International Journal of Pharmaceutics, 36 (1987) 81–88
Elsevier

IJP 01211

'Dry emulsion' — a sustained release form: modelling of drug transfers in liquids

N. Farah [2], J. Bouzon [1], M. Rollet [2], J.L. Taverdet [1] and J.M. Vergnaud [1]

[1] *Laboratory of Material and Chemical Engineering, U.F.R. of Sciences, University of St. Etienne, St. Etienne (France)* and [2] *Laboratory of Galenical Pharmacy, Faculty of Pharmacy, University of Lyon I, Lyon (France)*

(Received 23 July 1986)
(Modified version received 27 October 1986)
(Accepted 7 November 1986)

Key words: Dry emulsion; Silica; Sodium salicylate; Sustained release; Spherical form; Modelling of process; Transient diffusion

Summary

A galenic form made of a dry emulsion was described and tested by considering the drug release in synthetic liquids. It was obtained by mixing the two following phases: the one with water, sodium salicylate as drug and hydrophilic silica in powder form; the other being a lipidic phase with oil and hydrophobic silica. A model, based on a numerical method with finite differences, was applied to the case of spherical samples. The theoretical results for the kinetics of drug release were in good agreement with the corresponding experimental ones. Dry emulsion exhibited a significant sustained drug release, controlled by diffusion with a constant diffusivity and a coefficient of matter transfer characterizing the retardation in the transfer on the surface.

Introduction

Recently, efforts have been directed to the development of methods for the administration of drugs, which are more effective and safer than conventional methods such as an oral administration in a chemotherapy. The development of therapeutic systems that release a controlled amount of drug over a defined time period represents an interesting pathway for optimizing drug effects through galenic measures. These therapeutic systems offer important advantages over traditional dosage forms in diseases requiring the most constant possible effective blood levels over prolonged durations of therapy. Such dosage forms can often decrease the total daily dosage of the active agent, and in so doing decrease the number and frequency of side-effects (Heilman, 1984).

The techniques used for controlling the release of drug are generally divided into three classes based on the mechanism controlling the release of drug from the device. These mechanisms are diffusion, osmosis, and polymer erosion (Feijen, 1984). Special attention was given to the method using monolithic devices where the drug was previously dispersed in a polymeric matrix, this polymer being either inert or biodegradable (Fessi et al., 1982; Touitou and Donbrow, 1982; Focher et al., 1984; Heller, 1984).

A survey of the pertinent literature pointed out that very little attention was given to galenic forms

Correspondence: J.M. Vergnaud, Laboratory of Material and Chemical Engineering, U.F.R. of Sciences, University of St. Etienne, 23 Dr. P. Michelon, St. Etienne 42100, France.

based on the use of emulsions (Berthod, 1983), and especially dry emulsions (Richter and Sterger-Trippi, 1961; Basquin et al., 1972). These dry emulsions were not so known up to the present time, but they could be of interest because of their stability, and sustained release effect.

The dry emulsion studied in this paper was obtained as follows. An emulsion of water-in-oil with the drug dissolved in the water, was prepared. The difficult problems of the drying of both phases were studied, using various techniques (Le Hir, 1983). Finally, the problem was solved as described in previous publications (Farah and Rollet, 1986; Farah et al., 1986a and b) by adding successively, firstly hydrophilic silica adsorbing the water in the dispersed phase, and secondly hydrophobic silica capable of adsorbing the excess of oil in the continuous phase. As a result, the drug emulsion was made of a great number of dry particles, each of them consisting of a hydrophilic silica grain surrounded by several smaller hydrophobic silica grains, while the drug and water were adsorbed by hydrophilic silica and the oil by hydrophobic silica.

Another purpose of this paper was to develop a model able to describe all phenomena intervening in the process of release of drug from this dry emulsion when it was soaked either in a synthetic gastric liquid or synthetic gastrointestinal liquid. Generally, the process was found to be rather complicated for the release of the material, because two different matter transfers were playing a role; the transfer of the liquid entering the material and facilitating the transfer of the plasticizer into the liquid, as shown when plasticized PVC made contact with the liquid (Messadi et al., 1983; Taverdet and Vergnaud, 1984). In the case of a device where the drug was previously dispersed in a polymer matrix, the release of drug followed the same process with an additional step concerned with the dissolution of the drug in the liquid located in the galenic form (Higuchi, 1961; Higuchi, 1963; Higuchi et al. 1983; Droin and al., 1985; Malley and al., 1986). In both of these cases, both transfers were controlled by diffusion under transient conditions (Frish, 1978; Peppas and Segot-Chicq, 1985) and very often the diffusivity was concentration-dependent (Messadi et al., 1983).

Because of the difficulty of weighing the galenic form used in the present case, we were not able to determine the kinetics of the liquid transferred into the device. So, this study was only concerned with the kinetics of the release of drug into the liquid. The model previously described for the case of sheets was applied to the present case of galenic forms which were spherical in shape and with a constant concentration of the drug. It consisted of a numerical method with finite differences, taking into account the transfer of the drug by diffusion under transient conditions with a concentration-dependent diffusivity. However, a coefficient of matter transfer had to be introduced in the model, measuring the drug transfer through the device surface–liquid interface or perhaps the lipidic phase playing the role of a thin barrier. This coefficient, already used for another purpose and in another way (Taverdet and Vergnaud, 1986) was determined by experiments.

Experimental

Materials

Sodium salicylate (Coper) in powder form was chosen for the drug.

Two kinds of silica were selected for preparing the dry emulsion: (i) the hydrophilic one concerned with the absorption of the water and drug was Tixosil 38 (Rhône-Poulenc); and (ii) the hydrophobic one for the absorption of the lipidic phase was Aerosil AE60 (Rhône-Poulenc).

The characteristics of these silica are described in Table 1, as well as those of the final dry emulsion.

Preparation of dry emulsion

The dry emulsion was obtained by the following two-step process. (i) Dispersion of hydrophilic silica into the lipidic phase, and addition of the aqueous solution of drug, under a high rate of stirring. The oil was the continuous phase of the emulsion. (ii) Addition of hydrophobic silica which adsorbed the oil, stimulating the drying of the emulsion.

At the end, a great number of dry particles of about spherical shape, were obtained. Each of

TABLE 1

Properties of silica and dry emulsion

Material	Area (m^2/g)	mean diameter	% carbone	Porosity (cm^3/g)
Tixosil 38	160	18 μm	0	0.7
Aerosil AE 60	230	0.012 μm	3.1	0
Dry emulsion	0.3	1.25–2 mm	50	0

these particles proved to be a large hydrophilic silica grain surrounded by several smaller hydrophobic silica grains (Farah and Rollet, 1986; Farah et al., 1986a and b), the drug and water being adsorbed by hydrophilic silica and the oil by hydrophobic silica.

Test for determining the rate of drug release

The rate of drug release was determined by soaking 1 g of dry emulsion in 500 ml of synthetic gastric liquid kept at the constant temperature of 37°C. The liquid was continuously stirred during the release process.

Samples of liquid was taken at intervals for analysis of the drug using a UV-spectrophotometer (Beckman).

Six experiments were carried out in each case for 6 h, with the same liquid and drug formulation.

Two liquids were chosen and tested: the one simulating a gastric liquid with a pH of 1.2, the other simulating the intestinal medium with a pH of 7.4.

Theoretical

Assumptions

The following assumptions were made: (i) the sample was spherical in shape; (ii) the spherical sample was not modified during the test, as shown by experiments; (iii) the drug transfer was controlled by diffusion under transient conditions, with a constant diffusivity; (iv) the liquid transfer into the sample was not considered; and (v) a coefficient characterizing the drug transfer through the liquid–sample interface was introduced in the paper.

Mathematical treatment

Fick's laws describing the matter transfer by diffusion were considered, for the case of a spherical sample with a constant diffusivity:

$$J = -D \cdot \frac{\partial C}{\partial x} \tag{1}$$

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

The initial and boundary conditions were described by Eqns. 3 and 4:

$$t = 0 \quad 0 < r < R \quad C = C_i \quad \text{sample} \tag{3}$$

$$t > 0 \quad 0 < r < R \quad C = C_{r,t} \quad \text{sample} \tag{4}$$

Analytical solutions could be found for the simple case when the diffusivity was constant, and the concentration of drug on the surface of sample was zero as soon as it was soaked in the liquid (Cranck, 1975).

$$\frac{M_\infty - M_t}{M_\infty} = \frac{6}{\pi^2} \cdot \sum_{n=1}^{\infty} \frac{1}{n^2} \cdot \exp\left(-\frac{n^2 \cdot \pi^2 \cdot D \cdot t}{R^2}\right) \tag{5}$$

where M_t and M_∞ was the amount of drug released at time t and at infinite time, respectively. R was the radius of the sphere, n was an integer.

The series shown in Eqn. 5 was available for long and short tests. For very short tests, a simple equation was used (Crank, 1975):

$$\frac{M_t}{M_\infty} = \frac{1}{6} \cdot \left(\frac{D \cdot t}{\pi}\right)^{0.5} \tag{6}$$

Numerical analysis

As no analytical solution could be found for the case at hand, especially because of the coefficient of matter transfer at the liquid–sample interface, the problem had to be solved with the help of a numerical method with finite differences.

By considering the spheres with the following radius, $r+\Delta r$, r, $r-\Delta r$, and assuming that the concentration of drug was constant throughout the little interval Δr during the increment of time Δt (Fig. 1), the balance of matter enabled us to find the following.

Inside the sample:

$$CN(j) = C(j) + \frac{\Delta t}{2(\Delta r)^2 \cdot \left(j^2 + \frac{1}{12}\right)} \cdot [G(j+1) - G(j)] \quad (7)$$

the function being expressed as

$$G(j) = \left(j - \tfrac{1}{2}\right)^2 \cdot [D(j) + D(j-1)] \cdot [C(j) - C(j-1)] \quad (8)$$

where j was an integer (0, 1, 2,... n) defining the value of the radius of the sphere.

$$r = j \cdot \Delta r \quad \text{and} \quad \Delta r = \frac{R}{n} \quad (9)$$

In Eqn. 7, $CN(j)$ and $C(j)$ were the concentrations of the drug at the position r taken at the time $(i+1)\Delta t$ and $i \cdot \Delta t$, respectively, i being an integer for the time.

Middle of the sample:

As Eqn. 7 was not determined for the middle of the sphere ($r = 0$), the matter balance written for the sphere of radius $\Delta r/2$ enabled one to obtain:

$$CN(0) = C(0) + 12\frac{\Delta t}{(\Delta r)^2} \cdot G(1) \quad (10)$$

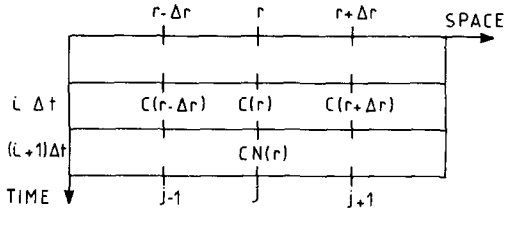

Fig. 1. Space–time diagram for calculation of concentration of drug. Explicit method with finite differences.

where $CN(0)$ and $C(0)$ were the concentration of drug at the middle of the sample ($r < \Delta r/2$).

Surface of the sample:

Following the vth assumption, a coefficient of matter transfer was considered at the liquid–sample interface, h.

The concentration on the surface of the sample was obtained by determining the matter balance within the spheres of radius R and $R - \Delta r/2$

$$CN(R) = C(R) + \frac{3 \cdot \Delta t \cdot R^2 \cdot h}{R^3 - \left(R - \frac{\Delta r}{2}\right)^3} \cdot [C_e - C(R)] - \frac{3 \cdot \Delta t \cdot \left(R - \frac{\Delta r}{2}\right)^2}{2\Delta r \cdot \left[R^3 - \left(R - \frac{\Delta r}{2}\right)^3\right]} \cdot [D(R) + D(R - \Delta r)] \cdot [C(R) - C(R - \Delta r)] \quad (11)$$

The coefficient of matter transfer h was obtained from the following equation, expressing the rate of the drug release at the beginning of the process.

$$\left(\frac{dM}{dt}\right)_{t=0} = 4\pi R^2 \cdot h \cdot (C_e - C_{in}) \quad (12)$$

where C_e was the concentration of drug at equilibrium and C_{in} the initial concentration of drug.

Remaining amount of drug in the sample

The amount of the drug remaining in the sample at any time t could be obtained by integrating the concentration of the drug in the spherical sample.

$$M_t = \int_0^R 4\pi r^2 \cdot C(r, t)\, dr \quad (13)$$

In our case, with the numerical method with finite differences, the amount of remaining drug

was expressed by Eqn. 14.

$$M_t = 4\pi(\Delta r)^3 \cdot \left[\frac{C(0)}{24} + \sum_{j=1}^{n-2} j^2 \cdot C(j) + \tfrac{9}{8}(n-1)^2 \cdot C(n-1) + \tfrac{3}{8}n^2 \cdot C(n) \right] \quad (14)$$

where the contribution of the small sphere of radius $\Delta r^2/2$, the spherical part between R and $R - \Delta r/2$ and all the other spheres of radius r, $r + \Delta r$, could be seen.

Results

After having determined the data useful for calculation, i.e. the diffusivity and the coefficient of matter transfer at the surface of the sample, the model was built and then tested by comparing the kinetics of drug release in the liquid obtained either from experiment or from calculation.

Determination of kinetic parameters

It was difficult to determine the diffusivity corresponding with the transfer of drug by using short tests (Taverdet and Vergnaud, 1984) because of the presence of the coefficient of matter transfer. So, we calculated this parameter by using the data obtained from experiments for very long times and the Eqn. 5. Some curves drawn in Fig. 2

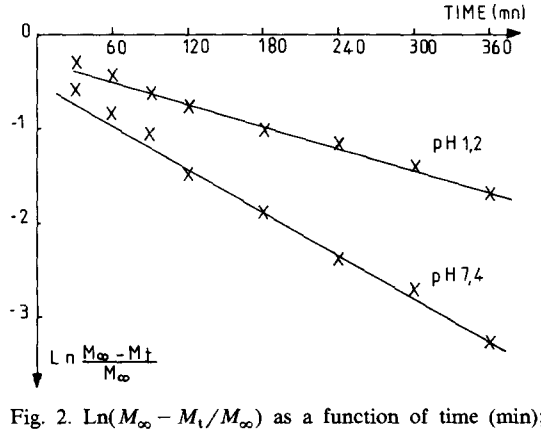

Fig. 2. $\mathrm{Ln}(M_\infty - M_t/M_\infty)$ as a function of time (min); for various initial concentrations of the drug for two various values of the pH (1.2–7.4), 37°C.

showed straight lines for two series of experiments carried out with two pH values. So in both these cases, the diffusivity for the drug could be considered as constant for each pH value.

Building of the model

Some observations were made on our sample with the help of electron microscopy and nitrogen adsorption measurements.

Fig. 3A shows a scanning electron micrograph of the drug and hydrophilic silica, and Fig. 3B the dry emulsion we have studied. The presence of the drug in crystal form can be observed in Fig. 3A, while no drug could be seen on the surface of the dry emulsion.

The total area and porosity of hydrophilic silica (Tixosil 38) and of the dry emulsion were determined from the amount of nitrogen physically adsorbed on this material at the temperature of boiling nitrogen, by using the well-known B.E.T. technique and the adsorption isotherm (Pommier et al., 1972). As shown in Table 1, the area and porosity of the dry emulsion were very low with regard to those of hydrophilic and hydrophobic silicas. This fact was probably due to the presence of oil in the pores of the hydrophobic silica (Aerosil AE 60) located on the surface of the dry emulsion, reducing the area and porosity of this silica to a significant extent.

On the other hand, the kinetics of the release of drug was especially studied by considering the following various materials: (i) the drug in powder form; (ii) the dry emulsion made of hydrophilic silica with the drug adsorbed on it, surrounded with hydrophilic silica saturated with oil. This emulsion was prepared in the same way as our dry emulsion; (iii) our dry emulsion. The only difference between the two dry emulsions described here is in the characteristic of the silica contacting the oil. Unlike case (iii), hydrophobic silica was used in case (iii).

TABLE 2

Kinetic parameters obtained from experiments

pH	D (cm^2/s)	h (cm/s)
1.2	4.2×10^{-8}	11.3×10^{-6}
7.4	8.3×10^{-8}	20.4×10^{-6}

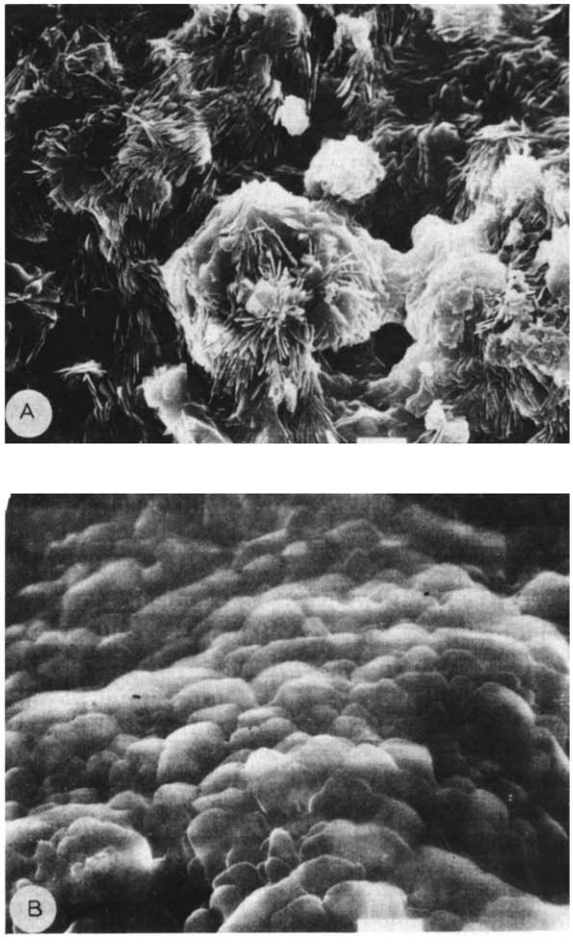

Fig. 3. Scanning electron micrographs. A: hydrophilic silica + drug (×800) B: surface of dry emulsion (×1000).

The results shown in Fig. 4 were of interest. The release of the drug itself was quite immediate, following its solution in water.

The release of the drug from our dry emulsion was found to exhibit a retarding effect with regard to the release of the drug obtained from the dry emulsion with hydrophilic silica (ii).

Validity of the model

The above results obtained by various techniques and observations (scanning electron micrography, surface measurements, kinetics of drug release), could convincingly bring us to the following scheme for our dry emulsion. As illustrated in Fig. 5 (Farah et al., 1986a and b), the elementary

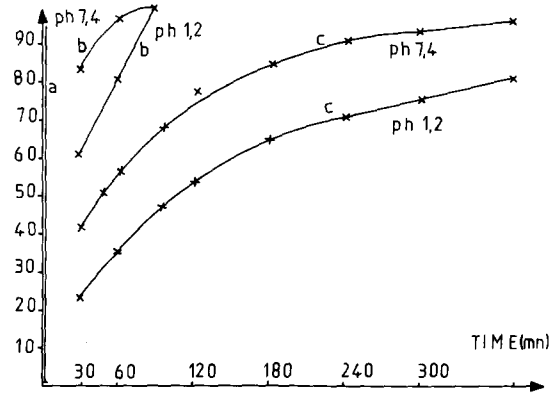

Fig. 4. Kinetic of release of drug in two liquids of various pH's (1.2–7.4). a = drug in powder form; b = drug deposited (adsorbed) on hydrophilic silica surrounded with oil; c = drug in the dry emulsion used in the paper.

particle of our dry emulsion could be described as: a hydrophilic silica particle containing the drug and water, and several hydrophobic silica particles saturated with oil, surrounding the hydrophobic silica, thus playing the role of hydrophobic coating with the lipidic phase.

The model was built in the theoretical part by considering this scheme.

The kinetic of the drug release in the liquid obtained either from experiments and from calculation by using the model, were drawn in Fig. 6, for two various values of the pH of the liquid and for the dry emulsion ranging from 1.25 to 2 mm. These curves enabled one to appreciate the validity of the model exhibited in these cases.

By considering the effect of the dry emulsion on the release of the drug, we could appreciate an interesting sustained drug release. Moreover, the stability of this galenic form would be of help for the development of this material.

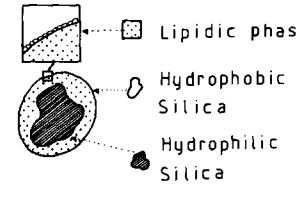

Fig. 5. Illustration of the shape and appearance of a unit of the drug emulsion.

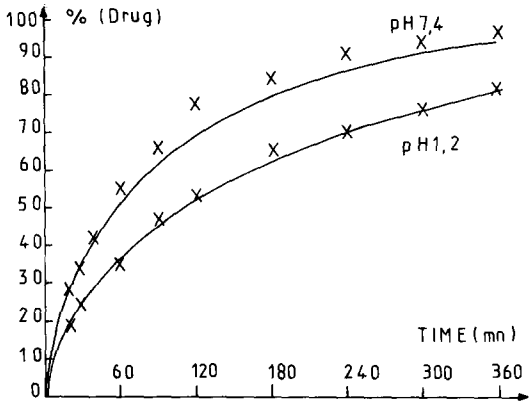

Fig. 6. Validity of the model for the transfer of sodium salicylate for two different pH's (1.2–7.4), 37°C. ———, calculated; ×, experimental.

Conclusions

Another galenic form, with dry emulsion, was especially studied in this paper, by considering the preparation of this material and also the kinetics of the drug release. This dry emulsion was obtained by mixing the following two phases: the one with water and sodium salicylate as drug and an hydrophilic silica, the other with a hydrophobic silica and oil. The final dry emulsion was shown to exhibit an interesting drug release in two different liquids with pH of 1.2 (synthetic gastric liquid) and of 7.4 (intestinal liquid).

A model, based on a numerical method with finite differences, was built by considering that the samples were spherical in shape. The drug transfer was found to be controlled by diffusion under transient conditions with a constant diffusivity and with a coefficient of matter transfer at the liquid–material interface. The kinetics of drug release obtained by experiments and calculation were in good agreement, proving the validity of the model.

Acknowledgements

Thanks are due to the Pasteur Institute, Lyon, and especially to Dr. Jolly, for the scanning electron micrographs.

References

Basquin, S., Guyot, A.M., Guyot, J.C. and Traisnel, M., Stabilité des arômes de fruits rouges en fonction du support, *Bull. Soc. Pharm. Lille*, 4 (1972) 155–169.

Berthod, A., La tensioactivité, physico-chimie des interfaces liquides. *Labo Pharma*, 333 (1983) 525–530.

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

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

Farah, N. and Rollet, M., Nouveaux procédés de préparation, à partir d'émulsions sèches, de formes crales solides à libération modifeé et retardée de leurs principes actifs. *French Patent*, no. 8602694 (1986).

Farah, N., Chaumat, C., Bardon, J., Sébert, P. and Rollet, M., Utilisation de différentes variétés de silice dans l'obentention d'"Emulsions sèches", *4ème Congrès International de Technologie Pharmaceutique, APGI, Paris, 3–5 Juin*, 1986a.

Farah, N., Rollet, M. and Berthod, A., Etude d'une préparation galénique: l'émulsion adsorbée sèche. Structure physico-chimique et effet sur la libération d'un principe actif hydrosoluble, *STP Pharma France*, (1986b), in press.

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

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.

Frisch, H.L., Simultaneous nonlinear diffusion of a solvent and organic penetrant in a polymer, *J. Appl. Polym. Sci.*, 16 (1978) 1651–1664.

Heilmann, K., *Therapeutic Systems Rate-Controlled Drug Delivery: Concept and Development*, Thième Stratton, New York, 1984.

Heller, J., Biodegradable polymers in controlled drug delivery, *CRC Crit. Rev. Ther. Drug Carrier Systems*, 1 (1984) 39–90.

Higuchi, T., Rate of release of medicaments from ointment bases containing drugs in suspension. *J. Pharm. Sci.*, 50 (1961) 874–875.

Higuchi, T., Mechanism of sustained action medication. *J. Pharm. Sci.*, 52 (1963) 1145–1149.

Higuchi, W.I., Ho., N.F.A. and Merkle, H.P., Design of oral drug delivery systems: past, present and future. *Drug Dev. Ind. Pharm.*, 9 (1983) 1227–1239.

Le Hir, A., *Abrégé de Pharmacie Galénique*, 4ème ed., Masson, Paris. (1983) pp. 141–163.

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.*, (1986), in press.

Messadi, D., Taverdet, J.L. and Vergnaud, J.M., Plasticizer

migration from plasticized PVC into liquids. Effect of several parameters on the transfer, *I and EC Product Res. Dev.*, 22 (1983) 142–146.

Peppas, N.A. and Segot-Chicq, S., Les dispositifs à libération contrôléé pour la délivrance des principes actifs médicamenteux. Modélisation des mecanismes diffusionnels. *STP Pharma*, 1 (1985) 208–216.

Pommier, B., Juillet, F. and Teichner, S., Appareillage pour la détermination de l'adsorption physique d'un gaz per une méthode chromographique dynamique, *Bull. Soc. Chim. Fr.*, (1972) 1268–1270.

Richter, A. and Sterger-Trippi, K., Untersuchungen über die zerstaubungstrocknung von emulgierten Arzneizubereitungen. *Pharm. Acta Helv.*, 36 (1961) 332–336.

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 maximum for liquid–time curves. *J. Appl. Polym. Sci.*, 31 (1986) 111–122.

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