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Modelling the process of drying of dosage forms made of drug dispersed in a polymer

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Summary

The phenomenon of drying of dosage forms is studied and models are constructed to describe the process. The dosage forms, spherical in shape, consist of a drug dispersed in a polymer matrix such as Eudragit. Ethanol is used to form a paste of the mixture which is pressed into beads, and it must be evaporated from the beads. The process of drying is complex, being controlled by diffusion through the polymer, and evaporation from the surface. The diffusivity in the present case is constant; the rate of evaporation is proportional to the difference between the actual concentration of liquid on the surface and the concentration which is at equilibrium with the surrounding atmosphere, the coefficient of proportionality being the rate of evaporation of the pure liquid under the same conditions. An analytical solution and a numerical model taking into account all these facts, describe the process very well, the kinetics of drying obtained by calculation being the same as the experimental ones.

Introduction

Efforts have been directed to the study of methods for the administration of drugs, which are more effective and safer than conventional methods (Heilman, 1984). Controlled release techniques have thus been developed, by using essentially the mechanisms of diffusion, osmosis and polymer erosion. Special attention was focused on regulating the amount of drug released by means of monolithic devices obtained by dispersing the drug in an inert polymer matrix. Both nondegradable and biodegradable polymers have been utilized for this purpose (Fessi et al., 1982; Touitou and Donbrow, 1982; Focher et al., 1984; Heller, 1984).

Various ways exist for preparing these monolithic devices, and three of them are worth noting:

(i) by compression of the materials in powder form either at room or at higher temperature (Droin et al., 1985; Malley et al., 1987);

(ii) by melting the mixture or at least the matrix alone (Magron et al., 1987; Laghoueg et al., 1989);

(iii) by using a way based on humidity, in making a paste of the polymer matrix in the mixture by using a liquid in which the drug is not soluble; the paste is then easy to shape into beads

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(Armand et al., 1987; Liu et al., 1988; Saber et al., 1988).

There are some advantages and drawbacks for each of these techniques. For instance, the last technique does not need a high pressure and high temperature to shape the bead; there is an inconvenience with the drying of the dosage form.

The main purpose of this paper is to study the process of drying of these dosage forms, when the polymer is Eudragit, a biocompatible polymer. Spherical beads are used, but the results can be applied to other shapes. The process of drying a polymer or a solid is not simple. As shown in previous studies carried out with elastomers of various shapes such as thin sheets (Khatir et al., 1986), cylinders of finite length (Khatir et al., 1987), the process is controlled by diffusion through the solid and by evaporation from the surface.

Another aim in this study is to build up a mathematical and a numerical model able to describe the process. The second model, based on a numerical method with finite differences, can be used when the diffusivity is concentration-dependent, while the first needs a constant diffusivity. With the two models, the rate of evaporation is proportional to the difference between the concentration of liquid on the surface and the concentration which is at equilibrium with the surrounding atmosphere, while the coefficient of proportionality is the rate of evaporation of the pure liquid under the same conditions. Some emphasis is placed in determining the effect of parameters such as the radius of the bead and the diffusivity of the liquid on the rate of drying.

Experimental

Preparation of dosage forms

Eudragit RL, a copolymer of dimethylaminoethyl acrylate and ethylmethacrylate (Röhm Pharma) of PM = 150 000 is used as the polymer, in powder form. A paste is obtained by making a paste with this polymer and ethanol, and pressed into spherical beads of various sizes.

These beads are characterized by their weight and their radius (Table 1).

TABLE 1

Characteristics of the beads

Bead			
Total weight (mg)	697.2	352.3	251.5
Radius (cm)	0.494	0.39	0.27
Alcohol weight (mg)	120	65	50

Kinetics of drying and calculations

The kinetics of drying of these beads is determined by weighing the beads at intervals. The beads are dried in open air at the constant temperature of 20 ° C.

Calculations are performed by using either the analytical expression or the numerical model. The analytical expression can be used, as the diffusivity is constant.

The rate of evaporation of the liquid is determined by following the weight of liquid evaporated under the same conditions in a flat flask of constant area.

Theoretical

Assumptions

The following assumptions are made in order to construct the models:

(i) The process of desorption of the solvent is controlled by transient diffusion within the solid and evaporation on the surface.

(ii) The rate of evaporation is proportional to the difference of the actual concentration of liquid on the surface and the concentration on the surface which is at equilibrium with the surrounding atmosphere, under the operational conditions, the coefficient of proportionality being the rate of evaporation of the pure liquid.

(iii) The bead is spherical in shape, and its dimensions do not change during the process.

(iv) The diffusivity is constant, as it is found from experiments.

(v) The concentration of liquid in the bead is uniform at the beginning of the process.

Mathematical treatment

The transfer of liquid within the bead is expressed by Fick's equation for a sphere:

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

with a constant diffusivity.

The rate of evaporation on the surface is defined by the surface condition:

$$-D\cdot\left(\frac{\partial C}{\partial r}\right)_R = \frac{F_0}{\rho}\cdot(C_s - C_{eq}) \tag{2}$$

where C_s is the actual concentration of liquid on the surface, C_{eq} is the surface concentration required to maintain equilibrium with the surrounding atmosphere, and F_0 is the rate of evaporation of the pure liquid.

As the sphere is initially at the uniform concentration C_{in} and the diffusivity is constant, the required solution of the above equations is:

$$\frac{C_{rt} - C_{eq}}{C_{in} - C_{eq}} = \frac{2LR}{r}\cdot\sum_{n=1}^{\infty}\frac{\sin\frac{\beta_n r}{R}}{\sin\beta_n\left[\beta_n^2 + L^2 - L\right]}\cdot\exp\left(-\frac{\beta_n^2 Dt}{R^2}\right) \tag{3}$$

where the β_ns are the roots of

$$\beta_n\cdot\cot\beta_n + L - 1 = 0 \tag{4}$$

with the dimensionless number L

$$L = \frac{R\cdot F_0/\rho}{D} \tag{5}$$

The amount of the liquid leaving the sphere is given by the expression (Crank, 1975)

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

Numerical model

A numerical model is also constructed, in order to resolve the problem when the diffusivity is concentration-dependent and the initial concentration of liquid is not uniform.

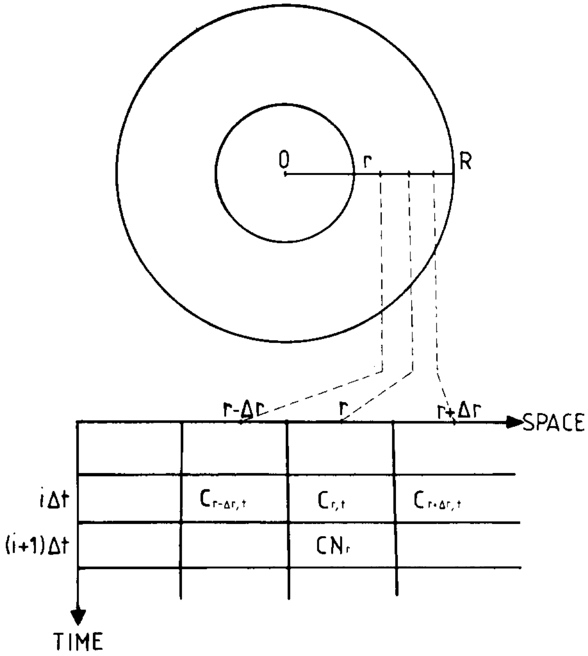

Fig. 1. Scheme for numerical analysis.

The radius of the sphere is divided into N slices of constant thickness Δr. The matter balance is calculated within the solid, by considering the spherical membrane centered on the position r:

$$\left[-D\cdot\left(\frac{\partial C}{\partial r}\right)\cdot S + D\cdot\left(\frac{\partial C}{\partial r}\right)S\right]\Delta t$$

$$\text{at } r - \frac{(\Delta r)}{2} \qquad \text{at } r + \frac{(\Delta r)}{2}$$

$$= 4\pi r^2\cdot\Delta r[CN_r - C_r] \tag{7}$$

$$\text{at } r - \frac{(\Delta r)}{2} \quad \text{at } r + \frac{(\Delta r)}{2} \tag{7}$$

On putting the function $G(r)$ such as:

$$G\left(r - \frac{\Delta r}{2}\right) = \left(r - \frac{\Delta r}{2}\right)^2\cdot(C_{r-\Delta r} - C_r)\cdot D_r - \frac{\Delta r}{2} \tag{8}$$

the new concentration within the spherical membrane at the position r after the elapse of time Δt is expressed in terms of the previous concentration at the same place and of the function G which can be calculated.

$$CN_r = C_r + \frac{\Delta t}{r^2(\Delta r)^2}\left[G\left(r - \frac{\Delta r}{2}\right) - G\left(r + \frac{\Delta r}{2}\right)\right] \tag{9}$$

The general equation cannot be used for the centre of the sphere. The matter balance is calculated for the sphere of radius $\Delta r/2$, and the new concentration at the center of the sphere after the elapse of time Δt is obtained as a function of the previous concentration and the function G.

$$CN_0 = C_0 + \frac{24 \cdot \Delta t}{(\Delta r)^4} G\left(\frac{\Delta r}{2}\right)$$

The matter balance calculated on the external spherical membrane of thickness $\Delta r/2$ gives:

$$\left[-\frac{F_0}{\rho}(C_R - C_{\text{ext}})4\pi R^2 + D\frac{C_{R-\Delta r} - C_R}{\Delta r}4\pi\left(R - \frac{\Delta r}{2}\right)^2\right]\Delta t = 4\pi\left(R - \frac{\Delta r}{4}\right)^2 \cdot \frac{\Delta r}{2} \cdot \left[CN_{R-\Delta r/4} - C_{R-\Delta r/4}\right] \tag{10}$$

On putting

$$CN_{R-\Delta r/4} - C_{R-\Delta r/4} = CN_R - C_R \tag{11}$$

this equation becomes:

$$CN_R = C_R + \frac{2\Delta t}{\left(R - \frac{\Delta r}{4}\right)^2(\Delta r)^2} G\left(R - \frac{\Delta r}{2}\right) - \frac{2R^2 \cdot \Delta t}{\left(R - \frac{\Delta r}{4}\right)^2 \cdot (\Delta r)} \frac{F_0}{\rho} \cdot (C_R - C_{\text{ext}}) \tag{12}$$

The amount of liquid remaining in the bead can be calculated by integrating the concentration with respect to space.

Results

Two parts are of interest in this study: the one devoted to the determination of the parameters such as the diffusivity and the rate of evaporation; the other which concerns the validity of the model. At last, an overview of the parameters can be made with respect to their effect on the rate of drying.

Determination of the parameters

The process of drying is controlled not only by the rate of evaporation, but also by diffusion of the liquid through the solid. The two parameters of interest are diffusivity of the liquid through the polymer, and the rate of evaporation of the liquid.

Diffusivity

The diffusivity of liquid can be determined by using the experimental kinetics of drying and Eqn 6. For long times, corresponding with a high value of M_t, such as $0.7 < M_t/M_\infty < 1$, the series in Eqn 6 converges very fast and the first term is pre-

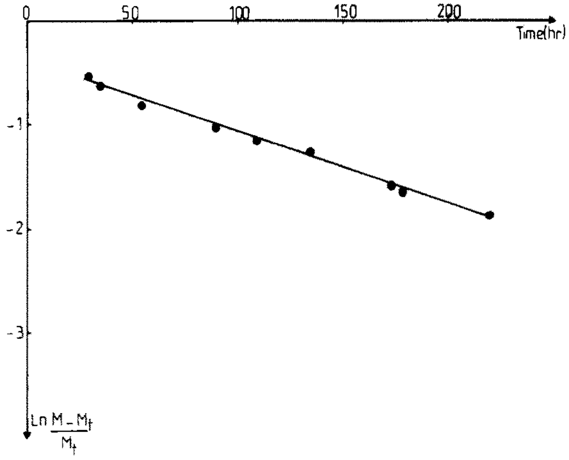

Fig. 2. $\ln[(M_\infty - M_t)/M_\infty]$ as a function of time, for the bead of weight 697.2 mg.

ponderant. By neglecting the other terms, the equation can be written as follows:

$$\ln\left(\frac{M_\infty - M_t}{M_\infty}\right) = -\frac{\beta_1^2 \cdot D}{R^2}t + \ln\frac{6L^2}{\beta_1^2 \cdot \left(\beta_1^2 + L^2 - L\right)} \qquad (13)$$

By plotting the first term of Eqn 13 as a function of time, a straight line is obtained as shown in Fig. 2. From the slope of this curve, the quantity $\beta_1 \cdot D/R^2$ is easily calculated. The value of diffusivity can thus be obtained by simple iterative calculus, because β_1 is also a function of the diffusivity as shown in Eqn 5.

Rate of evaporation

The rate of evaporation can be determined in two ways: (i) by evaporating the pure liquid under the same conditions of temperature and pressure as for the drying of the bead. Special attention is given to the shape of the flask which is flat, and full of liquid. The motion of air is also of interest; (ii) by using the initial rate of drying, when the concentration of the liquid is uniform and constant, and therefore when the process may be assumed to be controlled by evaporation (Khatir et al., 1986).

In this paper, the first technique is used. The values are listed in Table 2.

A better accuracy is obtained for the rate of evaporation than for the diffusivity. A precision of 25% is reasonable for the diffusivity.

Validity of the model

The validity of the model is tested by comparing the kinetics of drying of various beads when

TABLE 2

Diffusivity and rate of evaporation

D (cm²/s)	$4 \times 10^{-8} \pm 1 \times 10^{-8}$
F_0 (g/cm²/s)	2×10^{-4}

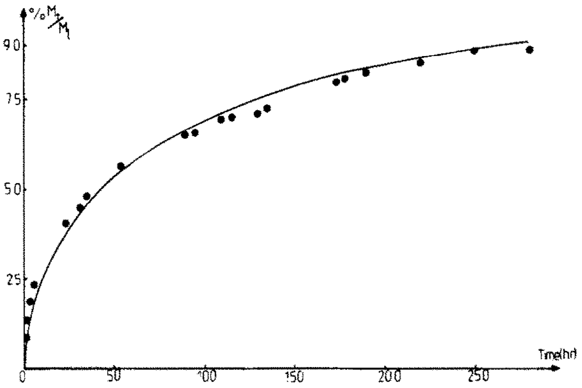

Fig. 3. Kinetics of drying (M_t/M_∞) at 20 °C. Weight, 697.2 mg; radius, 0.494 cm.

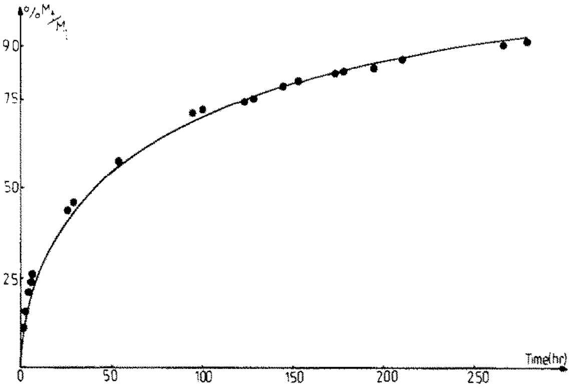

Fig. 4. Kinetics of drying (M_t/M_∞) at 20 °C. Weight, 352.3 mg; radius, 0.39 cm.

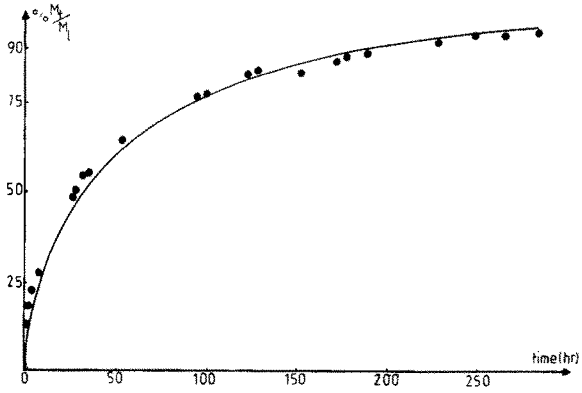

Fig. 5. Kinetics of drying (M_t/M_∞) at 20 °C. Weight, 251.5 mg; radius, 0.27 cm.

they are obtained either from experiments and calculation. Figs 3–5 illustrate the validity of the model, as well as the accuracy of the parameters such as the diffusivity and the rate of evaporation for three beads of various sizes.

The following conclusions can be drawn from these curves:

(i) The process of drying is very well described by the model taking into account not only the diffusion of the liquid through the bead but also the evaporation on the surface.

(ii) As the diffusivity is constant during the whole process, the analytical solution gives results in good agreement with experiments.

(iii) the process is controlled by diffusion, and the rate of drying is very high at the beginning of the process. This rate decreases regularly as the process proceeds.

(iv) At the end of the process, the rate of drying is very low, and an asymptote is obtained when the process of drying approaches completion.

Effect of the parameters on the process of drying

Three parameters are of interest: the radius of the sphere, the diffusivity and the rate of evaporation.

Radius

The value of evaporation has an effect on the evaporation and on the diffusion. On the one hand, a lower radius is responsible for a larger external area of the unit mass of the solid, and thus provokes a faster drying. On the other, the dimensionless term found in Eqns 3 and 6, $D \cdot t/R^2$, shows that the time of diffusion is proportional to the square of the radius. An increase in the radius is thus followed by an increase in the time of diffusion.

Diffusivity

The value of the diffusivity depends generally on the nature of the liquid and the polymer (Vergnaud, 1983). It increases with increasing temperature, often following an Arrhenius law with a constant energy of activation (Blandin et al., 1987). But, it is not possible to predict by calculation the effect of the temperature on the diffusivity, and experiments are necessary to obtain this knowledge.

Rate of evaporation

The rate of evaporation is a well-known parameter, as this rate is proportional to the vapor pressure of the liquid, and the vapor pressure is expressed in terms of the temperature by the classical Clausius-Clapeyron law.

Conclusions

The process of drying is of special interest for the dosage forms with controlled release which are prepared in a humid way. Generally a paste is obtained by wetting the mixture of the drug and the polymer matrix, and the final step of drying can lead to some difficulties.

The process is controlled by diffusion of the liquid through the polymer and by evaporation from the surface. The rate of evaporation is proportional to the difference between the concentration on the surface of the bead and the concentration which is at equilibrium with the surrounding atmosphere, the coefficient of proportionality being the rate of evaporation of the pure liquid.

As the diffusivity is constant in the present case, an analytical solution is available for describing the process, as well as a numerical method based on finite differences. The following three parameters are of concern for this process: the radius of the bead, the diffusivity and the rate of evaporation of the liquid.

Glossary

Symbol	Meaning
C	concentration of liquid in the bead (g/cm^3)
C_s, C_{eq}	concentration of liquid on the surface, at equilibrium with the surrounding atmosphere (0 in our case).
$C_{r,t}$	concentration of liquid at the position r and time t
C_{in}	concentration of liquid at the beginning of the process of drying
CN_r	new concentration at position r after elapse of time Δt
D	diffusivity (cm^2/s)
F_0	rate of evaporation of the pure liquid (g/cm^2 per s)
$G(r)$	function defined by Eqn 8, at position r
L	dimensionless number defined by Eqn 5
r	position in the bead, between 0 and R
R	radius of the bead
ρ	density of the liquid
M_t, M_∞	amount of liquid evaporated up to time t, at the end of the process
β_n	roots of Eqn 4
t	time
Δr, Δt	increments of space, of time

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