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Diffusional process of drug delivery from a dosage form with a Gelucire matrix

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Summary

This paper describes a study of dosage forms having the property of delivering the drug at a controlled rate, with the drug being dispersed in Gelucire, playing the role of a matrix, in synthetic gastric liquid. The process of drug delivery could be described on the basis of diffusional transport with constant diffusivity being considered. Analytical solutions are given for the two following conditions: (i) the case where the volume of liquid is so large with respect to the amount of drug in the dosage form that it may be taken to be infinite; and (ii) when the volume of liquid is so small with respect to the amount of drug that it should be considered as finite. In both cases, the analytical solutions provide a very satisfactory description of the process of drug delivery from the dosage form with a Gelucire matrix.

Introduction

All conventional forms of drug administration, except continuous intravenous perfusion, do not release the drug at a constant rate. In contrast, the liberation of drug occurs very rapidly from the form in which it is supplied or the excipient, thereafter undergoing dissolution in the gastric liquid. As a result, the concentration of drug in the stomach quickly rises to a high level, followed by an exponential fall until the next dose due to drug transport through the stomachic membrane (Heilmann, 1984).

In order to establish safer means of drug administration than with conventional methods, various dosage forms with the capability to deliver the drug to the stomach at a constant, or at least a controlled, rate have been developed and investigated. Particular attention has been paid to the regulation of the rate of drug release by means of monolithic devices, whereby prior dispersion of the drug in a polymer matrix is carried out (Heilmann, 1984; Vergnaud, 1990). Both biodegradable (Heller, 1984) and non-degradable polymers can be employed in polymeric drug delivery systems (Fessi et al., 1982; Touitou and Donbrow, 1982; Focher et al., 1984; Droin et al., 1985;

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Armand et al., 1987). Each of these forms exhibits some advantages but also a number of drawbacks either during preparation or when being used. Moreover, further investigations have been conducted on non-erodible polymers employed as a gel matrix.

A limited number of studies considered the case of an erodible polymer matrix, particular attention being focussed on Gelucire, a polymer of low molecular weight. Gelucire was used in two different ways: (i) as a polymer matrix in which the drug is dispersed (Bidah and Vergnaud, 1990, 1991a); and (ii) as shell surrounding a core composed of the drug dispersed in either a non-erodible polymer (Magron et al., 1987; Laghoueg et al., 1989; Bidah and Vergnaud, 1991b) or an erodible polymer (Bidah, 1991).

The dosage forms prepared by dispersing a drug in a Gelucire matrix are especially interesting from several viewpoints, including those of (i) ease of preparation, as the drug is dispersed in melted Gelucire at around 50°C and (ii) the facilitation of drug release from the dosage form as a result of Gelucire being slightly soluble.

The process of drug delivery from a dosage form where the drug is dispersed in Gelucire is rather complex and can be described in more than one way. A first attempt at elucidation of the process has recently been reported (Bidah and Vergnaud, 1990) in which the erosion of Gelucire was considered to be the driving force for drug delivery. The rate of drug delivery at any given instant of time is thus proportional to the actual surface area of the dosage form at that moment. For a spherically shaped bead, the rate of drug delivery is proportional to the square of the actual radius or to the amount of the dosage form at that time point raised to the power 2/3.

The main objective of the present paper was to demonstrate that the process of drug delivery from dosage forms comprising Gelucire may also be described according to another scheme, namely, that of a diffusional process. Two types of experimental methods and calculations were performed: one concerns the case in which the amount of synthetic gastric liquid is so large that it may be considered as infinite; the other refers to the situation where the amount of synthetic gastric liquid is so small that it should be taken to be finite. In both cases, since the diffusivity remains constant, an analytical series is able to describe the kinetics of drug delivery (Vergnaud, 1990).

Experimental

Materials

The following components were used: sodium salicylate in powder form (Coper) to simulate the drug and Gelucire 46.7 (Gattefossé, 1983) as the polymer matrix. Gelucire is a mixture of polyglycide fatty esters with defined properties of hydrophilicity. Gelucire 46.7 melts at 46°C (drop point: Mettler) and has an HLB (hydrophilic-lipid balance) value of 7, i.e., in the middle of the overall range (1–14).

Preparation of dosage forms

Grains of sodium salicylate were dispersed in melted Gelucire heated to around 50°C. The liquid mixture was stirred thoroughly in order to ensure that the components were fully distributed. Spherical beads of various sizes were prepared from the paste obtained from the liquid mixture and contained drug and Gelucire in the proportions of 50:50 (w/w%).

In vitro tests

Experiments were carried out using closed flasks with the regulation of both temperature (37°C) and rate of stirring. Beads placed in a fiber-glass basket were immersed in synthetic gastric liquid. The synthetic gastric liquid at pH 1.2 was prepared via the addition of 2 g NaCl and 80

TABLE 1

Experimental tests

Test no.	Bead weight (mg)	Radius (cm)	Volume of liquid (ml)
1	264	0.36	200
2	187	0.33	200
3	92	0.268	100

ml of 1 N HCl to 1000 ml water to yield an aqueous solution.

Samples having a small volume (0.2 ml) were removed at intervals for drug quantitation by employing a UV spectrophotometer (Hitachi U-1100) calibrated at 207 nm after appropriate dilution in liquid at pH 1.2.

The subsequent tests are detailed in Table 1.

Theoretical

Assumptions

The following assumptions were made in order to describe the known facts and to simplify the process.

(i) The dosage forms are spherical in shape. The drug is thoroughly distributed in the Gelucire matrix, and hence the dosage form is homogeneous.

(ii) A simple process of drug delivery is considered whereby drug release takes place only in the liquid.

(iii) The process of drug delivery is governed by transient radial diffusion with constant diffusivity, as demonstrated by the square root of time dependence of the amount of drug delivered.

(iv) The radius of the beads remains invariant during the process. This assumption is quite distinct from that made in the case of the process of erosion (Bidah and Vergnaud, 1990).

(v) The volume of liquid is greatly in excess with respect to the amount of drug in the dosage form for dosage forms 2 and 3. The concentration of drug in the liquid is therefore very low. The concentration on the surface of the beads falls to a very low value, immediately upon immersion of the dosage form in the liquid.

(vi) The volume of liquid is finite for dosage form 1. The concentration of drug in the liquid increases uniformly with time. The rate of release of drug from the dosage form is equal to that of dissolution of drug in the liquid throughout the entire duration of the process.

Mathematical treatment

The process of radial diffusion under transient diffusion is expressed by:

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

where the diffusivity, D, remains constant, and C denotes the concentration of drug at radial position r and time t.

The two cases referred to above (v and vi) are detailed below.

Very large volume of liquid. For an 'infinite', i.e., very large volume, the initial and boundary conditions are defined according to Eqns 2 and 3:

$$t = 0 \quad 0 \le r \le R \quad C = C_{in} \quad \text{dosage form} \tag{2}$$

$$t > 0 \quad r = R \quad C = 0 \quad \text{bead surface} \tag{3}$$

where R is the radius of the dosage form and C_{in} represents the uniform initial concentration of drug in the dosage form.

The amount of drug released from the dosage form up to time t, M_t, is expressed in terms of time t as a fraction of the corresponding quantity released after infinite time, M_∞, by the relation:

$$\frac{M_\infty - M_t}{M_\infty} = \frac{6}{\pi^2} \cdot \sum_1^\infty \frac{1}{n^2} \cdot \exp\left(\frac{-n^2 \cdot \pi^2}{R^2} D \cdot t \right) \tag{4}$$

where n is an integer.

Finite volume of liquid. This case has an initial condition that is also defined by Eqn 2. The boundary condition expresses the fact that, throughout the duration of the process, the rate of drug delivery remains equal to that at which the drug is brought to the surface by diffusion within the dosage form.

$$t > 0 \qquad V \cdot \left(\frac{\partial C}{\partial t} \right) = -D \cdot A \cdot \left(\frac{\partial C}{\partial r} \right)_{r=R} \tag{5}$$

where V represents the volume of the liquid and A is the surface area of the dosage form.

The total amount of drug, M_t, released from the sphere after time t is evaluated in terms of

the corresponding quantity after infinite time M_∞:

$$\frac{M_\infty - M_t}{M_\infty} = \sum_n^\infty \frac{6\alpha(1+\alpha)}{9+9\alpha+q_n^2\cdot\alpha^2}\cdot\exp\left(\frac{-q_n^2}{R^2}D\cdot t\right) \tag{6}$$

where the q_ns are the non-zero roots of

$$\tan q_n = 3q_n/(3+\alpha\cdot q_n) \tag{7}$$

and α denotes the solution/sphere volume ratio

$$\alpha = 3V/(4\pi R^3\cdot k) \tag{8}$$

with the partitioning factor, k, describing the distribution between drug in equilibrium in the sphere and in solution.

Short duration of drug delivery. For short periods of experimental time, for which the ratio $M_t/M_\infty < 0.3$, the following equation is obtained:

$$M_t/M_\infty = \frac{6}{R}\left(\frac{D\cdot t}{\pi}\right)^{0.5} \tag{9}$$

which has been found to be very useful in the determination of the values of diffusivity.

Results

Two types of results on the process of diffusional transport for drug delivery with oral dosage forms composed of Gelucire are treated below: (i) those where the volume of synthetic gastric liquid is very large in relation to the amount of drug and thus taken as being constant; and (ii) those in which the volume of the synthetic gastric liquid is finite.

Very large volume of liquid

The kinetics of drug delivery, as determined either experimentally or by means of calculation with the use of Eqn 4, are depicted in Fig. 1 for the three ensuing cases (1–3): (1) 264 mg dosage form in 200 ml of synthetic gastric liquid; (2) 187 mg dosage form in 200 ml liquid; (3) 92 mg dosage form in 100 ml.

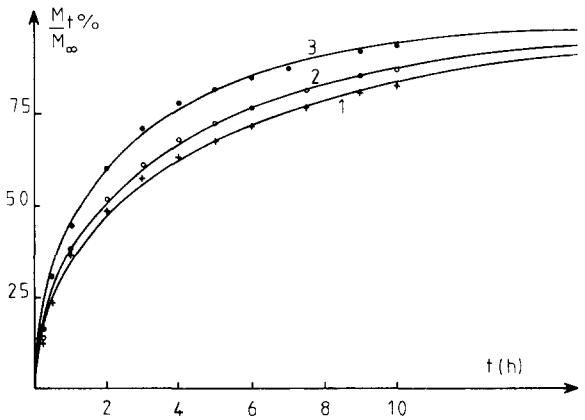

Fig. 1. Kinetics of drug release from oral dosage forms comprising Gelucire and sodium salicylate in a very large volume of synthetic gastric liquid. (1) Dosage form 1; (2) dosage form 2; (3) dosage form 3.

For cases 2 and 3, the ratio of the weight of the oral dosage form to the volume of liquid is almost identical, whereas in the first case, this value is considerably larger than in the latter two.

The diffusivity for drug delivery in the liquid is established by plotting the amount of drug released as a function of the square root of time, and employing Eqn 9. The values for D as calculated for all three cases are identical, i.e., $D = 4.9 \times 10^{-7}$ cm^2/s.

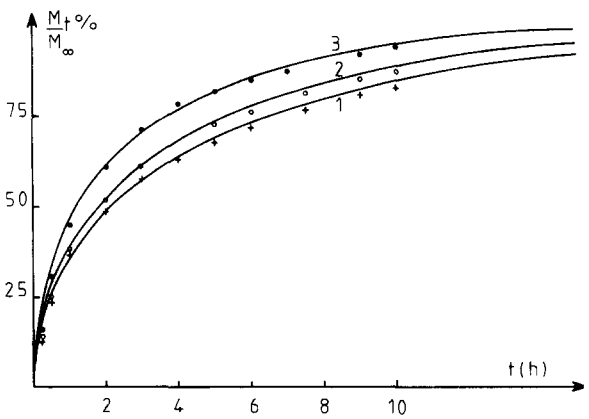

Fig. 2. Kinetics of drug release from oral dosage forms composed of Gelucire and sodium salicylate in a finite volume of synthetic gastric liquid. (1) Dosage form 1; (2) dosage form 2; (3) dosage form 3.

As demonstrated by the three curves shown in Fig. 1, the experimentally determined plots and those calculated based on theory are clearly in good agreement.

Finite volume of liquid

For the case of a finite volume of liquid, Eqn 6 must be used instead of Eqn 4. Calculation is performed with the consideration that the ratio of drug that is extractable from the dosage form amounts to 95% for dosage form 1.

The results on the kinetics as observed during experimentation and as calculated with the help of Eqn 6 are depicted in Fig. 2. As is clearly evident in Fig. 2, the close agreement between the two plots provides a further demonstration of the validity of this more complex model.

Conclusions

The main conclusion drawn from the present study is that the kinetics of drug delivery from dosage forms using Gelucire as a polymer matrix can be described on the basis of a diffusional process together with constant diffusivity. Analytical solutions exist for this simple case both when the volume of synthetic gastric liquid is very large and when very small as compared with the drug content of the dosage form.

This is an interesting conclusion from a practical point of view, since the kinetics of drug delivery can therefore be expressed in terms of time and of bead radius, in addition to being defined according to the liquid/bead volume ratio, by simple equations.

However, it should be borne in mind that the process follows a more complex course of development. Gelucire is slightly soluble in the liquid and the bead size decreases, as reported in a preceding paper (Bidah and Vergnaud, 1990). Thus, the rate of release of Gelucire is proportional to its actual surface area.

In fact, the process is perhaps even more complex than the description given by either of the two cases, with both diffusion and erosion playing contributory roles in the release of drug. Nevertheless, the general principle (Vergnaud, 1990) is still to be applicable. The liquid diffuses into the Gelucire, hence dissolving the drug which is then able to diffuse out of the dosage form through the liquid located therein. In addition to this classical scheme, Gelucire swells slightly when in contact with the liquid, subsequently undergoing dissolution at a sufficiently high concentration of liquid in Gelucire.

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