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Kinetics of in vitro release of sodium salicylate dispersed in Gelucire

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Summary

In order to obtain a controlled rate of delivery of sodium salicylate, spherical oral devices have been prepared and studied by using synthetic gastric liquid and in vitro tests. These devices have been prepared by dispersing the drug into Gelucire. The kinetics of release of drug has been found to be controlled by the erosion of Gelucire. The rate of drug delivery is then proportional to the actual area of the device, and a relationship between the time and the remaining weight of the device to the power one-third has been obtained. The effect of the (liquid volume)/(device weight) ratio on the rate of transfer has also been examined, and a decrease in this ratio provokes a decrease in the rate of transfer.

Introduction

Various ways have been explored to present oral dosage forms capable of delivering drugs at a constant rate, or at least a controlled rate. These techniques are based essentially on osmosis, diffusion and polymer erosion.

Monolithic devices have been prepared by dispersing the drug in a biocompatible polymer playing the role of a matrix, the polymer being either degradable (Heller, 1984; Malley et al., 1987) or non-degradable (Fessi et al., 1982; Touitou and Donbrow, 1982; Focher et al., 1984; Droin et al, 1985; Armand et al., 1987). Theories have been elaborated in order to describe the process of release of the drug. The dependence on the square root of time for drug delivery has been explained on the basis of diffusion of the drug through the polymer (Gurny et al., 1982; Touitou and Donbrow, 1982; Brossard et al., 1983; Teillaud and Pourcelot-Roubeau, 1984; Niklasson et al., 1985). In fact, the process is not so simple, and other studies have considered the simultaneous transfer of the liquid into and the drug out of the polymer matrix. Following these studies (Droin et al., 1985; Armand et al., 1987; Saber et al., 1989), the liquid enters the polymer inducing sometimes a swelling, dissolves the drug and then enables the drug to diffuse through the liquid located in the polymer matrix. Both these transfers have been found to be controlled by transient diffusion.

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These dosage forms are able to control the delivery of the drug, at a typical diffusion-controlled rate, the rate of delivery being very high at the beginning and decreasing gradually with time.

Other dosage forms able to deliver the drug at constant rate have been prepared. On the one hand, spherical dosage forms with a core and shell have been constructed and studied; the core consists of the drug dispersed in the polymer, while the shell is made of the pure polymer (Liu et al., 1988). On the other, spherical dosage forms with a core and erodible shell have been succesfully tested, the drug dispersed in a non-erodible polymer being located in the core (Magron et al., 1987; Laghoueg et al., 1989).

The main purpose of this paper has been to build up oral dosage forms by dispersing the drug in an erodible material such as Gelucire. Gelucire is a mixture of polyglycide fatty esters with controlled hydrophilic properties. Gelucire has been used for preparing hard gelatin capsules able to sustain release formulations of various drugs, or simulants (Doelker et al., 1983; Gateffosé, 1983). There is a large family of Gelucires, which are characterized by the melting point ranging from 33 to 64°C and by a hydrophilic-lipidic balance value. The material selected in this study is Gelucire 46-7 because it is slightly soluble in gastric liquid at 37°C, and then behaves as an erodible polymer. Another aim of the present study has been to develop a model able to describe the drug delivery, by considering that the rate of erosion is proportional to the actual area of the device. Particular attention has also been focussed on the volume of the device as well as that of the gastric liquid in which the device is immersed.

Theory

Assumptions

The following assumptions have been made in order to clarify the problem.

(i) The samples are spherical in shape.

(ii) The drug is properly dispersed into the bead.

(iii) The delivery of the drug is controlled by the erosion of the bead.

(iv) The rate of erosion of the bead is proportional to the actual external area of the bead.

(v) The initial weight of the bead and the volume of the liquid are taken into account, so that the concentration of drug in the solution can be established at the end of the process of delivery.

Mathematical treatment

The rate of erosion of the bead can be expressed via the rate of decrease in volume. Assumption iv is written as follows:

$$-\frac{\mathrm{d(volume)}}{\mathrm{d}t} = k(\mathrm{area}) = k(4\pi r^2) \tag{1}$$

By considering the values of the volume and external area of the spherical bead, eqn. 1 can be rearranged to yield:

$$-\frac{\mathrm{d(volume)}}{\mathrm{d}t} = 4\pi k\left(\frac{3}{4\pi}\cdot \mathrm{volume}\right)^{2/3}$$

$$= K' \cdot (\mathrm{volume})^{2/3} \tag{2}$$

Integration of eqn. 1 between the beginning of the process ($t = 0$) and time t gives:

$$(\mathrm{volume\ at}\ t=0)^{1/3} - (\mathrm{volume\ at}\ t)^{1/3}$$

$$= \frac{K'}{3}t = Kt \tag{3}$$

As the volume of the bead is proportional to its weight, Eqn. 3 is transformed as follows:

$$\left[\frac{M\ \mathrm{of\ bead\ at}\ t}{M\ \mathrm{of\ bead\ at}\ t=0}\right]^{1/3} = 1 - Kt \tag{4}$$

In the present study, measurements were carried out in the liquid and the weight of material in solution was determined. Eqn. 4 is then expressed by considering the values,

$$\left[1 - \frac{M_t}{M_\infty}\right]^{1/3} = \left[1 - \frac{M(\mathrm{dissolved\ at}\ t)}{M(\mathrm{dissolved\ at\ the\ end})}\right]^{1/3}$$

$$= 1 - Kt \tag{5}$$

Since all of the sample is dissolved at the end of the process and:

$$M(\text{of bead at } t = 0) = M(\text{dissolved at the end}) \quad (6)$$

Experimental

Materials

The following components have been used: Sodium salicylate (COPER) in powder form, for the drug; Gelucire 46-7 (Gattefossé, Lyon) for the erodible polymer matrix. Gelucire is a mixture of polyglycide fatty esters with controlled hydrophilic properties. The ratio between the number of quaternary ammonium and ester terminals is around 1 : 20. Each member of the Gelucire family is characterized by its melting point and the hydrophilic-lipidic balance value (HLB). The Gelucire selected melts at 46 °C (drop point : Mettler); the HLB value is 7, precisely in the middle of the 1–14 range.

Preparation of dosage forms

The grains of sodium salicylate were dispersed in melted Gelucire heated to around 50 °C. The heated mixture was stirred thoroughly in order to mix the components properly. The mixture was then cooled to room temperature. Various spherical beads were prepared from this paste with a ratio of drug to Gelucire of 50% w/w.

In vitro tests

Experiments were carried out in a closed flask with control of the rate of stirring. The bead inserted in a fiberglass basket is immersed into synthetic gastric liquid at 37 °C (composition (pH 1.2): 1000 ml of aqueous solution, 80 ml HCl (1 N) and 2 g NaCl).

At intervals, a small sample (1 ml) of liquid was taken for analysis. The concentration of drug in the liquid was determined by using a UV spectrophotometer (Hitachi U-1100) calibrated at 207 nm.

TABLE 1

In vitro test

Expt no.	Weight of bead (mg)	Radius of bead (cm)	Volume solution (ml)
1	210	0.34	221
2	95	0.28	100
3	266	0.38	100

Three kinds of experiments were performed and have been listed in Table 1. From the values in Table 1, it can be shown that the ratio (volume of solution)/(weight of bead) remains constant in Expts 1 and 2, despite the use of various weights of drug. For Expt 3, this ratio is 2.8-fold lower.

Results

The main results have been obtained for the kinetics of release of the drug into synthetic gastric liquid from devices made of the drug dispersed in Gelucire. Another feature has also been considered because it appears in both in vitro and in vivo tests,: namely, the effect of the (volume of drug)/(volume of liquid) ratio on the kinetics of release.

Kinetics of release of drug by erosion of the device

As the kinetics of drug release has been assumed to be controlled by erosion of the device, the rate of erosion (as well as that of release) has been taken to be proportional to the actual area of the device. The above mathematical treatment then led to the determination of the law relating the time to the weight of the bead to the power one-third, as shown in Eqns. 4 and 5. The values of $[1 - (M_t/M_\infty)]^{1/3}$ have been plotted as a function of time, for the three experiments described in Table 1 (Fig. 1).

Some results of interest have been drawn from the curves in Fig. 1:

(i) Straight lines are obtained from the beginning of the process to around 4 or 5 h. The slopes of these lines are equal to the value of the constant K in Eqn. 5.

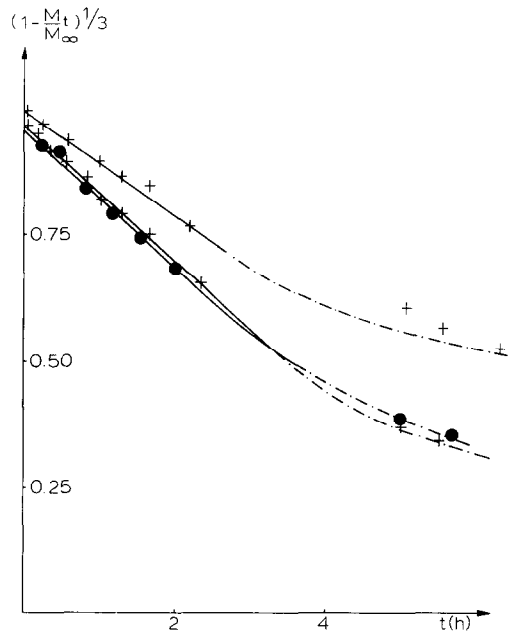

Fig. 1. $[1-(M_t/M_\infty)]^{1/3}$ plotted as a function of time (rate of release is proportional to the actual surface area).

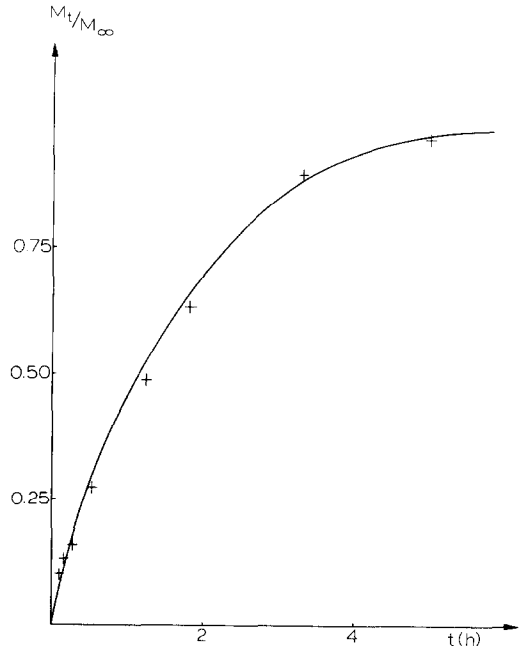

Fig. 2. Kinetics of release of drug. Weight of bead, 210 mg; volume of liquid, 221 ml. (———) Theoretical, (+) experimental.

(ii) The point of intersection of each of these straight lines with the vertical axis, denoted b, is near unity.

(iii) Following the results in (i) and (ii), the kinetics of drug release can be described by the erosion model, with a rate of release that is proportional to the area of the device or to the weight of the device to the power two-thirds.

The values of the constant K shown in Eqn. 5, which is equal to the slopes of curves drawn in Fig. 1, have been listed in Table 2, as well as the value of b.

The straight lines observed in Fig. 1, as well as the values of b of close to unity, demonstrate clearly that the process is controlled by erosion.

TABLE 2

Characteristics of the kinetics

Expt no.	Constant K (min^{-1})	b
1	2.21×10^{-3}	0.98
2	2.21×10^{-3}	0.96
3	1.74×10^{-3}	0.995

However, it is always better to compare the kinetics obtained from both experiments and calculations with the model.

The kinetics of release of drug in synthetic gastric liquid have been drawn in Figs. 2–4 for the cases listed in Table 1 as Expts 1–3, respectively, and have been obtained from experiments and via calculation.

A number of interesting results are indicated:

(i) Good agreement is obtained between the experimental and calculated kinetics of drug release for the entire process, except perhaps for Expt 3 in Fig. 4. (ii) In Expt 3 depicted in Fig. 4, the agreement between theory and experiment is perfect at the beginning of the process, but becomes steadily worse at the end of the process after 4 h of release.

(iii) The kinetics of release are described by the same equation in Expts 1 and 2, in spite of the fact that the weights of the devices were quite different (210 and 95 mg). The kinetics of release is slightly different in Expt. 3, with a lower value for the constant K (1.74 vs. 2.21 for Expts 1 and 2).

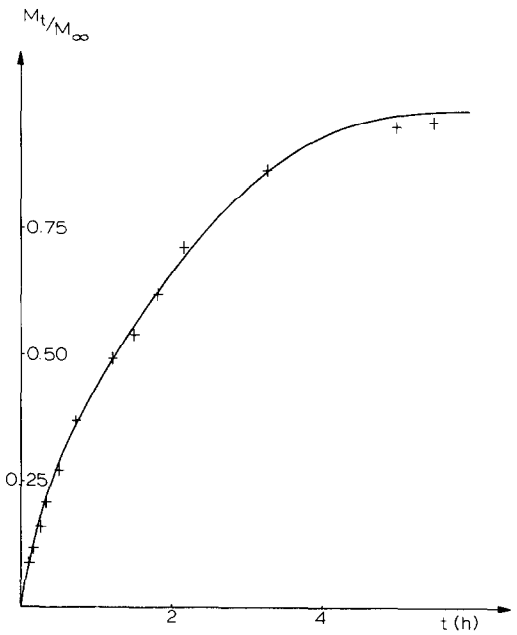

Fig. 3. Kinetics of release of drug. Weight of bead, 95 mg; volume of liquid, 100 ml. (———) Theoretical, (+) experimental.

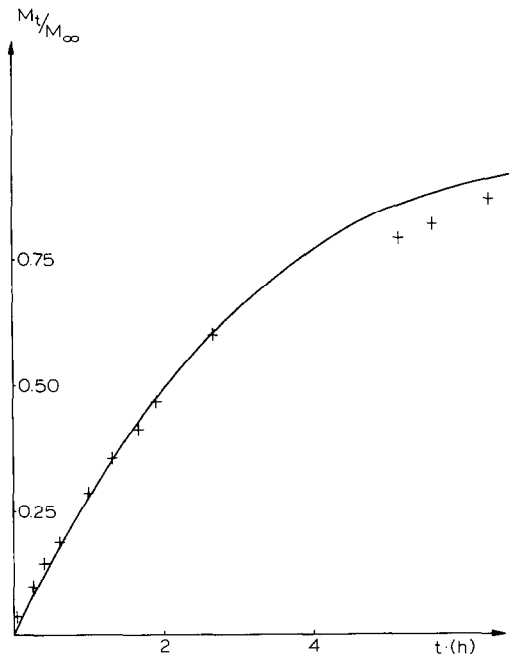

Fig. 4. Kinetics of release of drug. Weight of bead, 266 mg; volume of liquid, 100 ml. (———) Theoretical, (+) experimental.

(iv) The major factor concerned in all three cases is the ratio of the volume of liquid to the weight of the device.

Effect of the ratio (volume of liquid)/(weight of device)

For cases where the ratios (volume of liquid)/(weight of device) are equal, such as Expts 1 and 2, the same kinetics of drug release has been obtained, signifying that the rates of release are identical at any given time point, particularly at the beginning. For lower values of this ratio, e.g. as in Expt. 3, the kinetics of release differ slightly from those in the above two cases, and the rate of release of the drug is lower. This is clearly observed, especially for the initial stages shown in Fig. 4 (Expt 3).

Moreover, in Expt 3, with the lower value of the (volume of liquid)/(weight of device) ratio, the experimental and calculated curves are no longer superimposable after around 5 h of release, the experimental values being lower than those calculated.

This result is of interest with respect to both the kinetics of release and the matter transferred at the end of the process.

Conclusions

The process of release of drug has been studied by considering devices made of sodium salicylate dispersed in Gelucire. The kinetics of release has been described by assuming that the erosion of Gelucire plays the major role. The rate of release has then been found to be proportional to the actual area of the device, or to the actual weight of the device to the power two-thirds. Finally, the relationship between the time and the remaining weight of the device to the power one-third has been obtained.

Another parameter, concerned with the ratio (liquid volume)/(device weight) ratio, has also been studied by considering the value of the rate constant and the amount of drug transferred at the end of the process. The rate constant is identical in value for devices of various weights, when the above ratio remains constant. The value of the

rate constant decreases with decreasing values of this ratio.

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