ELSEVIER

International Journal of Pharmaceutics 176 (1999) 251–260

international journal of pharmaceutics

Plasma drug level assessment with controlled release dosage forms with a core and shell and lower concentration in the shell

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

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

Received 13 July 1998; received in revised form 30 September 1998; accepted 11 October 1998

Abstract

Calculation has been made for determining the plasma drug level with oral dosage forms consisting of a core and shell for which the drug concentration is smaller in the shell than in the core and the process of drug release is controlled by transient diffusion. The effect of the radius of the core on the process and especially on the plasma drug level is determined, by keeping the radius of the shell constant. The radius of the shell is determined as is the time of drug release in 24 h. Comparisons are made between various dosage forms with core and shell, and dosage forms with uniform drug concentration, and immediate release dosage forms. More constant plasma drug levels are obtained with dosage forms with core and shell with lower concentration in the shell and with the thicker shell.

Keywords: Controlled release; Oral dosage; Plasma drug level; In vitro/in vivo calculation; Core and shell; Diffusion

1. Introduction

The development of therapeutic systems that release a controlled amount of drug over a defined period of time represents a significant pathway for optimizing drug effects. They offer especially important advantages over traditional dosage forms with immediate release in diseases requiring the most constant possible effective blood levels over prolonged durations of therapy. Such dosage forms can decrease the peak concentration and achieve more uniform blood levels, and often smaller total amounts of drug are needed and side effects are reduced (Heilmann, 1983).

The most simple therapeutic systems for controlled release are made of a polymer matrix through which the drug is intimately dispersed. Depending on the nature of the polymer which can be either erodible (Heller, 1984) or stable, the

* Corresponding author. Tel.: +33-477-481568; fax: +33-477-251817.

0378-5173/99/$ - see front matter
PII: S0378-5173(98)00328-7

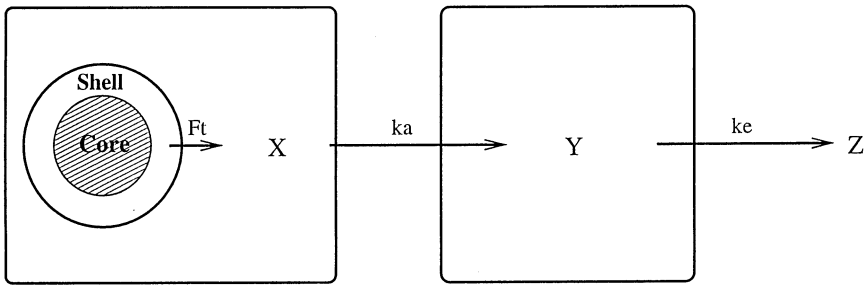

Fig. 1. Scheme of the process

process of drug release is quite different as well as the kinetics of dissolution (Feijen, 1984). The whole process is rather complex since the gastrointestinal liquid enters the dosage form, dissolves the drug and enables the drug to diffuse out of the dosage form through the liquid located in it (Armand et al., 1987), both these two transfers being connected with each other with concentration-dependant diffusivities. In the case of a lipidic matrix, the process of drug release was found to be controlled by the solubility of the drug in the liquid which progresses into the dosage form by taking the place of the drug and by the diffusion of the drug through the liquid located in the dosage form (Ainaoui and Vergnaud, 1997, 1998). However, the fact of interest is the kinetics of drug release out of the dosage form. In case of a stable polymer, the process of drug release can be described by diffusion with very often a constant diffusivity (Fessi et al., 1982; Vergnaud, 1993). When the amount of liquid absorbed by the polymer is much larger than the amount of drug dissolved, a swelling takes place making the process of release more complex (Peppas et al., 1980), and the diffusivity of the drug increases highly with the liquid concentration (Sabbahi et al., 1996). In the case of erosion, the process is still more complex as generally the liquid diffuses into the polymer which is dissolved when the amount of liquid is high enough, and diffusion and erosion may take place simultaneously.

A main drawback for dosage forms made of stable polymer with drug release controlled by diffusion appears with the shape of the kinetics of dissolution: the rate of drug release, very high at the beginning, decreases exponentially with time. Moreover, all the drug is released out of the dosage form after infinite time. In order to avoid or rather to reduce the first inconvenience resulting from the shape of the kinetics, various attempts have been made. Interesting dosage forms with a core and shell were studied, where the core made of stable polymer through which the drug is dispersed, is surrounded by a shell made of Gelucire 46-7; they were able to deliver the drug with a constant rate (Magron et al. 1987; Laghoueg et al., 1989). Another approach was made with dosage forms made of a core and shell with the same non-erodible polymer but with a lower drug concentration in the shell than in the core (Ouriemchi et al., 1994). These dosage forms have the same drawback being diffusion controlled but the kinetics however are more constant than those obtained with the same drug concentration in the core and shell.

The first purpose in this paper is to evaluate the dimensions of dosage forms made of a core and shell with different drug concentrations in the core and shell with the same stable polymer, so as to obtain various kinetics of drug dissolution (Fig. 1). Two improvement are made over the previous study (Ouriemchi et al., 1994): the implicit Crank Nicolson method is used instead of an explicit method for calculation; the dimensions of these dosage forms are calculated in such a way that a

Table 1
Pharmacokinetic parameters of aspirin (Vidal 1995)

$k_a = 2.77/h$	$k_e = 0.321/h$
$D = 2.5 \times 10^{-7}$ cm^2/s	

Table 2
Dosage form with controlled release with core and shell

Dosage form	Shell		Core	
	R_{ext}	C_{ext} (w/w)	R_{int}	C_{int} (w/w)
1	0.235	0.2	0.195	0.6
2	0.235	0.6	0.235	0.6

large amount (99%) of drug is released within 24 h.

The other objective of this study is to assess the plasma drug level obtained with these dosage forms and to make comparison with other two dosage forms with immediate release, with a uniform drug concentration. As shown in early studies, it is possible to evaluate the drug level in the plasma by using a numerical model taking all the known facts into account, namely, the kinetics of dissolution of the drug out of the dosage form, the kinetics of absorption into the plasma compartment and the kinetics of elimination (Ouriemchi and Vergnaud, 1996a,b). Some attempts were made for correlating in vitro kinetics of dissolution and in vivo plasma drug level (Skelly et al., 1987, 1990) but without definitive conclusions (Skelly and Shiu, 1993). The model considered in this paper is built by making the following assumption that the kinetics of absorption in the plasma remain constant along the process. But it must be said that the model can take into account a more complex process of drug absorption as shown in a deep study on the drug absorption (Amidon et al., 1995). Moreover, comparison being made between the plasma drug profile obtained for the three dosage forms, namely with immediate release, with controlled release with the core alone and with the core and shell, it stands to reason that the dosages forms with controlled release either with the core alone or with the core and shell follow the same gastrointestinal tract. The profiles of concentration of the drug developed through the spherical dosage form are drawn at various times for the dosage form made of either the core alone or with the core and shell, in order to give a fuller insight into the nature of the process.

2. Theoretical

2.1. Assumptions

The following assumptions are made in order to describe the process precisely:

(i) The process of drug transport is divided into three main stages: kinetics of release out of the dosage form, kinetics of absorption in the plasma compartment, followed by the kinetics of elimination.

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

(iii) The dosage forms are made of core and shell with lower drug concentration in the shell than in the core.

(iv) The processes of absorption into and elimination out of the plasma compartment are described by first-order kinetics.

(v) The rate constant of absorption is considered as constant along the process, as no additional information is given at the present time (Amidon et al., 1995).

(vi) The radius of the dosage form is calculated in such a way that 99% of the drug initially in the dosage form is released.

2.2. Mathematical treatment

The equation of radial diffusion through the dosage forms with constant diffusivity is (Crank 1975; Vergnaud, 1993):

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

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

The rate of drug release out of the dosage form time t is:

$$F_t = -A \cdot D \cdot \frac{\partial C_{r,t}}{\partial r} \quad (2)$$

where A is the area of the dosage form.

Of course, at the core–shell interface, the rate of drug transfer is the same on each face:

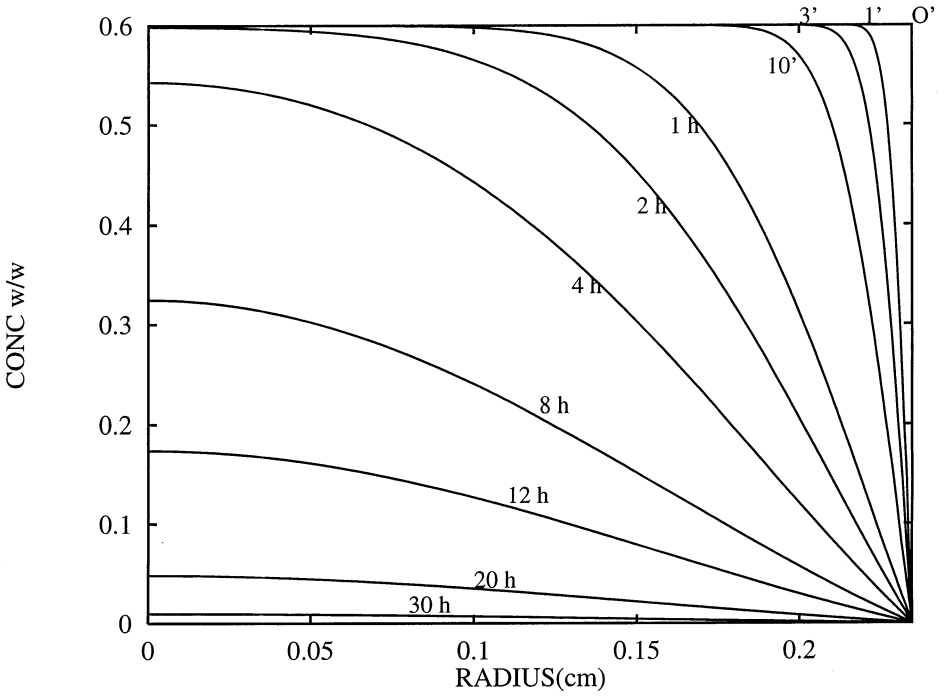

Fig. 2. Profiles of concentration of drug developed through the spherical dosage form made of the core alone. $R_{ext} = 0.235$ cm; $C_{in} = 0.6$.

$$D \cdot \left(\frac{\partial C}{\partial r}\right)_{core} = \quad D \cdot \left(\frac{\partial C}{\partial r}\right)_{shell} \tag{3}$$

2.3. Numerical treatment

The following stages are considered:

Amount of drug in the gastrointestine X

$$\frac{dX}{dt} = F_t - k_a \cdot X \tag{4}$$

where F_t is the rate of drug released out of the dosage form at time t

Amount of drug in the plasma Y

$$\frac{dY}{dt} = k_a.X - k_e \cdot Y \tag{5}$$

Amount of drug eliminated Z

$$\frac{dZ}{dt} = k_e \cdot Y \tag{6}$$

No analytical solution can be found for the whole process. A numerical method with finite differences (Crank Nicolson) is used.

3. Results and discussion

The main purpose is to assess the drug level in the various compartments.

The drug profiles are expressed by using the amount of drug as a fraction of the amount of drug initially located in each dosage form. The drug selected is aspirin with the pharmacokinetic parameters shown in Table 1. Various dosage forms with controlled release and core and shell have been studied, with the same radius of 0.235 cm and various thickness for the shell. Two of them are described in this paper, the one when there is no shell (2) and the other with a core and shell (1).The drug concentrations in the core and shell are expressed in w/w which are about the same as volume/volume (Table 2).

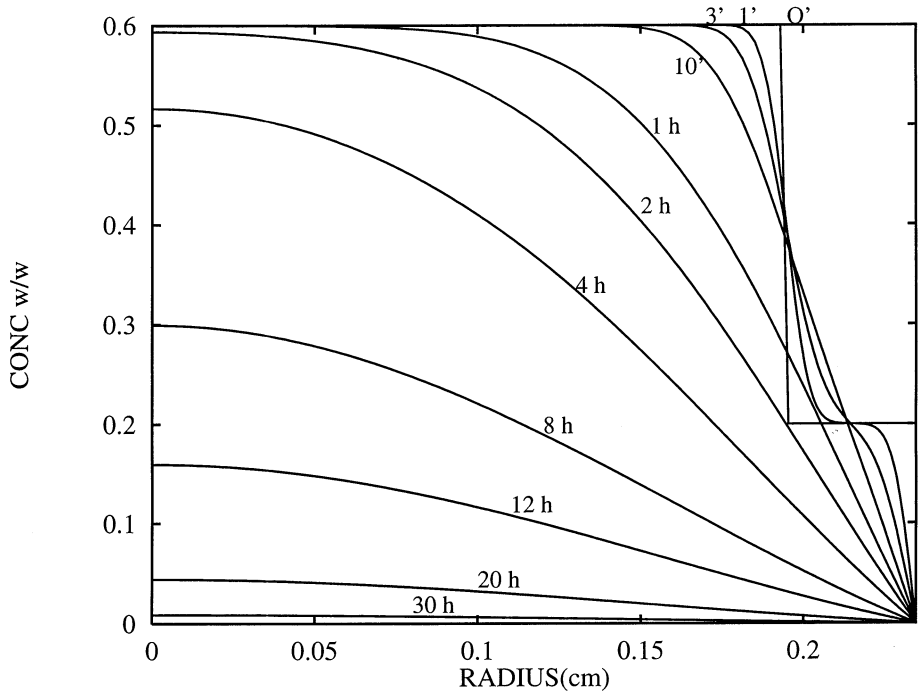

Fig. 3. Profiles of concentration of drug developed through the spherical dosage form made of a core and shell. $R_{int} = 0.195$ cm; $C_{int} = 0.6$; $R_{ext} = 0.235$ cm; $C_{ext} = 0.2$.

The diffusivity is that obtained for the release of aspirin out of dosage forms made of Eudragit as matrix (Vergnaud 1993).

The results are expressed in two ways:

(i) The profiles of concentration of the drug developed through the two dosage forms at various times.

(ii) The drug profiles in various compartments for the various dosage forms, as well as the kinetics of drug release and elimination;

(iii) The plasma drug level of the three dosage forms with immediate release, with controlled release with the core alone and with the core and shell as described in dosage form 1, taken once or twice a day.

3.1. Profiles of concentration of drug developed through the spherical dosage forms

The profiles of concentration of the drug developed through the spherical dosage forms are drawn at various times in Fig. 2 for the dosage form without shell and in Fig. 3 when the dosage form is made of a core and shell.

Because of the radial symmetry, the profiles are drawn along the radius of the beads.

The following conclusions are worth noting:

(i) These profiles of drug concentration developed through the beads give a fuller insight into the nature of the process.

(ii) For the two dosage forms, the concentration on the surface drops to zero as soon as the process starts. It results from the infinite value given to the coefficient of convective transfer on the surface. It must be said that with a good stirring, a value of 100 is obtained for the dimensionless number hR/D, and the kinetics of release with this value is close to that obtained with an infinite value of the coefficient of convection h (Vergnaud 1993; Siepmann et al., 1998).

(iii) The profiles of drug concentration are quite different in Fig. 2 and Fig. 3, because of the presence of the shell in Fig. 3. Thus at time 0, a lower concentration is shown in the shell.

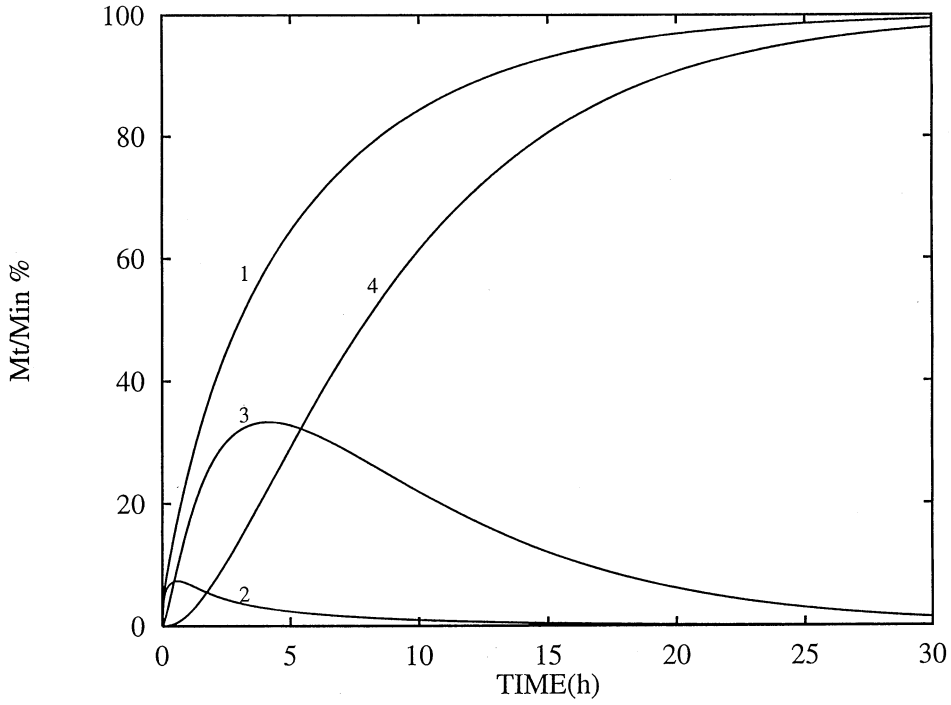

Fig. 4. Profiles of drug in various compartments with the dosage form with controlled release. $R_{int} = 0.215$ cm; $C_{int} = 0.6$; $R_{ext} = 0.235$ cm; $C_{ext} = 0.2$. (1) Cumulative amount released; (2) amount in the GI tract; (3) amount in the body; (4) cumulative amount eliminated.

(iv) In Fig. 3, as soon as the process starts two drug transfers take place: the one at the core–shell interface, the other at the external surface. These transfers can be seen separately at lower times than 10′.

(v) After a time of around 1 h the profiles have about the same shape in Fig. 2 and Fig. 3, with the main difference that they are obtained at a lower time with the core alone. It must be noticed that the retardation in the drug transport, rather important at the beginning, between 1 and 2 h., becomes less and important when the transfer proceeds, and quite the same after 12 h.

3.2. Kinetics of drug release and elimination and drug profiles in the gastrointestine and plasma

The kinetics of drug released out of the dosage form (1) and of drug elimination out of the plasma compartment (4), as well as the drug profile in the gastrointestine (2) and the plasma (3) are drawn in Figs. 4 and 5 for the two dosage forms with controlled release. Comparison between these dosage forms can lead to the following conclusions:

(i) The radius of all dosage forms is evaluated so that 99% of the drug is released within 24 hours. These results can be extrapolated for other polymers with different diffusivities. By using the relation $D \cdot t/R^2$(Vergnaud 1993), the square of the radius is proportional to the diffusivity and the obvious statement holds: the lower the diffusivity, the smaller the radius of the beads for the same time of release.

(ii) Of course, the kinetics of drug released out of the various dosage forms are quite different. The presence of a shell with a lower drug concentration is responsible for lower rate of drug delivery, especially at the beginning. Another statement holds: the thicker the shell with lower drug concentration, the lower the rate of drug delivery.

(iii) As shown in earlier studies with con-

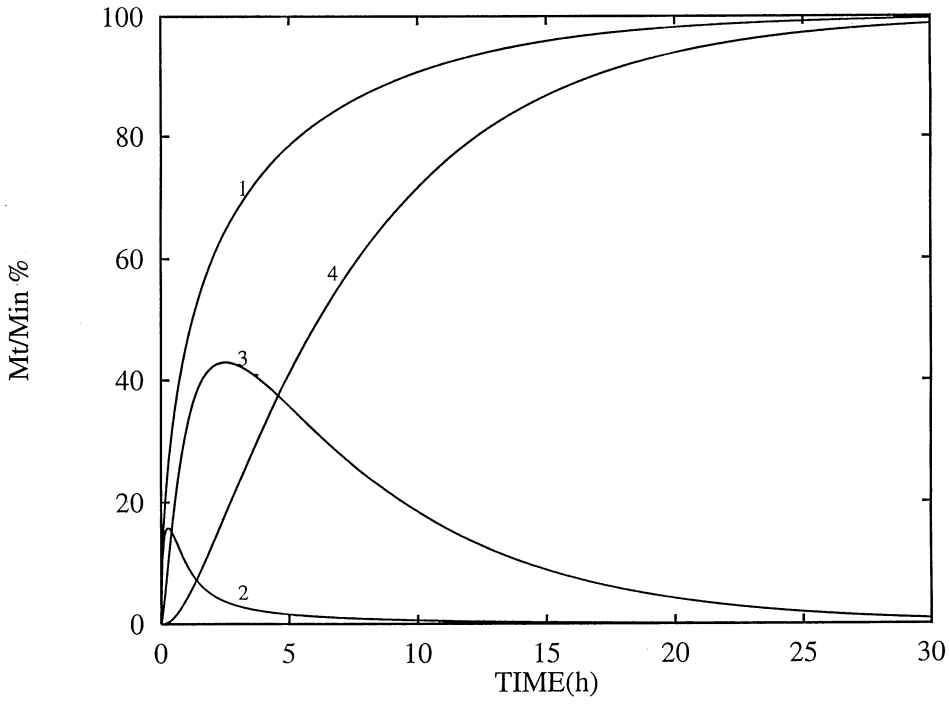

Fig. 5. Profiles of drug in various compartments with the dosage form with controlled release. $R_{ext} = R_{int} = 0.235$ cm; $C_{int} = 0.6$. (1) Cumulative amount released; (2) amount in the GI tract; (3) amount in the body; (4) cumulative amount eliminated.

trolled release dosage forms (Ouriemchi and Vergnaud, 1996a,b), the amount of drug in the gastrointestinal tract is very small. Comparison between the dosage forms with core and shell shows that the presence of the shell with lower drug concentration is responsible for lower amounts of drug in the gastrointestinal tract. Of course, the thicker the shell, the lower the amount of drug in the gastrointestinal tract.

(iv) Comparison between the plasma drug level obtained with the two dosage forms with controlled release is of special interest. It clearly appears that the presence of a shell with lower drug concentration is responsible for a lower peak reached at a longer time. This phenomenon appears more effective when the shell is thicker.

(v) The kinetics of drug elimination out of the plasma also depend on the presence of the shell with low drug concentration and of its thickness. The thicker the shell, the lower the rate of elimination.

3.3. Plasma drug profiles

The plasma drug profiles are drawn when three dosage forms are taken once a day (Fig. 6) and twice a day (Fig. 7), as they are obtained by calculation. The three dosage forms considered are: with immediate release (1), with controlled release without shell (dosage form 2) (2), and with a rather thick shell (dosage form 1) (3).

Some conclusions are worth noting from these profiles:

(i) The plasma drug profile obtained with the immediate release dosage form is typical either when taken once a day or twice a day, exhibiting a high peak and low trough.

(ii) The dosage forms with controlled release are associated with lower peaks and higher troughs, leading to a more constant drug level. The peak obtained with the dosage form 2 without shell is half that attained with the immediate release whatever the dose frequency. The trough is more than twice as high as that of the immediate

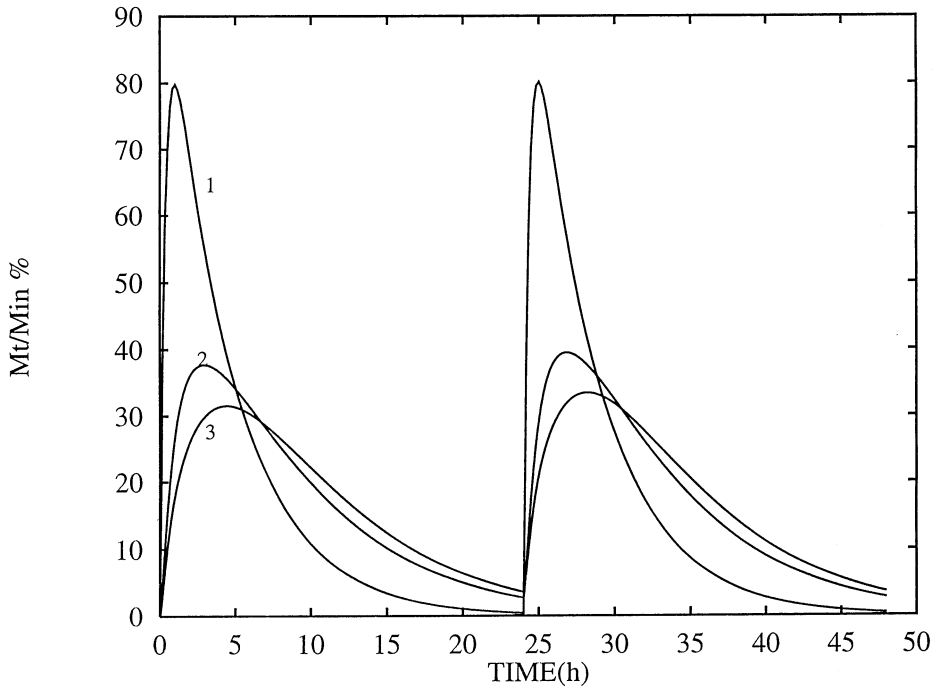

Fig. 6. Plasma drug level with the three dosage forms: with immediate release (1); with controlled release with core alone (2); with core and shell ($R_{int} = 0.195$ cm), taken once a day.

release when taken twice a day and about five times when taken once a day.

(iii) The dosage form with controlled release and the rather thick shell with low drug concentration delivers the drug with the more constant level in the plasma, with lower peaks and higher troughs.

4. Conclusions

It is well known that dosage forms with controlled release are able to deliver the drug in the plasma with a more constant level than immediate release dosage forms. A drawback still remains when the process of drug release is controlled by diffusion with a stable polymer matrix: the kinetics of drug release is very high at the beginning, and decreases exponentially with time. However, an improvement can be obtained for these dosage forms with controlled release made of a drug dispersed through a stable polymer matrix. It consists of using dosage forms made of a core and shell with a lower drug concentration in the shell than in the core. These new dosage forms are able to give a more constant drug level in the plasma, with lower peak and higher troughs.

These dosage forms with core and shell can be prepared in two stages, for the core and then for the shell, either by a dry or wet method.

5. Nomenclature

A	Area of the dosage form
$C_{r,t}$	Drug concentration in the dosage form at the radial abscissa r and time t. (volume/volume)
D	Diffusivity of the drug through the dosage form. (cm^2/s)
F_t	Rate of drug release out of the dosage form at time t.
r	Radial abscissa in the dosage form.
t	time.
X	Amount of drug in the gastrointestinal tract.

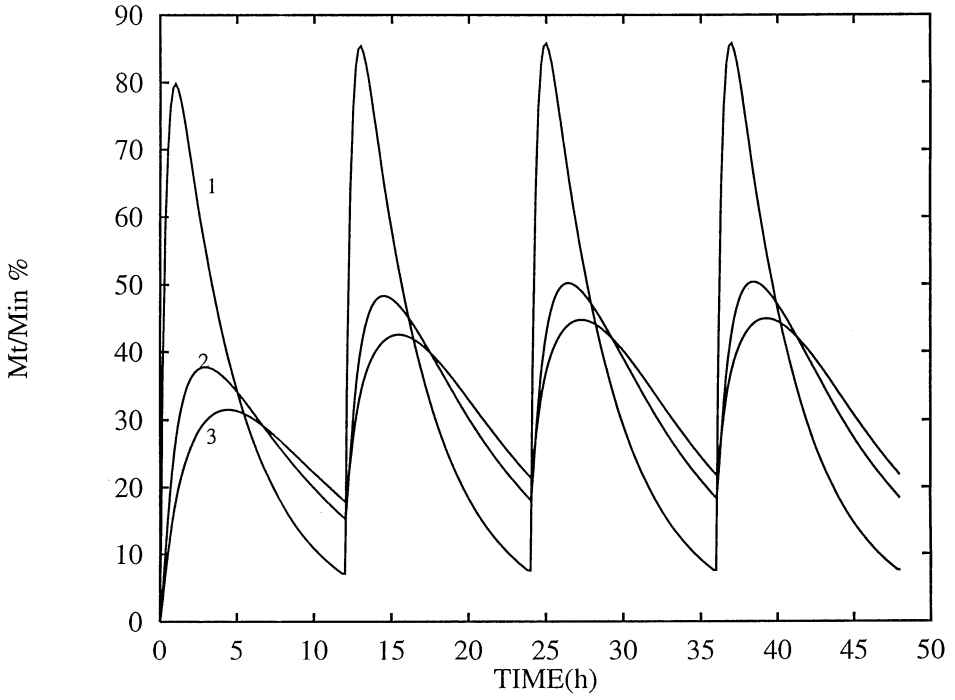

Fig. 7. Plasma drug level with the three dosage forms: with immediate release (1); with controlled release with core alone (2); with core and shell ($R_{int} = 0.195$ cm), taken twice a day.

Y Amount of drug in the body.
Z Cumulative amount of drug eliminated.

References

Ainaoui, A., Vergnaud, J.M., 1997. Process of drug release with oral dosage forms with a lipidic Gelucire matrix. J. Polym. Eng. 17, 245–255.

Ainaoui, A., Vergnaud, J.M., 1998. Modelling the plasma drug level with oral controlled release dosage forms with lipidic Gelucire. Int. J. Pharm. 169, 155–162.

Amidon, G.L., Lennernäs, H., Shah, V.P., Crison, J.R., 1995. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm. Res. 12, 413420.

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

Crank, J., 1975. The Mathematics of Diffusion. Clarendon Press, Oxford, pp. 89–100.

Feijen J. Controlled drug delivery based on the use of synthetic polymers, XIV Meet. of French Polymer Group, November, Rouen, 1984.

Fessi, H., Marty, J.P., Puisieux, F., Carstensen, J.T., 1982. Square root of time dependence of matrix formulations with low drug content. J. Pharm. Sci. 71, 749752.

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

Heller, J., 1984. Biodegradable in controlled drug delivery. CRC Crit. Rev. Ther. Drug Carrier Syst. 1, 39–90.

Laghoueg, N., Paulet, J., Taverdet, J.L., Vergnaud, J.M., 1989. Oral polymer-drug devices with a core and an erodible shell for constant drug delivery. Int. J. Pharm. 50, 133–139.

Magron, P., Rollet, M., Taverdet, J.L., Vergnaud, J.M., 1987. Spherical oral polymer-drug device with two polymers for constant drug delivery. Int. J. Pharm. 38, 91–97.

Ouriemchi, E.M., Vergnaud, J.M., 1996. Calculation of the plasma drug level with oral controlled release dosage forms. Effect of the dose frequency. Int. J. Pharm. 127, 177–184.

Ouriemchi, E.M., Vergnaud, J.M., 1996. Prediction of in-vivo blood level with controlled release dosage forms. Effect of the gastrointestinal tract time. J. Pharm. Pharmacol. 48, 390–394.

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

Peppas, N.A., Gurny, R., Doelker, E., Buri, P., 1980. Modelling of drug diffusion through swellable polymeric systems. J. Membr. Sci. 7, 241–253.

Sabbahi, A., Bakhouya, N., Vergnaud, J.M., 1996. Diffusion of a liquid through an elastomeric polymer with change in dimension and concentration-dependent diffusivity. Computat. Theoret. Polym. Sci. 6, 109–116.

Siepmann, J., Ainaoui, A., Vergnaud, J.M., Bodmeier, R., 1998. Calculation of the dimensions of drug-polymer devices based on the parameters of diffusion. J. Pharm. Sci. 87 (7), 827.

Skelly, J.P., Barr, W.H., Benet, L.Z., Doluisio, J.T., Goldberg, A.H., Levy, G., Lowenthal, D.T., Robinson, J.R., Shah, V.P., Temple, R.J., Yacobi, A., 1987. Report of the workshop on controlled-release dosage forms: issues and controversies. Pharm. Res. 4, 75–77.

Skelly, J.P., Amidon, G.L., Barr, W.H., Benet, L.Z., Carter, J.E., Robinson, J.R., Shah, V.P., Yacobi, A, 1990. In vitro and in vivo testing and correlations for oral controlled/modified release dosage forms. Pharm. Res. 7, 975–982.

Skelly, J.P., Shiu, G.F., 1993. In vitro/vivo correlations in biopharmaceutics: scientific and regulatory implications. Eur. J. Drug Metab. Pharmacokinet. 18, 121–129.

Vergnaud J.M. Controlled Drug Release of Oral Dosage Forms, Chichester, UK: Horwood, 1993:199–259.

Vidal, 1995. Editions du Vidal. Paris, France.

.