International Journal of Pharmaceutics, 50 (1989) 133–139
Elsevier

IJP 01690

Oral polymer–drug devices with a core and an erodible shell for constant drug delivery

N. Laghoueg, J. Paulet, J.L. Taverdet and J.M. Vergnaud

Laboratory of Materials and Chemical Engineering, Faculty of Sciences, University of Saint-Etienne, Saint-Etienne (France)

(Received 26 May 1988)
(Accepted 25 July 1988)

Key words: Sulfanilamide; Spherical oral dosage device; Core and shell; Eudragit; Gelucire; Constant drug delivery

Summary

A polymer–drug device with two polymers is prepared and tested in in-vitro tests. The device consists of a core obtained by dispersing the drug in Eudragit as polymer and of a shell made of an erodible polymer. The drug chosen in the paper is sulfanilamide, and the shell is made of "Gelucire". When in contact with synthetic gastric liquid, these types of dosage forms are able to deliver the drug with a constant rate throughout the whole process. Moreover, the value of this rate of drug delivery is inversely proportional to the thickness of the shell. Some parameters, as the temperature of liquid Gelucire and the time of contact, are of interest for controlling the thickness of the shell.

Introduction

With classical dosage forms administered via the gastrointestinal tract the release of drug is controlled by dissolution. The drug is then liberated very rapidly, and the drug concentration in the gastric liquid and blood builds up to a maximum value and then falls exponentially until the following dose. As a result, an undulating concentration history is obtained, low concentrations alternating with high concentrations (Heilman, 1984; Peppas et al., 1980; Peppas, 1985).

Optimization of conventional agent delivery to maximize agent availability with a minimum amount of the drug cannot be realized easily. The method is practical if we consider new types of dosage forms consisting of a protected supply of drug from which the drug is automatically released at a controlled rate over a long period of time. Monolithic devices where the agent is dispersed in an inert matrix have been studied. Both degradable (Heller, 1984) and non-degradable (Fessi et al., 1982; Touitou and Donbrow, 1982; Focher et al., 1984) polymers have been utilized for the matrix, the purpose being that these polymers are not absorbed in the body but pass through. Several theories have been put forward in an attempt to model the details of the delivery of drug. Invariably they are built on a combination of hydrodynamic (Nicklasson et al., 1985) and

Correspondence: J.M. Vergnaud, Laboratoire de Chimie des Matériaux et Chimie Industrielle, Faculté des Sciences et Techniques, 23 rue du Dr. P. Michelon, Université de St.-Etienne, St.-Etienne, 42100 France.

diffusion process which explain the square-root of time dependence of the drug delivery (Gurny et al., 1982; Touitou and Donbrow, 1982; Brossard et al., 1983; Teillaud and Pourcelot-Roubeau, 1984). Other studies have considered the simultaneous transfer of the liquid into, and the drug out of the polymer matrix, either in case of plasticized PVC in contact with a liquid (Messadi and Vergnaud, 1981; Messadi et al., 1983; Taverdet and Vergnaud, 1984, 1986) or in case of dosage forms prepared by dispersing the drug in a polymer (Droin et al., 1985; Malley et al., 1987; Armand et al., 1987). In all these above studies, the delivery of the drug is controlled by diffusion and the amount of drug delivered is proportional to the square root of time.

A release with a constant rate can be obtained by using devices based on the osmosis principle (Heilman, 1984) or with the help of more simple devices. Two types of these latter devices have been successfully tested. The one based on diffusion process with dosage forms made of a core and shell, the core containing the drug dispersed in a polymer matrix, and the shell in pure polymer (Liu et al., 1988). The other based on diffusion and polymer erosion consists of a core made of drug dispersed in a polymer as Eudragit RL, this core being surrounded by an erodible polymer (Magron et al., 1987).

The purpose of this paper is to show that the mechanism of drug release by diffusion and polymer erosion can be extended to many cases for preparation of dosage forms delivering the drug at a constant rate. The dosage form consists of a core and shell. The core is obtained by dispersing the drug sulfanilamide in Eudragit RL which plays the role of a matrix, and the shell is made of Gelucire which is a mixture of polyglycide fatty esters with controlled hydrophilic properties. The Gelucire 46-7 used is slightly soluble in gastric liquid at 37 °C, and then behaves as an erodible polymer. To get insight into the mechanism of drug release, and also to find out a relationship between the rate of drug release and a characteristic of interest of the shell, viz. thickness, a mathematical model is developed and verified. This model is based on the simple main principle that the shell plays the role of a spherical membrane (Crank, 1975) which separates two media with constant concentrations of the drug.

Theory

The whole problem is rather complex, because of the simultaneous and successive steps: the transfer of the liquid enters successively the shell (made of Gelucire) and the core (made of a dispersion of the drug in Eudragit), then the dissolution of the drug in the liquid located in the core, enabling the transfer of the drug out of the dosage form. At the same time, a slight erosion (or rather dissolution) of the shell takes place.

Assumptions

In order to simplify the problem and find a good solution, the following assumptions are made.

(i) The dosage form is made of two concentric spheres, the core of radius R_1 and the shell of external radius R_2. The core is obtained by dispersing the drug in the polymer (Eudragit), and the shell is made of pure Gelucire.

(ii) Two matter transfers take place simultaneously: the one with the liquid which enters the dosage form and dissolves the drug, the other with the drug in solution in the liquid absorbed into the dosage form (Droin et al., 1985; Malley et al., 1987).

(iii) The transfers of the liquid and drug are controlled by diffusion, the diffusivity being higher for the liquid than for the drug (Magron et al., 1987; Armand et al., 1987).

(iv) A very simple model is tested, by considering the shell as a spherical membrane, the diffusivity of the drug in the shell being lower than the diffusivity in the core.

Mathematical treatment

In order to describe the process in spite of its complexity, a mathematical treatment can be made with the help of the above assumptions (especially the fourth).

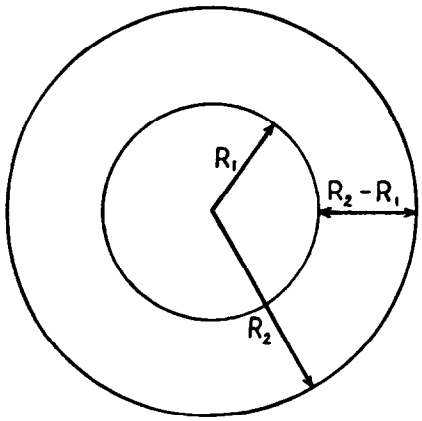

Fig. 1. Scheme of the dosage form, with core and shell. Core, drug and Eudragit RL; shell, Gelucire.

The transient diffusion through the sphere is described by the Fick's equation:

$$\frac{\partial C}{\partial t} = \frac{1}{r^2} \cdot \frac{\partial}{\partial r}\left[D \cdot r^2 \cdot \frac{\partial C}{\partial r} \right] \tag{1}$$

The initial and boundary conditions are as shown in Fig. 1.

$$\begin{array}{llll} t = & 0 \quad r \leqslant R_1 & C = C_{in} & \text{core} \\ & R_1 < r < R_2 & C = 0 & \text{shell} \end{array} \tag{2}$$

$$\begin{array}{llll} t > & 0 \quad r = R_1 & C = C_{in} & \\ & r \geqslant R_2 & C = 0 & \\ & 0 < r < R_2 & C = C_r & \end{array} \tag{3}$$

Under these simple conditions, an analytical solution can be found for Eqn. 1, especially when the diffusivity of the drug is constant (Crank, 1975, p. 99).

The amount of drug transferred up to time t into the exterior liquid is given by the series:

$$\frac{M_t}{4\pi \cdot R_1 \cdot R_2 (R_2 - R_1) C_{in}} = \frac{D \cdot t}{(R_2 - R_1)^2} - \frac{1}{6} - \frac{2}{\pi^2} \sum_{n=1}^{\infty} \frac{(-1)^n}{n^2} \exp\left[- \frac{D n^2 \pi^2 t}{(R_2 - R_1)^2} \right] \tag{4}$$

The transport through the membrane is then controlled by transient diffusion. But when $t \to \infty$, or when the time is high enough, the amount of matter transferred varies linearly with time:

$$M_t = \frac{R_1 \cdot D \cdot C_{in}}{R_2 (R_2 - R_1)} \left[t - \frac{(R_2 - R_1)^2}{6 \cdot D} \right] \cdot 4\pi R_2^2 \tag{5}$$

In fact, this linear relationship between M_t and the time has an intercept on the time axis given by:

$$t = \frac{(R_2 - R_1)^2}{6 \cdot D} \tag{6}$$

The slope of the straight line $M_t - t$, or the rate of matter transferred is proportional to the diffusivity D of the drug in the membrane.

$$S = \frac{C_{in} \cdot R_1 \cdot D}{R_2 (R_2 - R_1)} 4\pi R_2^2 \tag{7}$$

Symbols

C, C_{in}	:	drug concentration, initial concentration in the core
D	:	diffusivity of the drug in the shell
R_1, R_2	:	radius of the core, and the shell, respectively
$R_2 - R_1$	:	thickness of the shell (supposed constant)
n	:	integer
M_t	:	amount of drug delivered at time t
S	:	slope of $M_t - t$ line, constant rate of the drug delivered for the values of times higher than the time defined by Eqn. 6.

Materials and Methods

Materials

The following components are used: Sulfanilamide, the *p*-aminobenzene sulfamide, in white powder form, is chosen for the drug. Eudragit RL, a copolymer of dimethylaminoethylacrylate and ethylmethacrylate, of mol. wt. = 150,000 (Rhöm

Pharma) and a low number of quaternary ammonium terminals, is used as polymer matrix for the sphere of radius R_1. The ratio between the numbers of quaternary ammonium and esters terminals is around 1/20. Gelucire 46/07, a waxy solid made of partial glycerides and polyglycides fatty esters with controlled hydrophilic properties (Gattefossé, Lyon) is chosen for the shell surrounding the core. The drop point (Mettler) is 46 °C and the hydrophilic-lipophilic balance is 7, corresponding to a medium value.

Preparation of dosage forms

Eudragit and drug in powder form are intimately mixed in a mortar, and transformed into a thick paste with a small amount of ethanol which is a solvent of the drug and polymer. Spherical beads are prepared from this paste and dried at room temperature for 4 days (dosage form of type A).

The dosage form of type A is then surrounded by a spherical membrane of Gelucire, by dropping for 2–5 s the dosage form into Gelucire kept liquid at 60 °C. The Gelucire membrane hardens after cooling at room temperature. The thickness of this shell can be controlled by selecting the right values for the temperature of the liquid Gelucire and for time of contact.

Several dosage forms are prepared with various values of the thickness of Gelucire ranging from 0.011 cm (17 mg) to 0.05 cm (108 mg), by keeping a constant percentage of drug (50% w/w) in the core of radius R_1, and about the same weight (around 320–400 mg and R_1 between 0.38 and 0.4 cm).

In-vitro test

Experiments are carried out in a closed flask with a controlled rate of stirring. The bead (320–400 mg) inserted in a fiberglass basket is soaked into synthetic gastric liquid (100 ml) at 37 °C with the classical composition (pH = 1.2; 1000 ml of aqueous solutions, 80 ml HCl 1 N and 2 g NaCl).

At intervals the bead is weighed and small samples (1 ml) of liquid are taken for analysis. The amount of drug released in the liquid is determined by using a UV spectrophotometer (Hitachi U-1100) calibrated at 216 nm.

Results

The kinetics of release of the drug into synthetic gastric liquid is determined by using a device made of the core alone as well as devices made of the core and the shell. An attempt to correlate the rate of drug release with the thickness of the shell is then made by considering the model of the spherical membrane separating two media with a constant concentration of the drug.

Experimental results

Device with a core alone

First of all, the device made of the core alone, obtained by dispersing the drug in the polymer with the following concentration (50–50% w/w for the drug and polymer), is tested in a preliminary way. The kinetics of release of the drug in synthetic gastric liquid is shown in Fig. 2. Some conclusions can be drawn from these results.

Amount of drug released. About 95–100% of the drug previously dispersed in the device is released in the liquid at the end of the process, when equilibrium is attained. In case of a drug as sodium salicylate with a low solubility in gastric

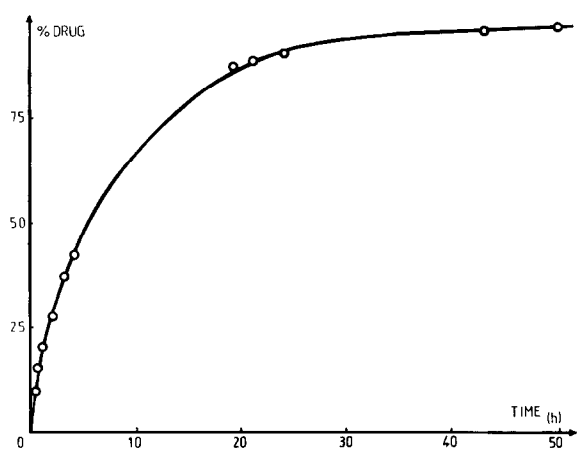

Fig. 2. Kinetics of drug released in synthetic gastric liquid from the core (Eudragit RL–Sulfanilamide, 50–50% w/w; 336.8 mg; R = 0.38 cm; 37 °C.

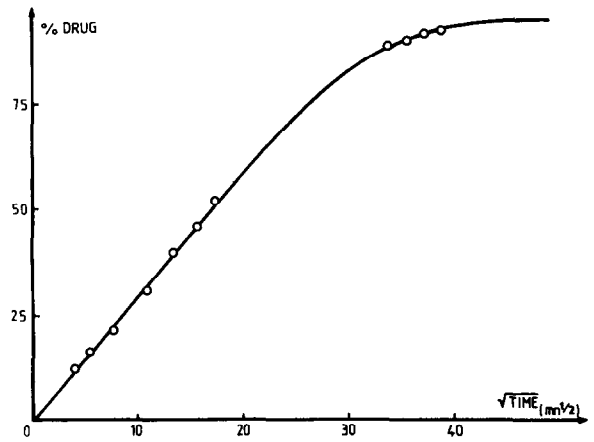

Fig. 3. Amount of drug released from the core as a function of the square root of time. 333.8 mg; $R = 0.38$ cm; Eudragit RL–sulfanilamide, 50–50% w/w.

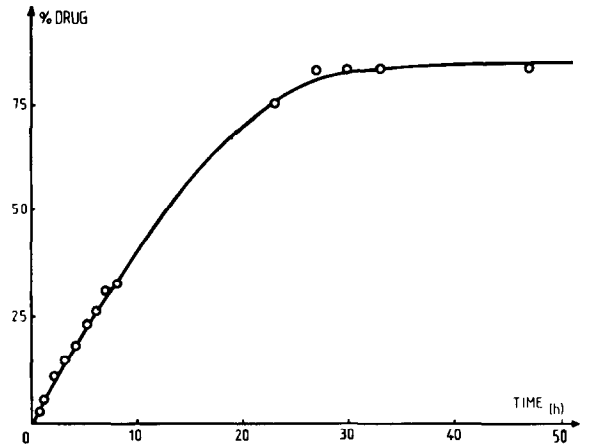

Fig. 5. Kinetics of drug released in synthetic gastric liquid from the device. Core: Eudragit RL–drug, 50–50% w/w; 396 mg; $R = 0.40$ cm. Shell: Gelucire 0.023 cm thick (29.7 mg).

liquid, only 65–70% of the drug will be released in the liquid under the same conditions (Magron et al., 1987). From this comparison, the effect of the solubility of the drug is shown to be a parameter of concern.

The rate of drug released. This is very high at the beginning of the process, and then decreases with time. The whole process is controlled by diffusion as proved by the square-root of time dependence with the amount of drug released (Fig. 3). This latter fact corresponds with a vertical value for the slope of the curve expressing the drug released as a function of time.

Devices with core and shell

The kinetics of drug released obtained with the devices made of a core and shell are shown in Figs. 4–7 with various values of the thickness of the erodible shell. The following results are worth pointing out.

The amount of drug delivered at equilibrium into the synthetic gastric liquid is around 90–95%,

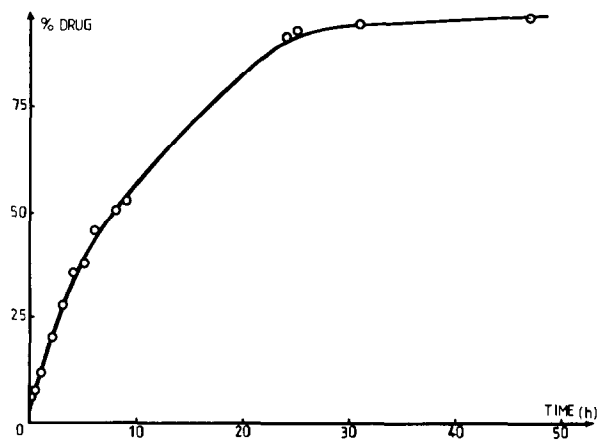

Fig. 4. Kinetics of drug released in synthetic gastric liquid from the device. Core: Eudragit RL–drug, 50–50% w/w; 368 mg; $R = 0.39$ cm. Shell: Gelucire 0.011 cm thick (17.3 mg).

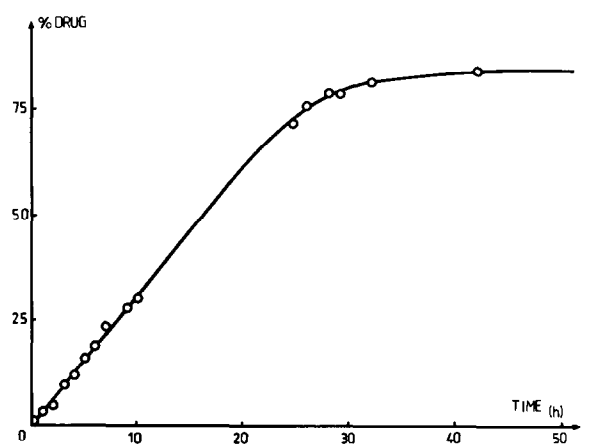

Fig. 6. Kinetics of drug released in synthetic gastric liquid from the device. Core: Eudragit RL–drug, 50–50% w/w; 373 mg; $R = 0.39$ cm. Shell: Gelucire 0.031 cm thick (46 mg).

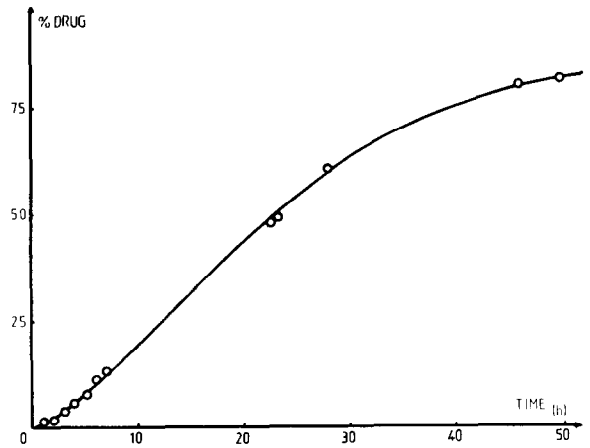

Fig. 7. Kinetics of drug released in synthetic gastric liquid from the device. Core: Eudragit RL–drug 50–50% in weight; 328 mg; $R = 0.38$ cm. Shell: Gelucire 0.050 cm thick (108 mg).

while it has been 60% in case of sodium salicylate (Magron et al., 1987).

The transfer of matter by a membrane process consists of two processes: the first, controlled by transient diffusion, followed by the second with a constant rate. The time at which the process is conducted under transient conditions is very short in the present case, and it is increased by increasing the thickness of the shell.

A constant rate of drug delivery is obtained during a very large part of the process, the time of transient diffusion being rather low.

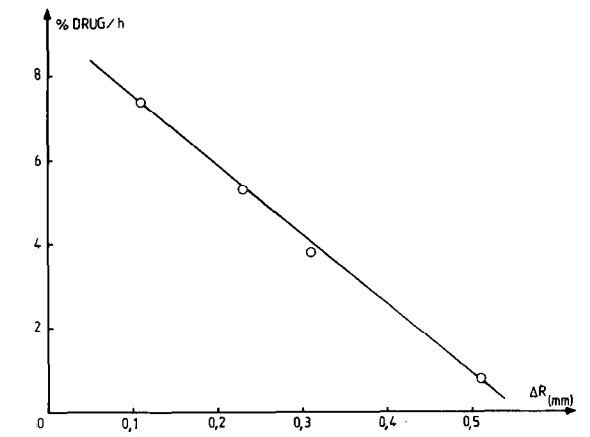

Fig. 8. Rate of drug released (% drug/h) as a function of the thickness of the shell (mm).

The rate of drug released in the liquid is inversely proportional to the thickness of the shell made of Gelucire, as shown in Fig. 8.

Theoretical attempt to describe the whole process

The whole process is very complex, with two matter transfers (the one with the liquid entering the shell and core, the other with the drug which diffuses out of the core and shell in the liquid state) and an erodible shell. A mathematical model has to take into account all these facts, and above all some information which is difficult to find from the experiments is needed for the mathematical simulation.

An attempt is made to build a simple model able to describe the whole process, and especially the drug delivery and the relationship between the thickness of the shell and the rate of drug released. A simple model is obtained by considering a spherical membrane separating two media kept at a constant concentration. In the present work, the shell made of Gelucire plays the role of the membrane.

Of course, two facts are in contradistinction to this simple model. (i) The concentration in the two media located on both sides of the shell, i.e., in the core and in the exterior liquid, is not constant. (ii) The thickness of the shell decreases during the process, because of the solubility of the Gelucire in gastric liquid.

The first assumption is not so drastic. On the one hand, the concentration of the drug in the exterior liquid remains very low during the process, even in in-vitro tests where the drug is accumulated constantly in the liquid. On the other hand, it is true that the mean concentration of the drug in the core is decreasing during the process. But the concentration of the drug on the surface of the core can be considered as about constant, because the rate of diffusion of the drug is higher in the core than through the shell, as it can be shown in comparing the kinetics obtained in Fig. 2 for the core itself and in Fig. 7 for the core and shell.

The second assumption for the membrane theory with a constant thickness of the shell is not defensible.

In fact, two main steps can be considered for the drug transfer in these kinds of galenic forms: one concerned with the transfer of the drug in the core, the other through the shell. The decrease in the concentration of the drug in the core during the process is followed by a decrease in the rate of the drug released out of the core. But this decrease in the rate of the drug in compensated by a decrease in the thickness of the shell. As a result from this compensation, a constant rate of delivery out of the dosage form is obtained.

In spite of the fact that this simple theory based on the membrane process is not fully acceptable, the actual result is of interest for determining the right value necessary for the thickness of the shell allowing the desired rate of drug delivery.

Conclusions

Oral dosage forms prepared with a core and shell were prepared and tested in synthetic gastric liquid. The main characteristics of these forms are as follows: the core is obtained by dispersing the drug in a non-erodible polymer matrix, and the shell is made of an erodible polymer.

These dosage forms are able to deliver the drug with a constant rate throughout the whole process. Moreover, the rate of delivery is inversely proportional to the initial thickness of the shell.

As a result, it is possible to prepare any dosage forms able to deliver the drug with the desired rate.

A simple model based on a spherical model is certainly criticizable from a theoretical point of view. But it remains of interest because of the relationship between the rate of delivery and the shell thickness which results from this assumption.

References

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

Brossard, C., Lefort des Ylouses, D., Duchene, D., Puisieux, F. and Cartensen, J.Y., Dissolution of a soluble drug substance from vinyl polymer matrices. *J. Pharm. Sci.*, 72 (1983) 162–169.

Crank, J., *The Mathematics of Diffusion*, 2nd edn., Clarendon, Oxford, 1975.

Droin, A., Chaumat, C., Rollet, M., Taverdet, J.L. and Vergnaud, J.M., Model of matter transfers between sodium salicylate-Eudragit matrix and gastric liquid. *Int. J. Pharm.*, 27 (1985) 233–243.

Fessi, H., Marty, J.P., Puisieux, F. and Carstensen, J.T., Square root of time dependence of matrix formulations with low drug content. *J. Pharm. Sci.*, 71 (1982) 749–752.

Focher, B., Marzetti, A., Sarto, V., Baltrame, P.L. and Carmitti, P., Cellulosic materials: structure and enzymatic hydrolysis relationships, *J. Appl. Polym. Sci.*, 29 (1984) 3329–3338.

Gurny, R., Doelker, E. and Peppas, N.A., Modelling of sustained release of water soluble drugs from porous hydrophobic polymers. *Biomaterials*, 3 (1982) 27–32.

Heilmann, K., *Therapeutic Systems' Rate-Controlled Drug Delivery; Concept and Development*, Thieme Stratton, New York, 1984.

Heller, J., Biodegradable polymers in controlled drug delivery. *CRC Crit. Rev. Therm. Drug Carrier Syst.*, I (1984) 39–90.

Liu, H., Magron, P., Bouzon, J. and Vergnaud, J.M., Spherical dosage form with a core and shell. Experiments and modelling. *Int. J. Pharm.*, in press.

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

Malley, I., Bardon, J., Rollet, M., Taverdet, J.L. and Vergnaud, J.M., Modelling of controlled drug release in case of Carbopol-sodium salicylate matrix in gastric liquid. *Drug. Dev. Ind. Pharm.*, 13 (1987) 67–81.

Messadi, D. and Vergnaud, J.M. Simultaneous diffusion of benzyl alcohol into plasticized PVC and of plasticizer from polymer into liquid. *J. Appl. Polym. Sci.*, 26 (1981) 2315–2324.

Messadi, D., Taverdet, J.L. and Vergnaud, J.M., Plasticizer migration from plasticized PVC into liquids. Effect of several parameters on the transfer. *I. E.C. Proc. Res. Dev.*, 22 (1983) 142–146.

Nicklasson, M., Brodin, A. and Sundelof, L.O., Studies of some characteristics of molecular dissolution kinetics from rotating discs. *Int. J. Pharm.*, 23 (1985) 97–108.

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

Peppas, N.A., Analysis of Fickian and non-Fickian drug release from polymers. *Pharm. Acta Helv.*, 60 (1985) 110–111.

Taverdet, J.L. and Vergnaud, J.M., Study of transfer process of liquid into and plasticizer out of plasticized PVC in using short tests. *J. Appl. Polym. Sci.*, 29 (1984) 3391–3400.

Taverdet, J.L. and Vergnaud, J.M., Modelization of matter transfers between plasticized PVC and liquids in case of a maximum for liquid–time curves. *J. Appl. Polym. Sci.*, 31 (1986) 111–122.

Teillaud, E. and Pourcelot-Roubeau, Y., Validation d'un nouveau modèle de libération in vitro. *Lab. Pharm. Probl. Techn.*, 32 (1984) 279–283.

Touitou, E. and Donbrow, M., Drug release from non-disintegrating hydrophilic matrices: sodium salicylate as a model drug. Int. *J. Pharm.*, 11 (1982) 355–364.