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Invited Review

Liquid transport controlled release processes in polymeric materials: Applications to oral dosage forms

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Summary

Polymers are being more widely used in many various applications, especially in pharmacy for the preparation of oral dosage forms, with controlled release of the drug. The drug is dispersed in the polymer which plays the role of a matrix, and one or two polymers can be used for the same dosage form, each polymer conferring a particular property. The process of release of the drug is rather complex. The gastric (or intestinal) liquid enters the polymer, dissolves the drug, and thus enables the drug to leave the dosage form through the liquid located in the polymer. These two matter transfers (liquid, drug) are controlled by transient diffusion. Moreover, the diffusivity of the drug is generally expressed in terms of the concentration of the liquid in the polymer. No mathematical treatment is effective, and numerical methods based on finite differences must be used to resolve the problem. Such numerical methods must take into account all the known facts. Generally, they are very efficient, and are able not only to predict the kinetics of release of the drug but also to determine the concentration profiles of both the liquid and the drug in the dosage form.

1. Introduction

Conventional dosage forms consist of drug (the active agent) and auxiliary substances called excipients (gelatin, lactose, starch, paraffin, etc.) which are used for binding the drug in order to ensure consistency and volume of supply in a form suitable for use by patients. As the drug is very rapidly liberated because of the high rate of dissolution, its concentration in gastric liquid increases considerably, and then falls exponentially due to absorption through the gastric membrane. As a result, undulations are exhibited by the pattern of behaviour of the drug concentration in the stomach, as well as in the blood and tissues. As a consequence, the optimal therapeutic level is attained only for a short time at any place in the body, and the treatment period is essentially occupied by overdosage and underdosage.

New therapeutic systems may release the drug at a constant rate over a given period of time, and thereby offer important advantages over conventional dosage forms. Many of these systems are made by dispersing the drug in a polymer playing the role of a matrix. The choice of the polymer is important, since it must be biocompatible, erodible or not, capable of being pressed into a given shape, and also able to absorb the gastric liquid and sometimes the intestinal liquid. The process

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of drug release is rather complex, and was elucidated in this way with the use of a non-erodible polymer (Droin et al., 1985; Armand et al., 1987; Malley et al., 1987): the liquid enters the polymer, dissolves the drug, and thus allows the dissolved drug to leave the dosage form through the liquid located in the polymer. These two transfers are controlled by transient diffusion, and generally the diffusivity of the drug depends not only on the concentration of the drug but also on the concentration of the liquid located in the polymer. The problem is thus rather complicated. In this case, the release of the drug is controlled by transient diffusion, and the kinetics follows a typical pattern with a rapid rate at the beginning of the process which continuously decreases with time.

Other more sophisticated devices have been constructed by using two types of polymers, with a core and shell (Magron et al., 1987; Liu et al., 1988; Laghoueg et al., 1989; Vergnaud, 1990). The core is prepared by dispersing the drug in a non-erodible polymer, thus being surrounded by a spherical membrane composed of an erodible polymer such as Gelucire (Gattefossé, 1983). The process of release of the drug is very complex, and to date, only simple models have described the process. Generally, with Gelucire, a constant rate of delivery of the drug is achieved, this rate being proportional to the relative thickness of the spherical membrane (Magron et al., 1987; Liu et al., 1988; Laghoueg et al., 1989; Vergnaud, 1990).

As the polymer plays the role of the matrix through which the liquid diffuses in the earlier stage of the process, it is of interest to gain a thorough knowledge on this process.

Diffusion of a Liquid in a Polymer

Generally diffusion is the process through which a liquid (or gas) is transferred from one place to another, as a result of random molecular motions. Of course, on average, the matter is transferred by diffusion from the region of higher to that of lower concentration of the liquid. In 1855, Fick put diffusion on a quantitative basis by adopting the same equation as that derived a few decades ago by Fourier for heat conduction. The rate of transfer of diffusing substance F through unit area of a section is proportional to the gradient of concentration measured normal to this section:

$$F = -D \cdot \partial C/\partial x \tag{1}$$

If the flux of transfer F and the concentration are expressed with the same unit of quantity, e.g., the diffusivity is independent of this unit and has the dimensions:

$$\text{length}^2 \cdot \text{time}^{-1} \text{ or } \text{cm}^2/\text{s} \tag{2}$$

A polymer can be in either the glassy or the rubbery state, depending on the temperature. Below the temperature of glassy transition, T_g the polymer is in the glassy state, and above, in the rubbery state. Diffusion of a liquid differs appreciably when it goes through a glassy or a rubbery polymer. Segments of the polymer chain are continually in motion, in the same way as Brownian motion of gases, creating voids. As the volume of these voids is of the same magnitude as that of a molecule of liquid, these motions enable this molecule to go through the polymer. Polymers have a wide spectrum of relaxation times associated with these structural changes. An increase in temperature or in concentration of liquid generally enhances the motion of the polymer segments and decreases the relaxation time.

Polymer in rubbery state (case I)

A polymer in the rubbery state responds rapidly to changes in its condition. The polymer chains adjust very quickly to the presence of the molecule of liquid. The rate of diffusion of the liquid is much less than that of relaxation of the segments of the polymer. The diffusion is Fickian, and the amount of liquid transferred at time t, M_t, varies linearly with the square root of time:

$$M_t = k \cdot \sqrt{t} \tag{3}$$

where k is constant depending on the amount of liquid transferred after infinite time, M_∞, the shape of the polymer and the diffusivity.

Polymer in glassy state (case II)

In a polymer in the glassy state, the stress may be slow to decay after the polymer has been stretched. Thus, the relaxation process is very slow compared with the rate of diffusion. The liquid diffuses through the polymer with a constant velocity, showing an advancing front which marks the limit of penetration of the liquid. Behind this advancing front of the liquid, the polymer may turn into a swollen gel or rubber polymer, while ahead of this front the polymer is in the glassy state. The amount of liquid sorbed at time t, M_t, is given by:

$$M_t = k \cdot t \tag{4}$$

Absorption of liquid in case III

When the rates of diffusion of the liquid and of the relaxation of the polymer are of the same order of magnitude, anomalous or non-Fickian diffusion is observed. This system is intermediate between cases I and II, and the amount of liquid sorbed at time t, M_t, is:

$$M_t = k \cdot t^n \tag{5}$$

where n is between 1/2 (case I) and 1 (case II).

Mathematical Treatment of Fickian Diffusion in the Case of a Sphere

Generally, the polymers which are used for a matrix in the dosage forms are in the rubbery state (case I), and the diffusion is Fickian (Vergnaud, 1990).

The mathematical treatment of diffusion is only feasible when the diffusivity is constant, and when the initial and boundary conditions are not excessively complex.

The general equation of diffusion for a sphere, when the diffusion is radial, is:

$$\frac{\partial C}{\partial t} = D \cdot \left[\frac{\partial^2 C}{\partial r^2} + \frac{2}{r} \cdot \frac{\partial C}{\partial r} \right] \tag{6}$$

where r is the radial abscissa.

The initial conditions are:

$$\begin{array}{llll} t = 0 & 0 < r < R & C_{in} & \text{sphere} \\ & r > R & C_{ext} & \text{surrounding} \end{array} \tag{7}$$

and the boundary conditions depend essentially on the rate h at which the liquid is transferred at the liquid-polymer interface and on the volume of the surrounding atmosphere.

$$t > 0 \quad r = R \quad C = C_{ext} = C_\infty \qquad \text{very high } h \tag{8}$$

$$t > 0 \quad r = R \quad -D \cdot \frac{\partial C}{\partial r} = h(C_{ext} - C_s) \qquad \text{finite } h \tag{9}$$

Eqn 9 expresses that the rate of transfer of liquid at the surface of the spherical polymer is constantly equal to the rate at which the liquid enters the polymer by diffusion. The rate of transfer is also proportional to the coefficient of matter transfer h and to the difference between the external concentration and the surface concentration. Since there is very often a partition factor of the liquid between the polymer and the liquid K:

$$K = \frac{\text{concentration in the polymer}}{\text{concentration in the liquid}} \tag{10}$$

it is better to consider C_{ext} as the concentration of liquid in the polymer which is at equilibrium with the surrounding.

Very high coefficient of matter transfer on the surface

When this coefficient is very high, the concentration on the surface reaches the value at equilibrium as soon as the process starts. The boundary conditions are thus expressed by Eqn. 8.

In this case, the concentration distribution of the liquid in the sphere is obtained by the method of separation of variables:

$$\frac{C_{r,t} - C_{in}}{C_\infty - C_{in}} = 1 + \frac{2R}{\pi r} \cdot \sum_{n=1}^{\infty} \frac{(-1)^n}{n} \cdot \sin \frac{n\pi r}{R} \cdot \exp\left(-\frac{n^2 \pi^2}{R^2} Dt \right) \tag{11}$$

and, at the centre, this equation becomes, as $\frac{\sin x}{x} \to 1$ when $x \to 0$:

$$\frac{C_{0,t} - C_{in}}{C_\infty - C_{in}} = 1 + 2 \cdot \sum_{n=1}^{\infty} (-1)^n \cdot \exp\left(-\frac{n^2\pi^2}{R^2} Dt\right) \tag{12}$$

The total amount of liquid entering or leaving the sphere at time t, M_t, is expressed as a fraction of the corresponding quantity after infinite time, M_∞, by the relation:

$$\frac{M_\infty - M_t}{M_\infty} = \frac{6}{\pi^2} \cdot \sum_{n=1}^{\infty} \frac{1}{n^2} \exp\left(-\frac{n^2\pi^2}{R^2} Dt\right) \tag{13}$$

The concentration can also be determined by the Laplace transform, and is thus expressed in terms of the error function:

$$\frac{C_{r,t} - C_{in}}{C_\infty - C_{in}} = \frac{R}{r} \cdot \sum_{n=0}^{\infty} \left[\operatorname{erfc} \frac{(2n+1)R - r}{2\sqrt{Dt}} - \operatorname{erfc} \frac{(2n+1)R - r}{2\sqrt{Dt}}\right] \tag{14}$$

and the amount of liquid entering or leaving the sphere is thus:

$$\frac{M_t}{M_\infty} = \frac{6\sqrt{Dt}}{R}\left[\frac{1}{\sqrt{\pi}} + 2 \cdot \sum_{n=1}^{\infty} i\operatorname{erfc} \frac{nR}{\sqrt{Dt}}\right] - 3\frac{Dt}{R^2} \tag{15}$$

Eqns 11–13 are of special interest for long times, and for $M_t/M_\infty > 0.8$, there is the well-known relation

$$\frac{M_\infty - M_t}{M_\infty} = \frac{6}{\pi^2} \cdot \exp\left(-\frac{\pi^2}{R^2} Dt\right) \tag{16}$$

as the first term of the series becomes preponderent.

Eqns 14 and 15 are of interest for short times. As the series in Eqn 15 vanishes for short times, there is:

$$\frac{M_t}{M_\infty} = \frac{6}{R}\sqrt{\frac{Dt}{\pi}} \quad \text{or} \quad \frac{M_t}{M_\infty} = \frac{6}{R}\sqrt{\frac{Dt}{\pi}} - 3\frac{Dt}{R^2} \tag{17}$$

depending on the desired accuracy.

Finite coefficient of matter transfer on the surface

When this coefficient is not very high, the boundary condition is given by Eqn. 9. The profile of concentration in the sphere is thus given by:

$$\frac{C_{r,t} - C_\infty}{C_{in} - C_\infty} = \frac{2PR}{r} \cdot \sum \frac{1}{\beta_n^2 + P^2 - P} \frac{\sin \beta_n \frac{r}{R}}{\sin \beta_n} \cdot \exp\left(-\frac{\beta_n^2}{R^2} Dt\right) \tag{18}$$

where the β_ns are the roots of

$$\beta_n \cdot \cot \beta_n + P - 1 = 0 \tag{19}$$

and the dimensionless number

$$P = \frac{h \cdot R}{D} \tag{20}$$

The total amount of liquid entering or leaving the sphere is expressed by:

$$\frac{M_\infty - M_t}{M_\infty} = \sum_{n=1}^{\infty} \frac{6P^2}{\beta_n^2\left[\beta_n^2 + P^2 - P\right]} \exp\left(-\frac{\beta_n^2}{R^2} Dt\right) \tag{21}$$

Some roots of Eqn 19 have been given (Vergnaud, 1990).

Numerical Treatment of Diffusion in the Case of a Sphere

When the diffusivity is concentration-dependent, a numerical treatment with finite differences

is necessary to resolve the problem. The sphere is divided into spherical membranes with the same thickness Δr, and the centre of each membrane is associated with an integer n. By evaluating the matter balance during the increment of time Δt within the spherical membrane of radius r, with the integer n, the new concentration after elapse of time Δt in this membrane can be expressed as a function of the previous concentration at the same and adjacent places.

$$CN_n = C_n + \frac{\Delta t}{n^2 \cdot (\Delta r)^2}[j_{n-0.5} - J_{n+0.5}] \qquad (22)$$

by putting the function J

$$J_{n-0.5} = (n-0.5)^2 \cdot D_{n-0.5}(C_{n-1} - C_n) \qquad (23)$$

At the centre of the sphere, the new concentration is given by:

$$CN_0 = C_0 + \frac{24 \cdot \Delta t}{(\Delta r)^2} J_{0.5} \qquad (24)$$

When the coefficient of matter transfer is very high, i.e., when $P = h \cdot R/D$ is high, the concentration on the surface is C_∞ as soon as the process starts.

When the coefficient of matter transfer is finite, and when $h \cdot R/D$ is not high, the new concentration on the surface is given by:

$$CN_N = C_N + \frac{2 \cdot \Delta t}{(N-0.5)^2 \cdot (\Delta r)^2} J_{N-0.5} - \frac{N^2 \cdot \Delta t}{(N-0.25)} \cdot \frac{2h}{\Delta r}(C_N - C_\infty) \qquad (25)$$

The amount of liquid located in the sphere is obtained by integrating the concentration of liquid with respect to space:

$$M_t = 4\pi(\Delta r)^3 \cdot \left[\frac{C_0}{24} + \sum_{n=1}^{N-2} n^2 \cdot C_n + \tfrac{9}{8}(N-1)^2 \cdot C_{N-1} - \tfrac{3}{8}N^2 \cdot C_n\right] \qquad (26)$$

Results

Some results have been reported for a dosage form made of sodium salicylate dispersed in Eudragit®, a copolymer of dimethylaminoethylacrylate and ethylmethacrylate (Röhm Pharma), when immersed in gastric liquid (Armand et al., 1987) during in vitro tests.

The diffusivities of the liquid and of the drug were found to be as follows:

$$D_l = 4.3 \times 10^{-6} \quad (\mathrm{cm^2/s}) \quad \text{liquid}$$

$$D_d = 6 \times 10^{-3} \times \exp - \frac{400}{C_l} \quad (\mathrm{cm^2/s}) \quad \text{drug}$$

The kinetics of the two matters transferred (liquid and drug) obtained either from experiments and by calculation with the numerical model are plotted in Fig. 1. As shown by these curves, good agreement is demonstrated, proving the validity of the model. Other information is of interest. The rate of absorption is higher for the liquid than for the drug. A vertical tangent is obtained for the kinetic curve of the liquid, expressing a high rate of absorption at the beginning of the process.

The model is also capable of calculating the profiles of concentration of the liquid and drug

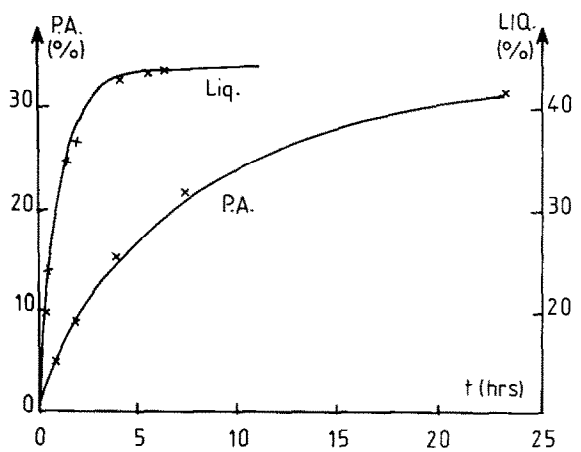

Fig. 1. Kinetics of the matter transferred (drug: PA, liquid). Drug/polymer, 50:50 Wt%; radius, 0.435 cm; pH 1.2 at 37°C. (+) Experiments; (———) calculated.

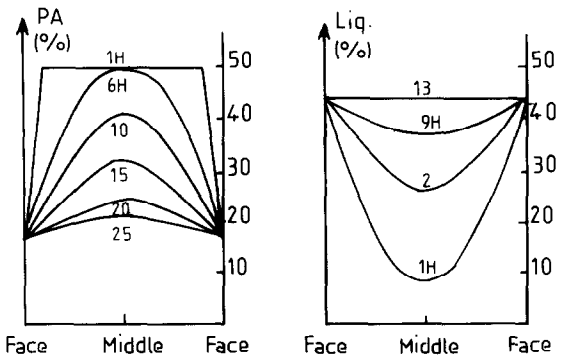

Fig. 2. Profiles of concentration developed within the dosage form. (Left) drug (PA); (right) liquid. Drug/polymer, 50–50 wt%; radius, 0.435 cm; pH 1.2 at 37°C.

developed within the sphere during the process (Fig. 2).

Some conclusions of interest can be drawn:

(i) Only a part of the drug is released from the dosage form. This is due to the fact that the volume of gastric liquid is low in the in vitro test, and the process is limited by the solubility.

(ii) The concentration on the surface reaches the value at equilibrium, as the coefficient of matter transfer on the surface h is high.

Conclusions

The process of delivery of the drug from a dosage form with a polymer matrix is rather complex, and the polymer plays an important role.

The mathematical treatment is feasible only when the diffusivity is constant. Two cases are considered:

(i) When the coefficient of matter transfer on the surface of the dosage form is very high, and the concentration at equilibrium is attained as soon as the process starts.

(ii) When this coefficient of matter transfer is not very high. This mathematical treatment is of interest for determining the diffusivity of the liquid which enters the dosage form.

The numerical treatment must be made when the problem is complex, and especially in the case of a dosage form where the transfers of the liquid and drug are coupled with each other, the diffusivity of the drug depending on the concentration of the liquid.

These numerical models are versatile, and they can be used in various cases by taking all the known facts into account.

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 galenic forms with Eudragit matrix. *Int. J. Pharm.*, 40 (1987) 33–41.

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.

Gattefosse, Gelucire puts liquid formulation into hard gelatin capsules, Private paper (1983).

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

Liu, H., Magron, P., Bouzon, J. and Vergnaud, J.M., Spherical dosage form with a core and shell. Experiments and modeling, *Int. J. Pharm.*, 45 (1988) 217–227.

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.

Vergnaud, J.M., Drug delivery and pharmaceutical applications. In *Liquid Transport Processes in Polymeric Materials. Modelling and Industrial Applications*, Prentice Hall, New York, 1990, Chap. 10, pp. 211–290.