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In situ absorption and in vitro release of microencapsulated cimetidine

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Summary

In vitro release and in situ (rat gut) absorption of free and ethyl cellulose microencapsulated cimetidine were studied. The $t_{50\%}$ value in vitro for encapsulated cimetidine was about 4 times greater than the $t_{50\%}$ of the free drug. In situ absorption studies showed that the disappearance of the drug from the small intestine was about two times slower in the case of microcapsules. A physical model was proposed to calculate the theoretical value of $t_{50\%}$ when microcapsules were used in situ.

Introduction

The potential application of microencapsulation to modify release of drugs in order to achieve the controlled or sustained release formulations has been often suggested (Paul, 1976). The search of literature shows that most of published papers describe investigations of in vitro release (dissolution) properties of microencapsulated drugs. Rather few reports are available to compare in vitro against in vivo assessments, or to correlate some of the in vivo parameters for free and microencapsulated drugs (De Sabata, 1976; Gardner et al., 1976; Somerville et al., 1976; Calanchi, 1979; Nixon, 1981; Vetter et al., 1981).

Since ethyl cellulose microcapsules were shown to possess a sustained release of drug in vitro (Nixon et al., 1978), we have prepared microcapsules with cimetidine,

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as a model drug, and studied the release properties of the drug both in vitro and in situ. The in situ technique originally proposed by Dolusio et al. (1969) was used here to study the disappearance of the free and microencapsulated drug from the small intestine of rat, because the technique was shown to provide meaningful data for an in vivo situation. A relatively simple technique of Dolusio et al. would possibly eliminate the need for more complicated in vivo studies during the preliminary steps of development of new dosage forms based on microcapsules.

Materials and Methods

Materials

Cimetidine (Tagamet, Belomet) was a gift from Podravka-Belupo, Zagreb, Yugoslavia. Ethyl cellulose had a viscosity of 45 mPas for a 5% w/w solution in toluene–ethanol mixture (80 : 20) w/w. All the chemicals used were of reagent grade purity.

Preparation of microcapsules

Microcapsules with a core-to-wall ratio of 1 : 1 were prepared from ethylcellulose solution in cyclohexane at 80°C by a modified method described by Nixon et al. (1978). The mean diameter ($\pm\sigma_g$) at 50% cumulative undersize was graphically determined and the value of 900 $\pm$ 208 μm was obtained.

Drug content in microcapsules

Triplicate samples of 50 mg of the microcapsules were accurately weighted and homogenized with 50 ml of Ringer solution. Aliquots of 100 μl were taken and diluted for spectrophotometric assay at 228 nm.

In vitro dissolution (release)

Dissolution of 10 mg of cimetidine or 20 mg of microcapsules was followed applying the flask and paddle method (Wagner, 1971). The dissolution medium (500 ml Ringer solution, pH 6), preheated to 37°C, was added to the 3-necked round-bottom flask with a 5 cm teflon propeller (stirring speed 50 rpm). 5 ml samples were removed at intervals and the drug content was determined. A constant volume of the dissolution medium was maintained by the addition of an equal volume of Ringer solution after each sampling.

In situ absorption

Male Fischer rats weighing 250–300 g were fasted 24–30 h prior to experiment. Water was allowed ad libitum. Twenty rats included in these experiments were anaesthetized 20 min prior to surgery with urethane (0.5 ml of 25% aq. urethane solution per 100 g body weight, injected intraperitoneally). Laparotomy was performed through a midline incision and two plastic cannulas were inserted into the small intestine at the duodenal and ileal end. Perfusion solution (Ringer solution, 37°C, pH 6) was passed through the intestinal segment (< 12 ml/min) until a clear

Fig. 1.

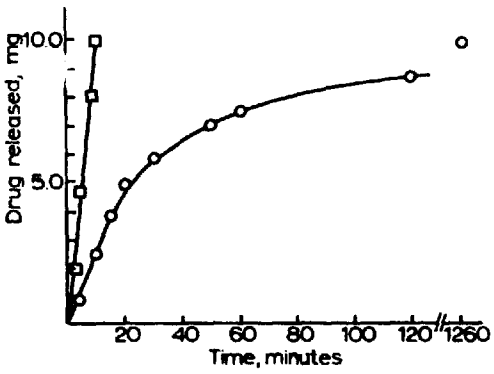

Fig. 2.

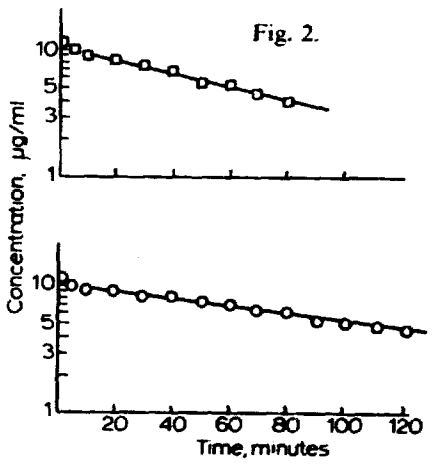

Fig. 1. In vitro drug release as a function of time (500 ml of Ringer solution, pH 6, 37°C): □, free drug; ○, microencapsulated drug.

Fig. 2. Semilog plot of rat intestinal lumen concentrations of drug against time (pH 6): □, free drug: ○, microencapsulated drug.

perfusate was obtained. The remaining perfusion solution was expelled by an air pump, and 10 ml of cimetidine solution (0.1 mg/ml) or an equivalent amount of microcapsule suspension was immediately introduced into the intestine. The samples were collected (0.1 ml) alternatively from duodenal and ileal syringe. Cimetidine concentrations in samples were determined spectrophotometrically at 228 nm.

Results and Discussion

The in vitro dissolution of unencapsulated cimetidine into the Ringer solution was rapid and under the conditions studied was completed within 12 min. The release profile of the drug from ethylcellulose microcapsules, illustrated in Fig. 1, shows a significant slowing down of the release rate in the case of capsules. The general shape of the curves followed the known pattern of drug release from ethylcellulose microcapsules. Since the solubility of cimetidine is 11.4 $mg \cdot cm^{-3}$ (0.045 M), sink conditions were observed during the in vitro experiments (10 mg of the drug in a 500 ml solution). The time required for 50% release, $t_{50\%}$ of cimetidine in vitro, for free cimetidine crystals and encapsulated cimetidine was graphically determined from the plots, and the values ($\pm$S.E.M.) obtained were 6 ± 1, and 24 ± 2 min, respectively.

In most in vitro and in situ gut preparations the apparent rates of drug absorption are relatively slow, whereas in humans and in intact animals they are quite rapid. On the contrary, the in situ technique by Dolusio et al. (1969) offers many opportunities for studying various aspects of the drug absorption process under conditions in which realistic absorption rates are obtained. Typical plots showing the disappearance of free and microencapsulated cimetidine from the

intestinal lumen solutions are given in Fig. 2. The results show that the drug disappears more rapidly in the early minutes of the experiments than at later times. After approximately 10 min in the intestine, decrease of drug concentration follows apparent first-order kinetics. For the purposes of this report, half-times for cimetidine disappearance from gut lumen, $t'_{50\%}$ were calculated from the straight lines of the semilog plots. For the free drug, the $t'_{50\%}$ value from 12 experiments was 54 ± 15 min. On the contrary, disappearance of encapsulated drug was found to be remarkably slower. The obtained value was 95 ± 20 min (8 experiments).

These data indicate a possibility of achieving a sustained drug release by using microencapsulated drug instead of crystal form. Furthermore, this study was carried out with only one type of microcapsule, but varying the characteristics of capsules (e.g. the amount of incorporated drug, the capsule size and porosity) one can modulate the time of release in vitro, and presumably in vivo.

Physical model

The data were analyzed by a physical model (Fig. 3A) which assumes that the permeation of the drug from the core of microcapsules to the blood side takes place through a 3-layered barrier. The permeability properties were calculated for each layer in order to get a theoretical value of the time required for 50% of the drug to disappear from the intestinal lumen when the absorption of the drug occurs from microcapsules in situ, $t'_{50\%,T}$.

The permeation process under pseudo-steady-state conditions is generally given by Fick's first law:

$$\frac{dm}{dt} = \frac{DA}{h}(c_I - c_{II}) \qquad (1)$$

where dm/dt is the diffusion rate at time t, D is apparent diffusion coefficient, A is the surface area, and h is the membrane thickness; c_I and c_{II} are drug concentrations inside microcapsules and in the receptor sink. Since $c_{II} = 0$, $c_I = c_s$ (solubility of

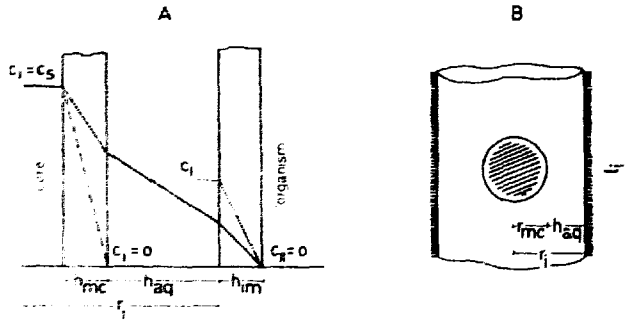

Fig. 3. Theoretical model of drug absorption from microcapsules in situ. (A) - - - - - -, microcapsules, in vitro; · · · · · ·, free drug, in situ; ———, microcapsules, in situ. (B) $l_i = 17$ cm, $r_i = 0.18$ cm, $r_{mc} = 0.09$ cm.

drug), $m = c/v$, and $DA/vh = k$, Eqn. 1 becomes:

$$\frac{dc}{dt} = kc_s \tag{2}$$

where k is the rate constant.

For a 3-layered barrier Eqn. 2 can be given as:

$$\frac{dc}{dt} = k_T c_s;$$

$$k_T = \frac{1}{\frac{h_{mc}v_{mc}}{D_{mc}A_{mc}} + \frac{h_{aq}v_{aq}}{D_{aq}A_{aq}} + \frac{h_{im}v_{im}}{D_{im}A_{im}}} \tag{3a,3b}$$

where k_T is speculated to be the "overall" rate constant, and it can be calculated in a way similar to the total permeability coefficient, with the difference being the introduction of respective values of v and A, which are not equal for each layer. The parameters needed (i.e. D, A, v and h) in each term were calculated separately as follows.

In case of microcapsules Eqns. 1 and 2 were rearranged to give:

$$\frac{h_{mc}v_{mc}}{D_{mc}A_{mc}} = \frac{c_s v_{mc}}{(dm/dt)_{mc}} = 52\ s^{-1} \tag{4a}$$

where $c_1 = c_s$ (the solubility of cimetidine is 11.4×10^{-3} g · cm^{-3}), $v_{mc} = m_{mc}/$ density $= 2 \times 10^{-2}$ cm^{-3}, and the slope of straight line (zero-order release in vitro) is 0.44×10^{-5} (Fig. 1).

The aqueous layer characteristics (see Fig. 3B) were:

$$\frac{h_{aq}v_{aq}}{D_{aq}A_{aq}} = 4380\ s^{-1} \tag{4b}$$

where $h_{aq} = r_i - r_{mc} = 0.135$ cm, $A_{aq} = 2\ r_i l_i \pi = 19.2$ cm^2, and $v_{aq} = 10$ cm^3 (the volume of sample introduced into the rat intestine). The diffusivity of cimetidine in water was calculated using the Stokes-Einstein equation ($D_{aq} = 1.6 \times 10^{-5}$ cm^2 · s^{-1}). It appears that D_{aq} might be the most erroneous determined parameter, because the effect of unstirred water layer on the diffusivity was not considered.

The term $(hv/DA)_{im}$ for the intestinal membrane was evaluated using the data obtained for the first-order absorption of the cimetidine solution in situ (Fig. 2). Since the first-order process the $t'_{50\%}$ (experimental = 3240 s) is given as: $0.693 = k_{im}t'_{50\%}$ it follows:

$$\frac{h_{im}V_{im}}{D_{im}A_{im}} = \frac{1}{k_{im}} = \frac{t'_{50\%}}{0.693} = 4670\ s^{-1} \qquad (4c)$$

Coming back to Eqn. 3b, the "overall" rate constant, k_T, was calculated from the above values (Eqn. 4a, b, c), and the theoretical value, $t'_{50\%,T}$ was calculated using: $t'_{50\%,T} = 0.693/k_T$. The value of 105 min was obtained, in very good agreement with the experimentally found value (95 min).

The future experiments should be aimed at the evaluation of microcapsular systems with various characteristics in order to investigate the applicability of the physical model for prediction of in situ behavior.

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