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Evaluation of the characteristics of oral dosage forms with release controlled by erosion

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Abstract

This paper is concerned with oral dosage forms with controlled release based on the erosion of the polymer matrix. A numerical model taking all the facts into account, i.e., the kinetics of release and pharmacokinetic parameters of the drug, makes it possible to calculate the plasma drug level. Diagrams are built which connect the half life times obtained either through i.v. or with these dosage forms as a function of the full time of erosion of the polymer. Thus, it is possible to determine the right dosage form matrix associated with the desired therapy. Their interest stands for possible bioadhesion extending the gastrointestinal tract time.
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Keywords: Oral dosage forms; Controlled release; Erodible polymer matrix; Half life time; Modelling; Master curves; Diagrams; Preparation of dosage forms

1. Introduction

Oral dosage forms are most suitable for the patient, avoiding the additional costs associated with intravenous administration in the hospital. Moreover, either to facilitate the compliance of the patient or to allow a more uniform blood level, oral therapeutic systems have been proposed, based on the controlled release of the drug from a polymer matrix. Oral dosage forms whose release is controlled by diffusion are well known, while their counterparts obtained by dispersing the drug through an erodible polymer are not well present on the market, although they have a great potential interest.

Oral dosage forms with release controlled by erosion are prepared by dispersing the drug through an erodible polymer. With these erodible polymers, the problem of drug release can sometimes be rather complex, when the process is initiated by diffusion of the liquid into the polymer and followed by dissolution of the polymer on the surface where the concentration of liquid reaches a high level. However, some erodible polymers exist for which the process seems to be strictly controlled by erosion [1–4].

Biodegradable polymers can be obtained in two ways, either by using pure polymers or by introducing some additives in the polymer which dissolve by provoking progressive disintegration. An example of the first case is observed with Na carboxymethyl cellulose, the dissolution being related to the rheological properties of the gelled polymer [5]. Another example has been pointed out with Gelucires for which the process of drug release is controlled either by diffusion with lipidic material or in the other case by erosion [1,4], depending on the hydrophilic-lipidic balance.

Moreover, the great interest of these erodible dosage forms results from the fact that they can be used in bioadhesive delivery systems, as over the short period of time defined by the gastro intestinal tract GIT, it ensures that all the components of the dosage forms are released and delivered to the patient. Thus the problem of bioadhesion is of high concern. While various books and reviews have attempted to attain this objective [6,7], only a few examples are summarised in order to give a very brief overview on the importance of the problems encountered [8–11]. On the whole, it can be said that the mucoadhesion has been related to the rheological properties of the polymer [12–14] as well as to its molecular weight by considering the poly dispersity [15] or by insisting on the moisture absorption by hydroxypropyl cellulose [16]. Various methods

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and techniques have been developed and used in order to study the mechanism of bioadhesion [17–20] and its subsequent effect with the retention of the dosage form [21]. In short, it can be said that these various studies have attempted to give the answer to the fundamental questions which have been put forward concerning the bioadhesion [22] and its consequences for the dosage forms with erosion-controlled release.

In order to resolve the problem set by the FDA concerned with the in vitro/in vivo correlations [23], which did not find any positive answer [24], a method was developed using a numerical treatment taking all the facts into account [25–27].

A consistent upward trend has been maintained since the beginning of this century, and various ways can be distinguished in the matter of bioadhesion and biodegradation, depending on the applied target. Thus the following sites are considered in succession: vaginal mucus [28], buccal mucosa [29–35], gastric mucus [36,37] and general mucoadhesion [38–40]. The advantages of buccal adhesive systems result from the fact that the first-pass hepatic is avoided. In all these cases, the rate of drug release controlled either by pure erosion or by a 0th-order kinetics process can be treated by the method developed in this paper.

The following objectives are on the basis of this paper:

The process of drug transport is described, by considering the successive stages: the release of the drug out of the dosage form along the GI tract, the drug absorption in the plasma through the GI membrane and its elimination. The rate constant of elimination of the drug is proved to play the main role to characterize the drug, while the polymer is defined by the rate of erosion. Finally, the full time of erosion of the dosage form takes into account the dimensions and shape of the dosage form as well as the nature of the polymer.

The second objective is to point out the importance of the nature of the drug, characterized by its pharmacokinetic parameters, and this fact leads to the necessity to adapt the polymer matrix to the drug and thus to build a typical dosage form in each case.

The more important objective is to develop a method able to help the pharmacists in their preparation of the right dosage form adapted to the drug. Thus tables are drawn which connect the half life times of the drug obtained either through intravenous bolus injection or with these oral dosage forms whose release is controlled by erosion; this connection is made by way of the main characteristic of the dosage form, e.g., the time of full erosion and thus of full drug release which depends on both the nature of the polymer and the size and shape of the dosage form.

2. Theoretical

2.1. Calculation of the kinetics of drug release

The equations have been established for various shapes of these dosage forms, defining the kinetics of release of the drug as they are determined through in vitro measurements [25–27].

Whatever the shape, the rate of erosion is expressed by the linear form:

$$v = \frac{\mathrm{d}L}{\mathrm{d}t} \tag{1}$$

Thus a sheet of initial thickness $2L_0$ immersed on both sides in the liquid, becomes at time t, when the rate of erosion is constant:

$$L_t = L_0 - v \cdot t \tag{2}$$

The sheet is completely eroded after the time of full erosion t

$$t_\mathrm{r} = \frac{L_0}{v} \tag{3}$$

By introducing the time of full erosion, Eq. (2) becomes

$$L_t = L_0 \left[1 - \frac{t}{t_\mathrm{r}}\right] \tag{4}$$

And finally, the amount of drug released at time t, M_t, as a fraction of the amount initially in the dosage form M_in, is proportional to the ratio of times:

$$\frac{M_t}{M_\mathrm{in}} = \frac{t}{t_\mathrm{r}} \tag{5}$$

In the same way, for a dosage form, spherical in shape, at time t, the new radius is

$$R_t = R_0 - v \cdot t = R_0 \left[1 - \frac{t}{t_\mathrm{r}}\right] \tag{6}$$

The amount of drug released from the spherical dosage form at time t, M_t, is thus related to the times and the initial amount M_in by the relation

$$\frac{M_t}{M_\mathrm{in}} = 1 - \left[1 - \frac{t}{t_\mathrm{r}}\right]^3 \tag{7}$$

Let us remark that the same Eq. (7) is obtained for a cube of sides $2a$. However, the time of erosion is not the same in these two cases, as it is proportional to either the radius of the sphere or to half the edge of the cube.

2.2. Calculation of the plasma drug level

Assumptions for calculating the plasma drug profile:

(1) The process of drug transfer is described in Fig. 1 where the following stages appear in succession: release of the drug out of the dosage form along the GI tract, kinetics of absorption into- and elimination out of the plasma compartment.
(2) The process of drug release out of the dosage form is controlled by erosion, with a constant rate (in fact, this strict assumption is not necessary, provided that the process of the change in the rate of erosion along the GIT is known).
(3) The phenomena of absorption and elimination are described by first-order kinetics with the two rate constants k_a and k_e expressed in h^{-1}.

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