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Effect of temperature of the drying process of dosage forms prepared by a humidity technique

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Summary

Some dosage forms are prepared by using a humidity technique, and this is of special interest when a polymer is used for the matrix. This technique exhibits advantages, but also drawbacks as the final material must be dried to completion. Analytical solutions successfully tested in simple cases, as well as numerical models in all cases, are able to describe the process. The drying process is rather complex in the sense that it is controlled by diffusion of the liquid through the solid and by evaporation of the liquid from the surface. Two parameters of interest, such as the radius of the spherical dosage form, and temperature, are especially studied. Temperature acts not only on the rate of evaporation but also on the rate of diffusion, as the diffusivity is temperature-dependent according to Arrhenius' law.

Introduction

Considerable attention has been paid in recent years to oral dosage forms which are able to deliver the drug at a controlled rate. Many of these dosage forms consist of a polymer playing the role of a matrix in which the drug is dispersed. Among the ways for preparing these forms, one uses the humidity technique, by making a paste from the polymer with a liquid in which the drug is not soluble, shaping the paste into appropriate forms and then drying the final materials (Armand et al., 1987; Liu et al., 1988; Saber et al., 1988).

This preparative procedure exhibits advantages and drawbacks. High pressure is not needed to shape the dosage form, but the final material must be dried, and the process of drying a polymer is not easy, (Blandin et al., 1987a, b; Aboutaybi et al., 1989; 1990a,b).

The first objective of this paper is to study the process of drying for dosage forms made of a Eudragit matrix, in order to determine the best operational conditions. As shown in previous studies (Khatir et al., 1986, 1987), the problem is rather complex, the evaporative process being diffusion controlled in the sense that the rate of evaporation depends largely on the rate at which the liquid is supplied to the evaporating surface by internal diffusion. Analytical solutions (Crank, 1975) in simple cases and numerical models in all cases have been successfully tested for various shapes of the material.

The second aim in this study is to determine the effect of parameters of interest such as the radius of the bead and temperature on the kinetics of drying. Temperature plays a leading role, because it acts not only on the rate of evaporation of the liquid but also on the rate of diffusion of the

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liquid within the solid, as diffusivity is generally temperature dependent.

Experimental

Dosage form

The polymer used for the matrix of the dosage form is Eudragit RL, a copolymer of dimethylaminoethyl- acrylate and ethylmethacrylate (Röhm Pharma) of PM = 150 000. The paste obtained from this polymer by using ethanol is pressed into spherical beads of various sizes. The values chosen for the radius range from 0.33 to 0.525 cm and the percentage of alcohol is initially 18%.

Kinetics of drying

The beads are dried in a surrounding atmosphere of large volume, constantly stirred at constant temperature. The temperature range is from 20 to 60 °C.

The kinetics of drying are determined by weighing the bead at intervals up to constant weight.

Theoretical

Assumptions

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

(i) The process of drying is controlled by transient diffusion through the solid and evaporation from the surface.

(ii) The rate of evaporation is proportional to the difference in concentration of liquid on the surface and this concentration which is at equilibrium with the surrounding atmosphere.

(iii) The dosage form is spherical in shape, and its dimensions do not vary during the process.

(iv) For the analytical solutions, the diffusivity is constant, and the initial concentration of liquid in the bead is uniform.

(v) For the numerical model, the diffusivity can be concentration-dependent, and the initial concentration of liquid can be uniform or non-uniform.

Mathematical treatment

The diffusion of liquid through the bead is given by the Fick's equation with constant diffusivity.

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

The rate of evaporation from the surface is constantly equal to the rate at which the liquid is supplied to the evaporating surface by internal diffusion.

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

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

Analytical solution

When the diffusivity is constant, and the initial concentration within the bead is uniform, an analytical solution is found (Crank, 1975) in terms of a series:

$$\frac{M_\infty - M_t}{M_\infty} = \sum_{n=1}^{\infty} \frac{6L^2}{\beta_n^2 (\beta_n^2 + L^2 - L)} \cdot \exp\left(- \frac{\beta_n^2}{R^2} D\, t \right) \tag{3}$$

with the dimensionless number L

$$L = \frac{F_0 R}{\rho D} \tag{4}$$

the β_ns being the roots of:

$$\beta_n \cdot \cot \beta_n + L - 1 = 0 \tag{5}$$

Numerical model

The numerical model can be used when the diffusivity is concentration-dependent, or when the initial concentration of liquid within the bead

is not uniform. The following equations are obtained in various places. Within the solid:

$$CN_r = C_r + \frac{\Delta t}{r^2 \cdot (\Delta r)^2}\left[G\left(r - \frac{\Delta r}{2}\right) - G\left(r + \frac{\Delta r}{2}\right)\right] \tag{6}$$

with the function G defined as follows:

$$G\left(r - \frac{\Delta r}{2}\right) = \left(r - \frac{\Delta r}{2}\right)^2 \cdot (C_{r-\Delta r} - C_r) \cdot D_{r-\frac{\Delta r}{2}} \tag{7}$$

centre of the solid:

$$CN_0 = C_0 + \frac{24 \cdot \Delta t}{(\Delta r)^4} \cdot G\left(\frac{\Delta r}{2}\right) \tag{8}$$

surface of the solid:

$$CN_R = C_R + \frac{2\Delta t}{\left(R - \frac{\Delta r}{4}\right)^2 \cdot (\Delta r)^2} G\left(R - \frac{\Delta r}{2}\right) - \frac{2R^2 \cdot \Delta t}{\left(R - \frac{\Delta r}{4}\right)^2 \cdot (\Delta r)} \cdot \frac{F_0}{\rho}(C_R - C_{ext}) \tag{9}$$

where C_r and CN_r are the concentration of liquid at position r at time t, and after the elapse of time Δt, respectively. Δr and Δt are the increments of space and time.

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

Results

The results are given for the following analyses: testing the validity of the model under the various conditions of temperature; determination of the diffusivity as a function of temperature; and the effect of the radius of the bead and temperature on the profiles of concentration of liquid in the beads.

Validity of the model

The parameters of interest are determined from experiments: the diffusivity is calculated from the slope of the straight lines obtained by plotting the logarithm of the amount of liquid evaporated as a function of time (Eqn 10):

$$\ln\left(\frac{M_\infty - M_t}{M_\infty}\right) = -\frac{\beta_1^2 \cdot D}{R^2} t + \ln\frac{6L^2}{\beta_1^2 \cdot (\beta_1^2 + L^2 - L)} \tag{10}$$

This equation results from Eqn 3 which is reduced to the first term for long times $M_t/M_\infty > 0.8$.

The rate of evaporation is determined from experiments at room temperature, and the values are calculated at the other temperature by considering the two facts: (i) the rate of evaporation is proportional to the vapor pressure of the liquid; (ii) the vapor pressure is expressed in terms of temperature by Clausius Clapeyron's law.

The values of the diffusivity and rate of evaporation are shown in Table 1 for the three temperatures.

The analytical solution and numerical model are successfully tested by comparing the theoretical and calculated kinetics at the three temperatures. As shown in Fig. 1, good superimposition of all curves is observed, proving the validity of the models. The analytical solution can be used in the present case as the diffusivity is constant and the initial concentration of liquid is uniform.

The kinetics in Fig. 1 are drawn by using the dimensionless coordinates M_t/M_∞ (%) as a function of time. These curves are of interest, because these results can be useful for determining the

TABLE 1

Diffusivity and rate of evaporation

	Temperature (°C)		
	20	40	60
D (cm^2/s)$\times 10^7$	0.6	1.63	4.0
F_0 (g/cm^2 per s)$\times 10^4$	2.7	7.8	19.8

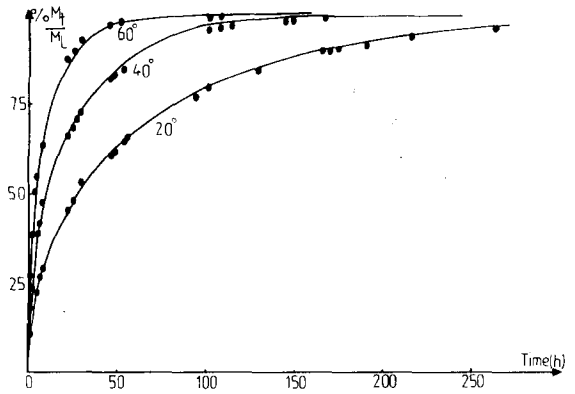

Fig. 1. Kinetics of drying at various temperature by using dimensionless coordinates: M_t/M_∞ (%) vs time. (1) 20 °C, (2) 40 °C, (3) 60 °C. (———) Theoretical, (+) experiments.

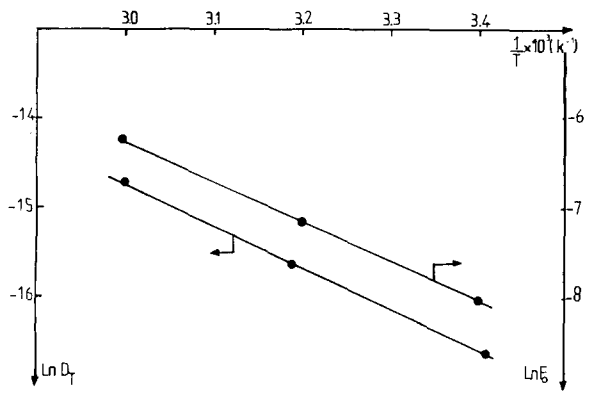

Fig. 2. Temperature dependence of the diffusivity and of the rate of evaporation.

effect of the radius of the bead: for instance, it is clear that the time necessary for the amount of liquid evaporated to reach a given value is proportional to the square of the radius.

Effect of temperature on the kinetics of drying

The temperature dependence of the diffusivity is determined by considering the Arrhenius' expression:

$$D_T = D_0 \cdot \exp\left(-\frac{E}{RT}\right) \tag{11}$$

where D_T is the diffusivity at temperature T (Kelvin), D_0 is a constant, and E the activation energy.

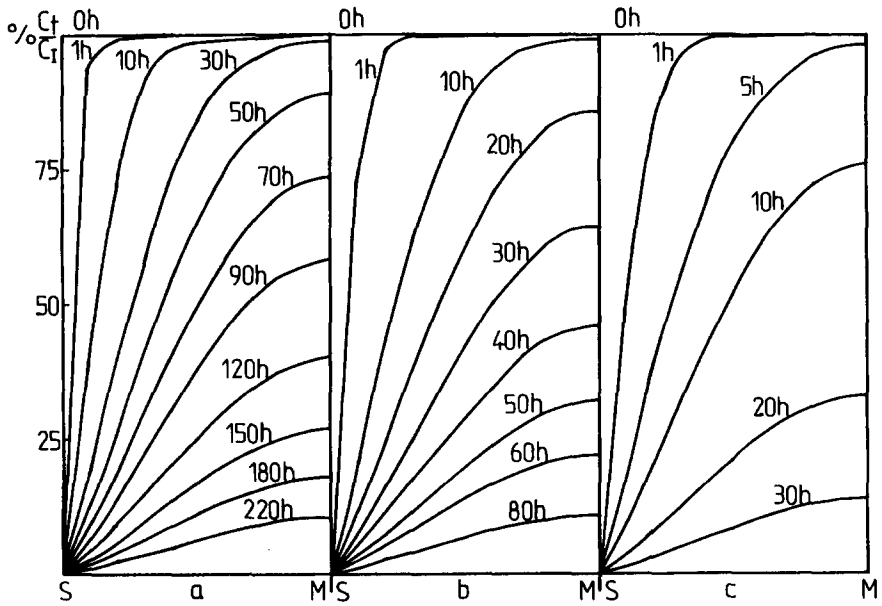

Fig. 3. Profiles of concentration of liquid expanded through the spherical bead, at various temperatures: (a) 20 °C, (b) 40 °C, (c) 60 °C. Radius, 0.4 cm.

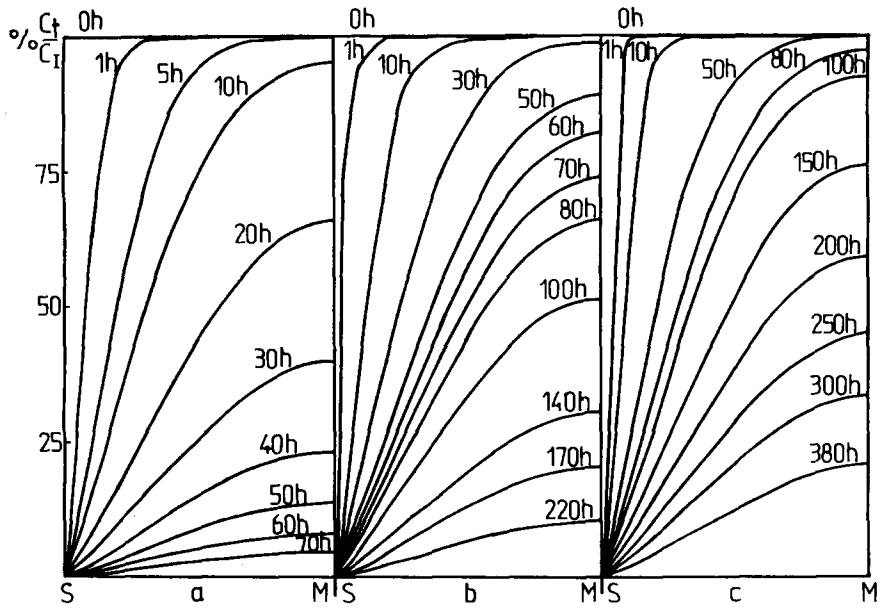

Fig. 4. Profiles of concentration of liquid developed within the spherical bead, for various values of the radius, at constant temperature (20 °C). (a) $R = 0.2$ cm, (b) $R = 0.4$ cm, (c) $R = 0.6$ cm.

The logarithm of diffusivity is plotted vs reciprocal temperature in Fig. 2; the activation energy is readily evaluated from the slope of this straight line.

The values of E and D are as follows: D_0 (cm^2/s) = 0.46 and E (cal/mol) = 9 300.

The effect of temperature on the kinetics of evaporation is illustrated in Fig. 1, where the three curves are drawn at various temperatures (20, 40 and 60 °C).

The profiles of concentration of liquid expanded through the bead are drawn in Fig. 3 for the above three temperatures at a constant value of the radius (0.4 cm).

The profiles of concentration of liquid developed through the bead are also drawn (Fig. 4) at the same temperature (20 °C) for various values of the radius (0.2, 0.4, 0.6 cm).

The following conclusions are drawn from these results:

(i) The effect of temperature on the kinetics of drying is illustrated in Fig. 1. This parameter is of great concern because it acts not only on the rate of evaporation but also on the rate of diffusion.

(ii) The effect of temperature on the profiles of concentration expanded through the bead is also very significant. These curves give complementary information, and also greater insight into the process.

(iii) The rate of evaporation, which is proportional to the vapor pressure of the liquid, varies with temperature according to Clausius-Clapeyron's law. The diffusivity is expressed in terms of the temperature by Arrhenius' law. These two parameters vary exponentially with temperature.

(iv) The effect of the dimensions of the bead on the process of drying is also an important parameter. As already shown in Fig. 1, the time necessary for the amount of liquid evaporated to reach a given value is considerably longer when the bead is larger. A simple law can be considered: the time necessary for drying a bead is proportional to the square of the radius.

Conclusions

The process of drying of dosage forms consisting of a polymer matrix is studied by considering especially the effect of parameters such as the

Glossary

Symbol	Meaning
C	concentration of liquid in the bead (g/cm^3)
C_R, C_{eq}	concentration of liquid on the surface, at equilibrium with the surrounding atmosphere (0 in our case)
C_r	concentration of liquid at the position r
C_0	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 4
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 5
t	time
Δr, Δt	increments of space, of time

radius of spherical forms and the temperature of drying. Experimental kinetics determined within the temperature range 20–60 °C are in good agreement with theoretical kinetics calculated with the help of an analytical solution and a numerical model.

The effect of these parameters on the process of drying is of great interest.

The radius of the spherical form plays an important role, as the time necessary for drying the bead is proportional to the square of the radius.

The temperature acts not only on the rate of evaporation of the liquid from the bead surface, but also on the rate of diffusion of the liquid within the bead. The temperature dependence of the diffusivity is found to follow the Arrhenius' equation with a constant activation energy.

It is thus possible to determine the best operational conditions for the process of drying of dosage forms made of polymers, by performing experiments in order to obtain the diffusivity and the rate of evaporation, and by using the models.

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