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A Controlled-Release Anti-Inflammatory Drug

Studies on Microcapsules

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ABSTRACT

A procedure to obtain a controlled-release microencapsulated anti-inflammatory drug based on a solvent evaporation method is described. The present method makes use of ethylcellulose as the polymer and methylene chloride as solvent. The evaporation of solvent is controlled by means of an air stream. Variations in the preparative procedure and their effects on capsule dimensions and permeabilities were studied. The release behavior of the drug is determined, and two different diffusion constants are also determined: 7.0×10^{-10} cm^2/s and 1.2×10^{-10} cm^2/s, corresponding to low and high release time. Based on these results it is proposed that these microcapsules have a nonhomogeneous polymeric wall, and are more porous in the outer surface. This model might be applicable to the microcapsules obtained by means of the solvent evaporation method.

Index Entries: Microcapsules, solvent evaporation method for; controlled release indomethacin, preparation and properties of microcapsules of; indomethacin microcapsules, diffusion constants and permeability of; permeability, ethylcellulose microcapsules of indomethacin.

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INTRODUCTION

Microencapsulation is the principal technology used to obtain controlled-release drugs (*1–4*). Thus it is important to have information about the permeability characteristics of the polymeric walls under conditions in which the drug must be used. However, few papers have been published on this subject (*5–7*). The present work deals with studies on the permeability of indomethacin microcapsules prepared by a solvent evaporation method (*8*).

EXPERIMENTAL

Preparation of Microcapsules

The procedure to obtain indomethacin microcapsules is one based on film formation from polymer solutions by solvent evaporation. The polymer used was ethyl cellulose and the solvent was methylene chloride. Crystals of indomethacin were dispersed in an ethyl cellulose–methylene chloride solution. The dispersion thus prepared was poured into an aqueous solution of gelatin and the system was stirred until an emulsion was formed. After evaporation of the solvent, the microcapsules were separated.

Determination of Drug Release

Drug release was measured by placing microcapsules in an extraction medium at pH 6.9. The amount of drug that moved into the medium at different time was measured using a ADP Alycar Apparatus type N. Formulary XIII.

To 60 mL of extraction solution in a tube immersed in a constant temperature bath at 37°C, a 15–20 mg quantity of microcapsules was added. The system was stirred during suitable time intervals and then the microcapsules were filtered off. The resultant liquid after suitable dilution was measured at transmittance of 319 nm. Indomethacin release was calculated.

Estimation of Permeability

By assuming a mechanism of permeable membrane and applying the first Fick's law:

$$\frac{dm}{dt} = -DA\frac{dc}{dx} \tag{1}$$

In this equation: dm/dt = moles per unit time passing to outer medium; D = diffusion coefficient; A = surface area through which diffusion takes place; dc/dx = concentration gradient.

By supposing a uniform concentration gradient of drug through the wall, unidirectional flux, and a thickness of wall constant during diffusive process, it is possible to integrate (*1*), the result being:

$$\ln C/C_o = -DA/VL\ (t - t_o) \qquad (2)$$

A and V = area and volume of microcapsules, considered not variable during diffusive process.

From the obtained release data and by plotting: log C/Co against $(A/2.303VL)(t - t_o)$, the diffusion constant was calculated.

RESULTS AND DISCUSSION

Effects of Selected Variables on the Indomethacin Release

The values obtained when making the measuring of drug release in a specified medium are depending on microcapsules size and characteristics of polymer wall: concentration and type of polymer used.

Figure 1 shows the influence of microcapsules size on drug release. For microcapsules obtained in the same process batch, a wide range of drug release is possible, depending on the microcapsules size.

Figure 2 shows that drug release decreases when polymers of increasing viscosity were used as wall material.

Figure 3 shows mean release time against concentration of drug in microcapsules. For our system, it is evidently not convenient to use concentrations lower than 60% and higher than 85%, because drug release values that are too low or too high are obtained. When making a design

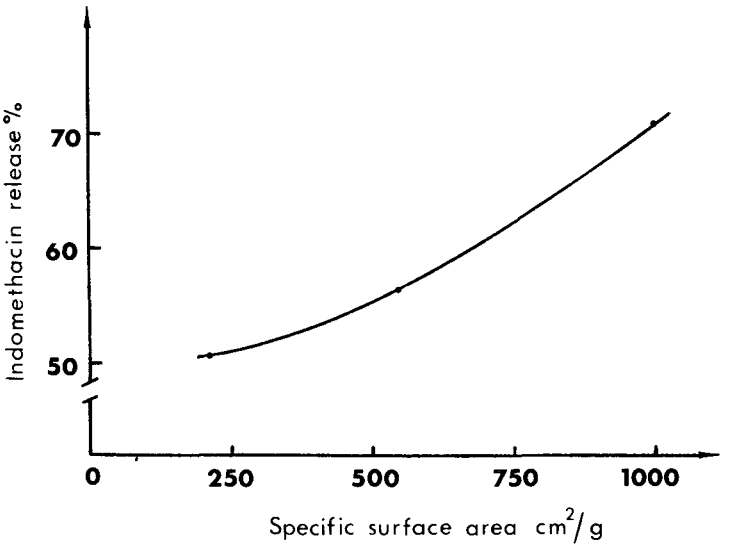

Fig. 1. Plot showing the effect of microcapsular surface area on indomethacin release in a 2 h extraction with solution at pH 6.9.

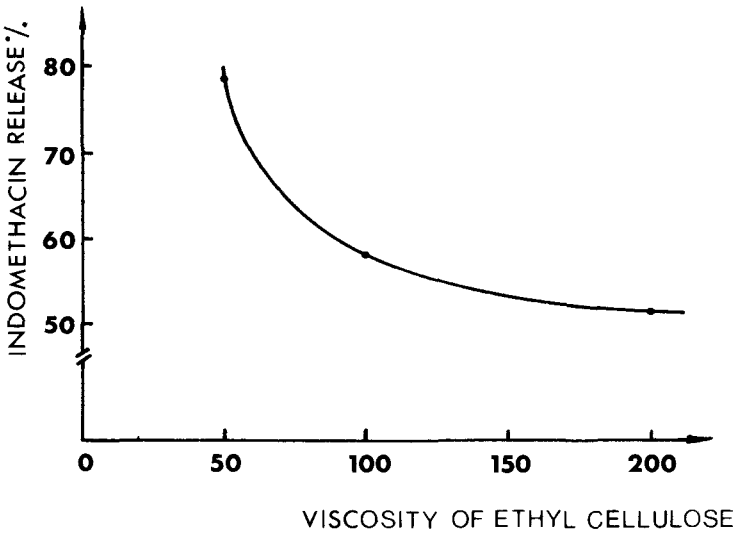

Fig. 2. Plot showing the effect of different viscosities of ethylcellulose N type, used as wall material, on indomethacin release in a 2 h extraction with solution at pH 6.9.

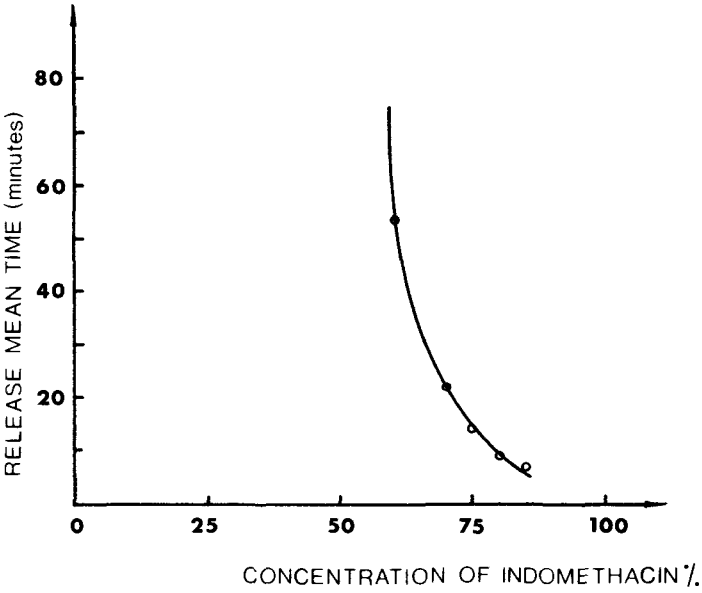

Fig. 3. Plot showing the effect of the initial concentration of indomethacin in microcapsules on the mean release time of indomethacin when extracted with a pH 6.9 medium.

of controlled-release microcapsules, the concentration of drug and the type of polymer to use as the wall may be selected for convenience. The final size of the microcapsules is the result of many process variables affecting the size of emulsion. The type and rate of stirring, the internal

phase/vehicle mass rate, the composition of vehicle, and the concentration of polymeric solution were studied.

Diffusion Constant

In the drug release mechanism, it is possible to consider three steps:

1. Permeation of extraction medium into the microcapsules.
2. Dissolution of drug by the extraction medium.
3. Permeation of dissolved drug out of microcapsule.

The release curves vs time obtained did not show an induction period as observed by Thies (*4*). In Fig. 4 the log of drug retained in microcapsules is plotted vs time of extraction for different concentrations of drug. It is possible to consider two zones: the first corresponding to 0–10 min and 0–40 min., and the second for longer times. The second zone corresponds to straight lines that obey Fick's law and the slope of which in absolute value is lower than the limit slope assigned to the first zone. It is observed that the zone of constant slope starts at an extraction time of 10 min for capsules with lower concentrations of drug, whereas for capsules of highest concentration it starts just at 40 min. In Fig. 5 it is possible to measure two perfectly designed slopes that correspond to two different values of diffusivity for the microcapsules using ethylcellulose N 50-type as wall polymer. These values are: 7.0×10^{-10} and 1.2×10^{-10} cm^2/s.

These observations could be explained by the existence of a nonhomegeneous membrane as the wall of the capsule.

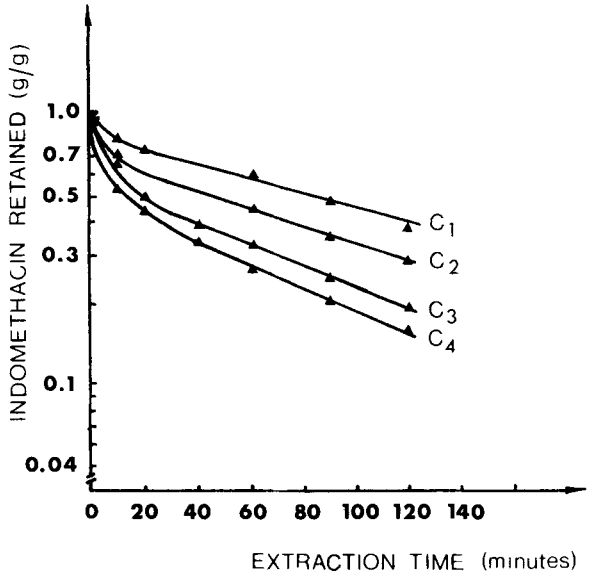

Fig. 4. Plot of the log of indomethacin retained in microcapsules against the time of extraction with a solution at pH 6.9 for different concentrations of drug. C_1, C_2, C_3, C_4 = 60, 70, 75, and 80 g%/g indomethacin in microcapsules.

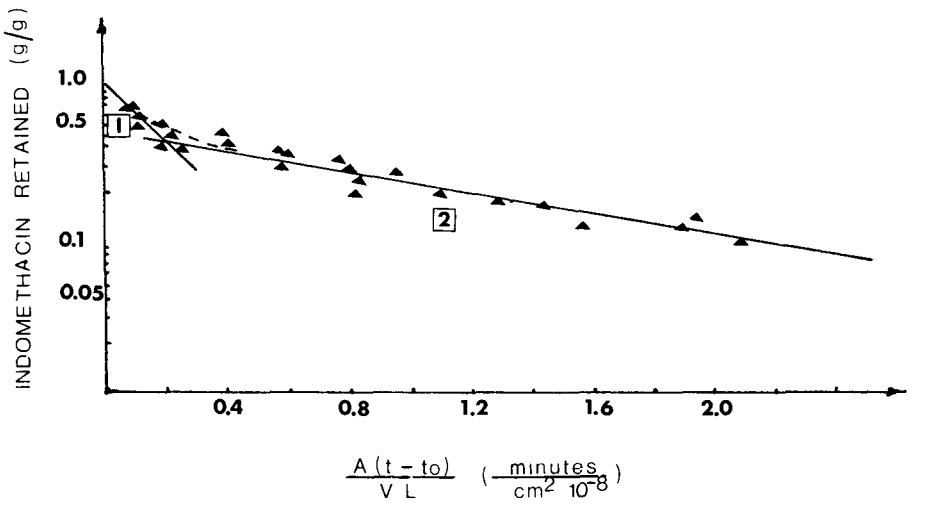

Fig. 5. Plot of log of indomethacin retained in microcapsules against $A(t - t_o)/LV$. Slope of 1 = $7.0 \times 2.303 \times 10^{-10}$ cm^2/s; Slope of 2 = $1.2 \times 2.303 \times 10^{-10}$ cm^2/s.

Model of Microcapsule Structure

The experimental data obtained could be explained by considering a microcapsule formed by concentrical spherical "layers," effective diffusivity of which decreases toward the center of the microcapsule. Likewise it could be assumed that there exists a decreasing concentration of drug gradient from the center toward the surface, and an increasing gradient of polymer in the same direction. The polymer would be porous at the surface and the porosity decreases toward the center of the microcapsule. Therefore it could be assumed that the layer involved in permeation at the first minutes correspond to a more porous "layer." The existence of porous "layers" at the surface could be explained by the mechanism of evaporation of solvent. This model, based on indomethacin microcapsules, could be extended to other microcapsule systems obtained by the solvent evaporation method.

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