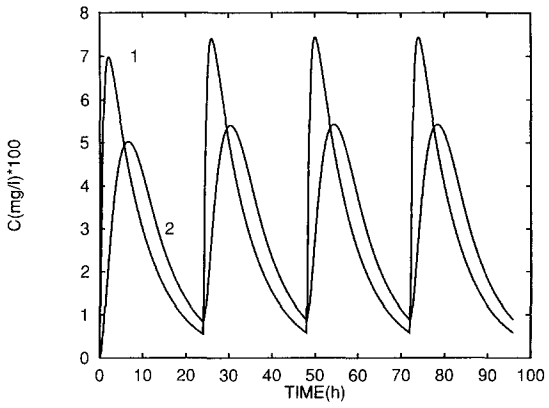

Fig. 7. Drug level-time histories in the plasma compartment for desethylciprofloxacine, obtained with dosage forms: (1) with immediate release; (2) with controlled release by erosion. Dosage forms taken once a day.

5. Conclusions

Immediate release oral dosage forms exhibited some drawbacks, with high peaks and deep troughs, necessitating a high frequency in doses. The oral dosage forms whose release was controlled by erosion presented some advantages over the former forms. Since they delivered the drug with a rather constant rate, the blood level in the plasma was more constant with lower peaks and higher troughs.

A parameter appeared of importance, with the dose frequency. Of course, increasing the dose frequency was responsible for more constant drug level in the blood compartment. The rate constant of erosion was a parameter which depends on the nature of the dosage form and the polymer and on its dimension.

Of course, the pharmacokinetic parameters strongly intervened on the process, and especially the rate constant of elimination. A drug with a rather high value of the rate constant of elimination is quickly eliminated and necessitates a controlled release dosage form.

The numerical model described in the paper was able to take into account all the known facts, namely, the stage of release, of absorption and of elimination. Of course, it could be improved if necessary.

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