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Drying of dosage forms prepared by a humidity technique using a programmed temperature system

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Summary

Dosage forms prepared using a humidity technique, and consisting of a polymer matrix in which the drug is dispersed, must be dried. The process of drying is rather complex, in the sense that it is controlled not only by evaporation of the vapour out of the surface but also by diffusion of the liquid through the solid. Generally, the diffusivity of the liquid through the polymer as well as the rate of evaporation increases with temperature exponentially. High temperature is able to reduce the time of drying, but a drawback appears with distortion of the shape of dosage forms because of the plasticity of humid beads at high temperature. A programmed temperature process is thus necessary to achieve drying under the best conditions, the rate of heating being a parameter of interest.

Introduction

In order to control the rate of delivery of the drug in the patient's stomach, various types of dosage forms have been studied and prepared. Among them, particular attention has been focussed on monolithic devices obtained by dispersing the drug in a biocompatible polymer playing the role of a matrix. Three main procedures are followed to prepare these dosage forms with the polymer: (i) a dry method with compression of the components in powder form (Droin et al., 1985; Malley et al., 1987); (ii) by melting the polymer matrix (Magron et al., 1987; Laghoueg et al., 1989); (iii) by using a humidity technique, in making a paste of the polymer matrix in which the drug is dispersed, by addition of a liquid in which the drug is not soluble; the paste can thus be easily shaped into beads at low temperature (Armand et al., 1987; Liu et al., 1988; Saber et al., 1988).

Each of these techniques exhibits some drawbacks and advantages. The humidity technique does not necessitate a high pressure as in the first method, or a high temperature to shape the bead as needed to melt the polymer in the second procedure. However, an inconvenience exists with the humidity technique because the dosage forms must be dried.

As shown in earlier studies devoted to drying of polymers, the process, which is generally rather

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complex (Vergnaud, 1990) when the polymer is homogeneous as in elastomers (Khatir et al., 1986, 1987), may become very difficult in the case of plasticized PVC where gradients of concentration of plasticizer exist (Aboutaybi et al., 1989, 1990). In all cases, the drying stage is controlled not only by evaporation of the vapour from the surface, but also by diffusion of the liquid through the solid, the diffusivity being either constant (Laghoueg-Derriche and Vergnaud, 1991) or concentration-dependent (Blandin et al., 1987a).

Of course, temperature plays an important role in the rate of drying, since the rate of evaporation increases with temperature according to the Clausius-Clapeyron law, and since the diffusivity of the liquid generally also increases with temperature exponentially. However, high temperatures cannot be used in order to reduce the time of drying without taking precautions due to the plasticity of the humid polymer which is often enhanced by increasing temperature, the result being a distortion in the shape of the final product.

The first objective in this paper is to develop the process of drying of dosage forms by using a programmed temperature system, the heating rate being constant or not. The programmed temperature system is defined in order to address the two problems of how to reduce the time of drying, and how to achieve this purpose without modifying the shape of the material.

The second purpose in this study is to build up a numerical model that is able to describe the process, and to predict the best operational conditions for a defined objective. No analytical solution exists in this case (Crank, 1975; Vergnaud, 1990). This model, based on a numerical method with finite differences, takes all the facts into account: the rate of evaporation and diffusivity with their temperature dependency. 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. Two parameters are especially examined, the rate of heating or the heating system coupling constant temperature and programmed temperature, as well as the radius of the spherical dosage form.

Theoretical

Assumptions

The following assumptions are made:

(i) The process of drying is controlled by transient diffusion of the liquid within the polymer and evaporation from the surface.

(ii) The dosage forms are spherical in shape, and no change in dimensions appear during the process (Senoune et al., 1990).

(iii) 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. It is also equal to the rate at which the liquid is brought to the evaporating surface by internal diffusion.

(iv) The concentration of liquid which is at equilibrium with the surrounding atmosphere is zero, as this atmosphere has a large volume (Laghoueg-Derriche and Vergnaud, 1990).

(v) The diffusivity and rate of evaporation are temperature-dependent, and this dependency follows exponential behavior.

(vi) As the rate of heating is rather low and the dimension of the dosage forms is small, the temperature is always uniform within the solid, this temperature being constantly equal to that of the heating system.

(vii) The diffusivity depends only on temperature in the present case, but the model can work with a concentration-dependent diffusivity.

Mathematical treatment

The transport of liquid within the bead is expressed by Fick's equation for a sphere with a constant diffusivity.

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

The rate of evaporation from the surface is defined by the surface condition

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

where C_R is the concentration of liquid on the surface, C_{eq} is the concentration required to maintain equilibrium with the surrounding atmosphere, and F_T is the rate of evaporation of the pure liquid under the same conditions.

Numerical analysis

No analytical solution is obtained in the case of programmed temperature, and a numerical model with finite differences is used.

The sphere of radius R is divided into N spherical membranes of constant thickness Δr. The matter balance is determined at various positions during the increment of time Δt (Laghoueg-Derriche and Vergnaud, 1991) (Fig. 1).

Within the solid (at position r) The new concentration after elapse of time Δt is expressed in terms of the previous concentration by the relation

$$CN_r = C_r + \frac{\Delta t}{r^2 \cdot (\Delta r)^2} \cdot \left[G\left(r - \frac{\Delta r}{2}\right) - G\left(r + \frac{\Delta r}{2}\right)\right] \qquad (3)$$

where the function G is given by

$$G\left(r - \frac{\Delta r}{2}\right) = \left(r - \frac{\Delta r}{2}\right)^2 \cdot [C_{r-\Delta r} - C_r] \cdot D\left(r - \frac{\Delta r}{2}, T\right) \qquad (4)$$

The diffusivity D_T is a function of temperature

$$D_T = DA \cdot \exp\frac{-E}{RT} \qquad (5)$$

DA being a constant, and E playing the role of an activation energy, temperature T being expressed in Kelvin.

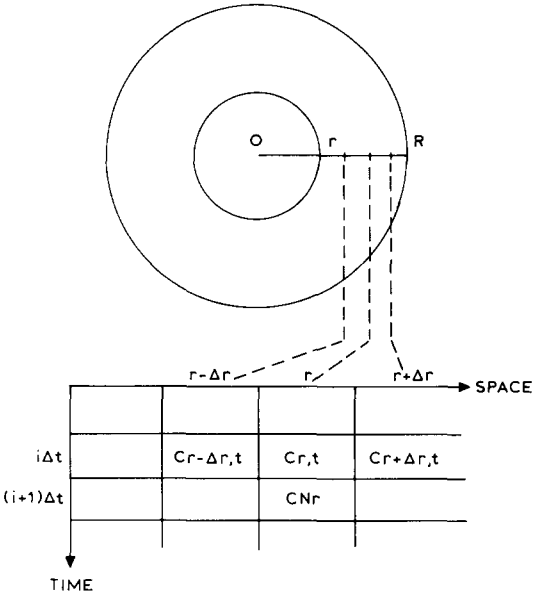

Fig. 1. Diagram for numerical analysis.

Centre of the spherical bead (r = 0) The following equation is obtained (Laghoueg-Derriche and Vergnaud 1991).

$$CN_0 = C_0 + \frac{24 \cdot \Delta t}{(\Delta r)^4} \cdot G\left(\frac{\Delta r}{2}\right) \qquad (6)$$

with the function G and diffusivity defined in Eqns 4 and 5.

Surface of the spherical bead (R) The new concentration CN_R on the surface is expressed as a function of the previous concentration C_R after elapse of time Δt, by the relation:

$$CN_R = C_R + \frac{2\Delta t}{\left(R - \frac{\Delta r}{4}\right)^2 \cdot (\Delta r)^2} \cdot G\left(R - \frac{\Delta r}{2}\right) - \frac{2R^2 \cdot \Delta t}{\left(R - \frac{\Delta r}{4}\right)^2 \cdot \Delta r} \cdot \frac{F_T}{\rho}(C_R - C_{eq}) \qquad (7)$$

where the function G is defined by Eqn 4.

The diffusivity in Eqn 4 is a function of temperature (Eqn 5). The rate of evaporation also

varies with temperature according to the following relation:

$$F_T = FA \cdot \exp\frac{-\Delta H}{RT} \tag{8}$$

where FA is a constant, and ΔH is the enthalpy of vaporization of the liquid.

The temperature of the bead is a function of time, with the constant heating rate b:

$$T_t = T_{t_0} + b(t - t_0) \tag{9}$$

Experimental

Preparation of dosage forms

Eudragit RL, a copolymer of dimethylaminoethylacrylate and ethylmethacrylate (Rhöm Pharma) of PM = 150000, is used as the polymer in powder form. The paste obtained by adding a small amount of ethanol to the polymer is pressed into spherical beads of various sizes.

Kinetics of drying

The kinetics of drying is determined by recording the weight of the bead, as well as the temperature. The volume of the surrounding atmosphere is so large that the concentration of vapour is very small and negligible.

These thermogravimetric studies are carried out by using a Ugine Eyraud G70 apparatus (SETARAM, Lyon, France) equipped with a PRT 540 temperature programming system. This apparatus can work either under dynamic conditions with constant heating rate, or under isothermal conditions.

Results

The following results are considered:

(i) Determination of the parameters of interest: the diffusivity and rate of evaporation of the liquid, as well as their variation with temperature.

(ii) As the validity of the model has already been tested in a previous paper (Laghoueg-Derriche et al., 1991) only a brief description is given here.

(iii) The effect of the rate of heating on the process of drying. Moreover, some more complex temperature-time histories are also considered.

(iv) The effect of the radius of the beads.

Determination of the parameters

The parameters of interest, such as the diffusivity and rate of evaporation, are determined from experiments carried out under isothermal conditions at various temperatures: 20, 40, 60 °C.

Diffusivity

The diffusivity is calculated from the slope of the straight line obtained by plotting the logarithm of the amount of liquid evaporated as a function of time (Eqn 10).

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

This equation results from the analytical solution of diffusion-evaporation of liquid out of a sphere (Crank, 1975; Laghoueg-Derriche and Vergnaud, 1991; Laghoueg-Derrich et al., 1991). The first term of the series becomes preponderant for long times, when $M_t/M_\infty > 0.8$.

β_1 is also a function of diffusivity, being the first root of

$$\beta_n \cdot \cot \beta_n + L - 1 = 0 \tag{11}$$

with the dimensionless number L:

$$L = \frac{RF_T}{D\rho} \tag{12}$$

The value of diffusivity is thus obtained by iteration when the rate of evaporation is known. The accuracy of diffusivity is tested by comparing the experimental and calculated kinetics of drying.

TABLE 1

Diffusivity and rate of evaporation

	Temperature (°C)		
	20	40	60
$D(\times 10^7)$ (cm^2/s)	0.6	1.6	4.0
$F_T(\times 10^4)$ (g/cm^2 per s)	2.7	7.8	19.8

TABLE 2

Variation of D and F with temperature

DA (cm^2/s)	E (cal/mol)	FA (g/cm^2 per s)	ΔH (cal/mol)
0.46	9300	3000	9500

Rate of evaporation

The rate of evaporation of the liquid from the dosage form is determined from the kinetics of drying at the beginning of the process when the concentration of liquid is uniform (Khatir et al., 1986; Blandin et al., 1987b).

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

The temperature dependence of the diffusivity is obtained by considering an Arrhenius expression while the rate of evaporation is expressed in terms of temperature by the Clausius-Clapeyron equation, the rate of evaporation being proportional to the pressure of vapour at equilibrium with the liquid (Eqns 5 and 8).

The values of the pre-exponential term, and of E and ΔH are obtained from the values of the diffusivity and rate of evaporation at various temperatures (Table 1), and are shown in Table 2.

The effect of temperature on the process of drying is illustrated in Fig. 2 where the kinetics of drying obtained under isothermal conditions are depicted at three temperatures: 20, 40, 60 °C. A good agreement is observed between experiment and theory, with good superimposition of the curves obtained from experiments and calculation with the help of the model (Laghoueg-Derriche et al., 1991).

Drying with programmed temperature

Temperature can be programmed in many ways, but heating at a constant heating rate is the most usual, as well as various heating histories combining in successive programming of temperature and isothermal conditions.

Programmed temperature with constant heating rate

The programmed temperature technique displays a great advantage over the method run under isothermal conditions in the sense that drying can begin at a rather low temperature and end at a temperature as high as possible. This advantage is

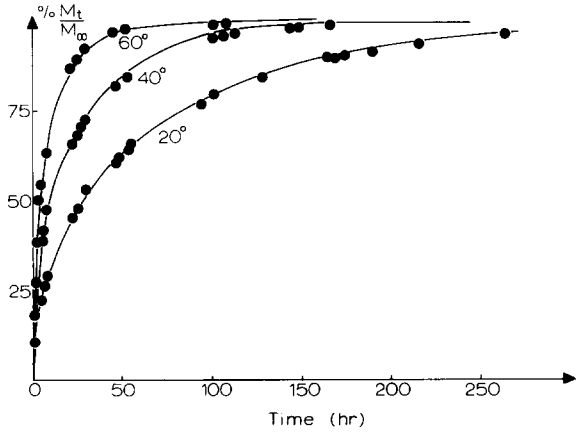

Fig. 2. Kinetics of drying under isothermal conditions, at various temperatures: 20, 40, 60 °C; radius, 0.49 cm.

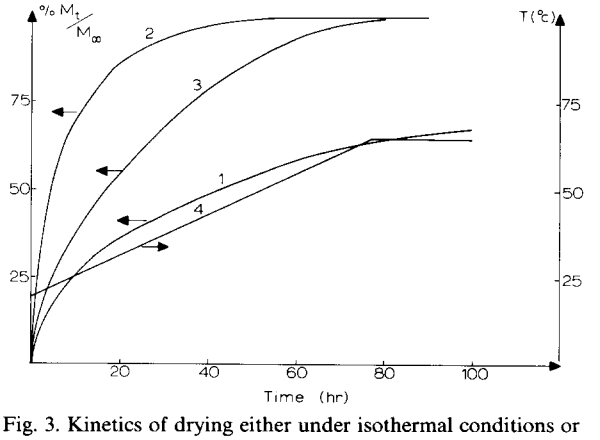

Fig. 3. Kinetics of drying either under isothermal conditions or with programmed temperature. (1) 20 °C; (2) 60 °C; (3) heating rate, 0.01 °C/min; (4) heating history; radius, 0.39 cm; $M_\infty = 60$ mg.

clearly illustrated in Fig. 3 where the kinetics are illustrated for the three sets of conditions: isothermal conditions at 20 and 60 °C, with programmed temperature from 20 to 65 °C and a heating rate of 0.01 °C/min.

As the rate of evaporation of the liquid increases with temperature, as well as the diffusivity within the dosage form, the process of drying is accelerated by using a programmed temperature system. In Fig. 3, the kinetic curve of drying obtained with the programmed temperature is located between the kinetic curves obtained under isothermal conditions at 20 and 60 °C. The following conclusions are worth noting:

(i) It is possible to have rather low rate of drying at the beginning of the process, by using a constant heating rate. This fact is especially of interest when the material of the dosage form becomes plastic, because of the presence of a large amount of liquid in the solid at a high temperature.

(ii) Because of the heating rate, the time necessary to evaporate to dryness is only a little longer with the programmed temperature process than with the constant temperature at 60 °C.

The heating rate is a relevant factor with the programmed temperature system, as well as the initial and final temperatures selected during the heating stage.

The effect of the heating rate on the process of drying is determined by drying samples of same

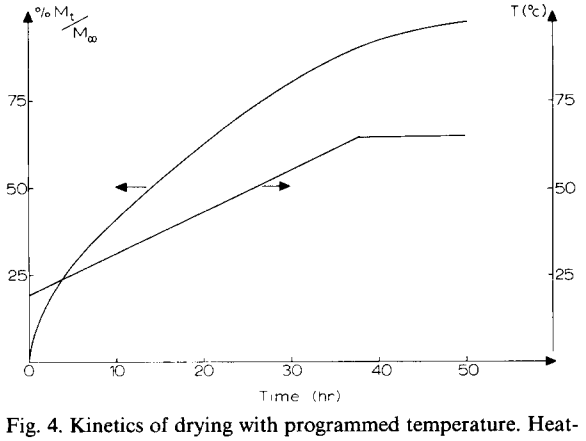

Fig. 4. Kinetics of drying with programmed temperature. Heating rate, 0.02 °C/min; radius, 0.39 cm; $M_\infty = 60$ mg.

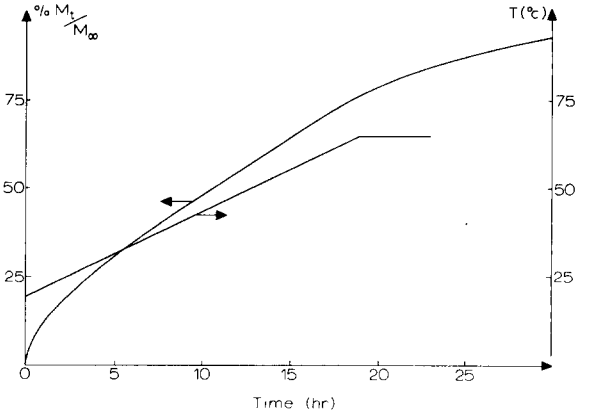

Fig. 5. Kinetics of drying with programmed temperature. Heating rate, 0.04 °C/min; radius, 0.39 cm; $M_\infty = 60$ mg.

size with various values of the heating rate: 0.01 °C/min (Fig. 3), 0.02 °C/min (Fig. 4) and 0.04 °C/min (Fig. 5). The three kinetic curves are drawn with their temperature-time histories. Some conclusions are worth noting:

(i) The time of drying is reduced by using a higher value of the heating rate.

(ii) The time of drying is not inversely proportional to the heating rate.

Temperature-time histories

When the material of the dosage form is highly plastic, a rapid increase in temperature is responsible for distortion of the shape at the beginning of the process when the proportion of liquid is still high. In this difficult but very common case, the other two possibilities for improving the process are of interest, in addition to using a low heating rate: (i) by starting the process of drying under isothermal conditions during a period of time long enough to make the dosage form less plastic; (ii) by using a rather low temperature at the beginning of the drying process.

The effect of these temperature-time histories on the process is determined in Fig. 6 where two heating histories are followed: curve 1, when the initial temperature is 20 °C, and curve 2, when this initial temperature is 10 °C. For all these curves, the other conditions are the same, with a heating rate of 0.01 °C/min starting after a period of time of 5 h at the constant initial temperature.

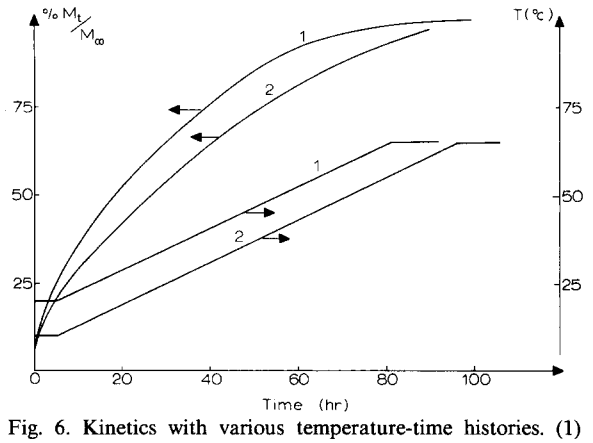

Fig. 6. Kinetics with various temperature-time histories. (1) 20 °C for 5 h followed by a heating rate of 0.01 °C/min from 20 to 65 °C; (2) 10 °C for 5 h followed by a heating rate of 0.01 °C/min from 10 to 65 °C.

Of course, a lower value for the initial temperature is responsible for a longer time of drying. But this lower initial temperature also brings with it the advantage of evaporating the liquid at lower temperature. Thus, 25% of liquid is evaporated up to 12 °C in the second case with the initial temperature at 10 °C, while the same amount is extracted at 25 °C in the first case (initial temperature, 20 °C).

Effect of the dimension of dosage forms

As the process of drying is controlled not only by the rate of evaporation but also by diffusion through the solid, the dimensions of the dosage form play an important role in the kinetics.

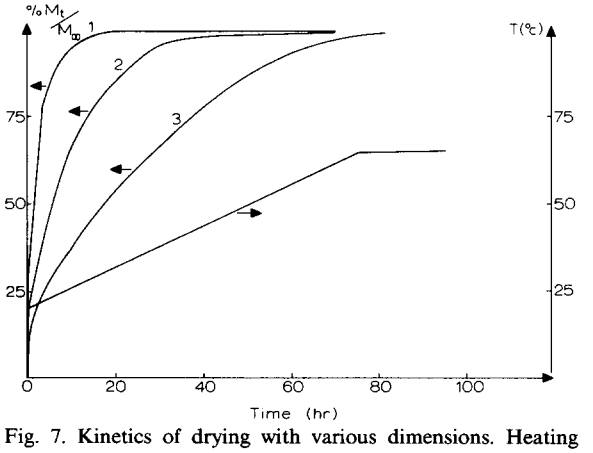

Fig. 7. Kinetics of drying with various dimensions. Heating rate, 0.01 °C/min from 20 to 65 °C; radius: (1) 0.1 cm, (2) 0.2 cm, (3) 0.4 cm.

The effect of the radius of spherical dosage forms on the kinetics of drying is clearly illustrated in Fig. 7, with a heating rate of 0.01 °C/min starting at 20 up to 65 °C.

Conclusions

The process of drying dosage forms prepared by the humidity technique can be achieved not only by heating the solid under isothermal conditions, but also with a programmed temperature system.

As the process of drying is controlled by diffusion and evaporation, and the diffusivity and rate of evaporation are increased by increasing temperature, the programmed temperature technique is of interest.

Glossary

Symbol	Meaning
b	constant heating rate
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 ($C_{eq} = 0$ in our case)
C_r	concentration of liquid at the position r
C_0	concentration of liquid at the middle of the bead
CN_r	new concentration at position r after elapse of time Δt
DA	constant of Eqn 5
D_T	diffusivity at temperature T (K)
E	activation energy (cal/mol)
F_A	constant of Eqn 8
F_T	rate of evaporation at temperature T
$G(x)$	function defined by Eqn 4, at position x
L	dimensionless number defined by Eqn 12
r	position in the bead, between 0 and R
R	radius of the bead
ρ	density of the liquid (g/cm^3)
M_t, M_∞	amount of liquid evaporated up to time t, at the end of the process
β_n	roots of Eqn 11
T	temperature
t, t_0	time
ΔH	enthalpy of vaporization of the liquid (cal/mol)
Δr, Δt	increments of space, of time

The process is well described by a numerical model taking into account the diffusion of the liquid through the solid and evaporation from the surface, as well as the temperature dependency of the diffusivity and the rate of evaporation. As the rate of heating is rather low, ranging from 0.01 to 0.04 °C/min, the temperature within the solid can be considered as uniform during the process.

This technique with programming of temperature involves three parameters of concern: the heating rate, the initial and final temperatures.

Moreover, various temperature-time histories can be followed by combining in succession the heating period with isothermal periods of time. These techniques are of interest to keep the dosage form in shape even if the solid is plastic and the plasticity increases considerably with temperature.

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