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Evaluation of permeation through polymeric membranes as a model for the release of drugs from gelatin–acacia walled microcapsules

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Summary

The evaluation of gelatin–acacia membranes as suitable models for the release of various N-7-theophylline derivatives from similar walled microcapsules prepared by a coacervation technique has been studied. The dependence of transfer rate on partition coefficient and phase boundary resistance is discussed. The validity of the diffusional film model is tested. The rapid release of theophylline and caffeine from this type of microcapsule is shown to agree with predictable theory.

Introduction

Many attempts have been made to produce microencapsulated sustained release products and research still continues in this field (Herbig, 1968; Luzzi and Palmieri, 1984). The walling material is of major importance in controlling the rate of release, but because of the small size of the product it is difficult to determine the normal diffusional parameters. The potential for using films of walling material as a model in the study of release kinetics from microcapsules has been suggested (Konig and Goodman, 1977), and both Palmieri (1977) and Gayot et al. (1978) have discussed the use of such films for diffusional studies. However, Benita and Donbrow (1982) had only limited success in correlating model film and microcapsule permeability, possibly due to preparative differences between their polymer films and microcapsules.

Materials and Methods

Materials

Gelatin: acid oisein, Bloom Nr 200 (Kodak). Acacia: B.P. (MacCarthy). Aminophylline anhydrous (Sigma). Theophylline anhydrous (Fluka AG). N-7 theophylline acetic acid (Fluka AG). Etofylline (Amido F_2 Laboratories). Diprophylline (Berck Pharmaceuticals). Formalin (Fison). Octon-1-ol (Fison). Glass-distilled water was used throughout.

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Methods

Preparations and characterisation of gelatin–acacia coacervate film. Methods for the preparation of the films have been reported in detail by Wong and Nixon (1986) and are depicted diagrammatically in Fig. 1. The morphological characteristics were examined using a scanning electronmicroscope (Philips EM 501B). The swelling behaviour in water is given by: swelling value (SV) = weight of water uptake in film/weight dry film. Values were determined at regular intervals. Before weighing, excess surface water was removed.

Permeation through gelatin–acacia films. The detailed procedure has been described by Wong (1987). Initial concentrations of caffeine, theophylline, etofylline and aminophylline were 0.001 M and of N-7-theophylline acetic acid and diprophylline 0.001 M. The concentration changes in both donor and receptor cell compartments were monitored using a continuous-flow system attached to a UV spectrophotometer (Cecil CE 292). All measurements were made at $37 \pm 0.5\,^{\circ}$C.

Preparation and characterisation of gelatin–acacia walled microcapsules. The standard coacervate technique for the preparation of complex coacervate walled microcapsules was used to encapsulate theophylline, caffeine and N-7-theophylline acetic acid. The surface structure was examined by electron microscopy, whilst aqueous mounts showing the internal structure were viewed using an optical microscope (Nikon, type 104). Densities of both the microcapsules and the drug core were determined using a Beckman air-comparison pycnometer. The total drug content of the microcapsules was determined by UV spectrophotometry after refluxing with isopropanol at $80\,^{\circ}$C for one hour. The thickness of the microcapsule wall was calculated using the equations of either Luu Si-Nang et al. (1973):

$$h = \frac{r_2(1-F)\rho_c}{3F\rho_p + (1-F)\rho_c}$$

or Benita and Donbrow (1982):

$$h = r_2 - r_1 = \left\{\left(\frac{\rho_c}{\rho_p}\left(\frac{1}{F} - 1\right) + 1\right)^{1/3} - 1\right\} r_1$$

where r_1 is mean core radius, r_2 mean microcapsule radius, h microcapsule wall thickness, F drug fraction, ρ_c core density and ρ_p polymer coating density.

Dissolution from microcapsules. A computerised dissolution system (Copley: Ultraspec TDS 4052 and Apple IIe computer) was used. Weighed microcapsules giving a total equivalence of less than 5% saturation, a stirring speed of 100 rpm and a temperature of $37 \pm 0.5\,^{\circ}$C was used throughout.

Results and Discussion

The pre-requisite for the use of a polymeric film as a model of release from microcaps is to be capable of preparing it by a technique simulating the way in which the colloid components of the microcapsule wall interact and are deposited from solution. The technique depicted in Fig. 1 allows 3 variations in casting technique to be studied. The most satisfactory films, corresponding closely to the complex coacervate microencapsulation process, are those in which the supernatant equilibrium liquid was removed prior to casting (Fig. 1).

The thermodynamics of polymer separation, both in film formation and microencapsulation, follow the Flory-Huggins theory (Flory, 1953; Molyneux, 1984) which uses the balance between the free energy change of mixing and interaction. In complex coacervation the maximum electrostatic interactions occur at an optimum pH, whilst the favourable entropy contribution is partly due to the release of bound counterions into the supernatant liquid. The total free interfacial energy of the system is reduced by the coalescence of liquid polymer droplets, which decreases the surface area of the wall material.

This is supported by the scanning electron micrographs of the films (Fig. 2). Methods 1 and 3 (Fig. 1) produced films in which incomplete fusion of the coacervate droplets could still be seen (Fig. 2A and B). By contrast, the film formed by slow phase separation, Method 2, produced complete fusion of the coacervate droplets (Fig. 2C and D). These latter 'dense' films showed marked similari-

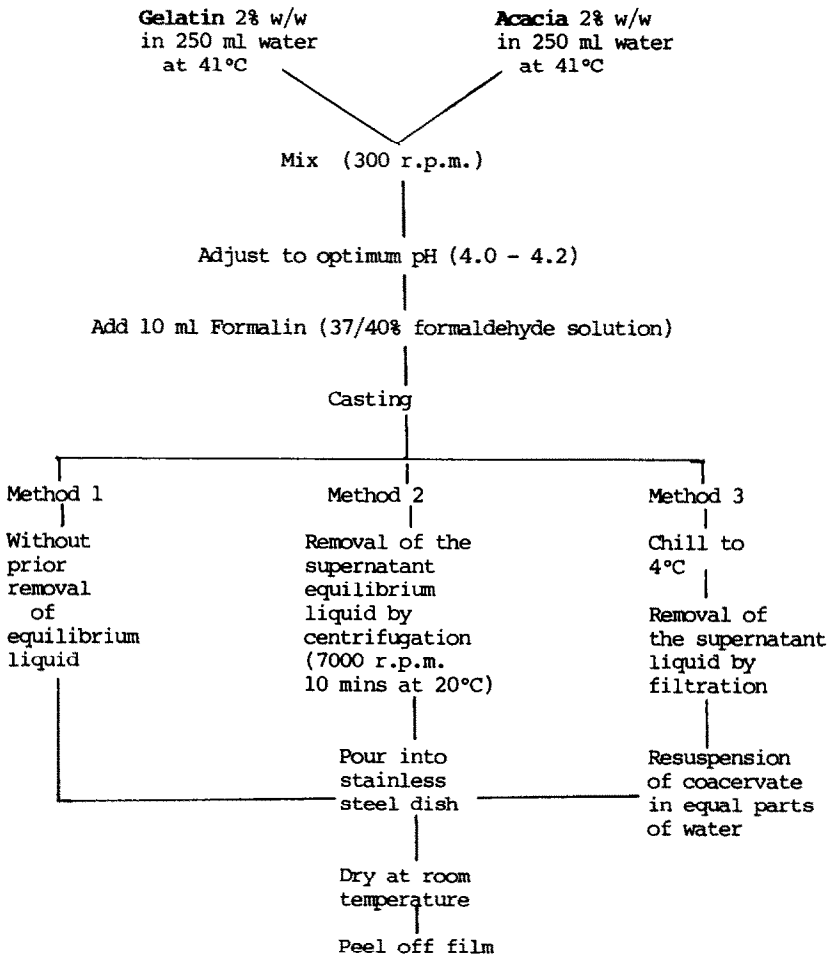

Fig. 1. The preparation of gelatin–acacia coacervate film.

ties to their corresponding microcapsules, whose walls are generally non-porous and smooth (Fig. 3).

Dissolution from microcapsules normally occurs in an aqueous environment and the use of model films allows the swelling associated with the coacervate wall to be studied directly. Bixter and Sweeting (1971) postulated an enhanced permeability of polymer films due to swelling of the polymer structure after sorption of the permeant. Swelling in the gelatin–acacia films may be shown to depend on the degree of cross-linking (Fig. 4). However, only a qualitative comparison could be made between cross-linked and non-cross-linked films, although in the latter, the entanglement of the polymer chains may act as a physical cross-linking. Gelatin–acacia coacervate film behaves as a hydrogel and the solute diffusion coefficient will depend on the equilibrium water content (Yasuda et al., 1968). Ratner and Hoffman (1976) have reported that as the water content of the gel increased, the fraction of 'bulk' water, as opposed to 'bound' water, also increased. Because of the flexible nature of the hydrophilic polymer chains in the gelatin–acacia coacervate film, a large amount of 'bulk' water can be absorbed, giving a

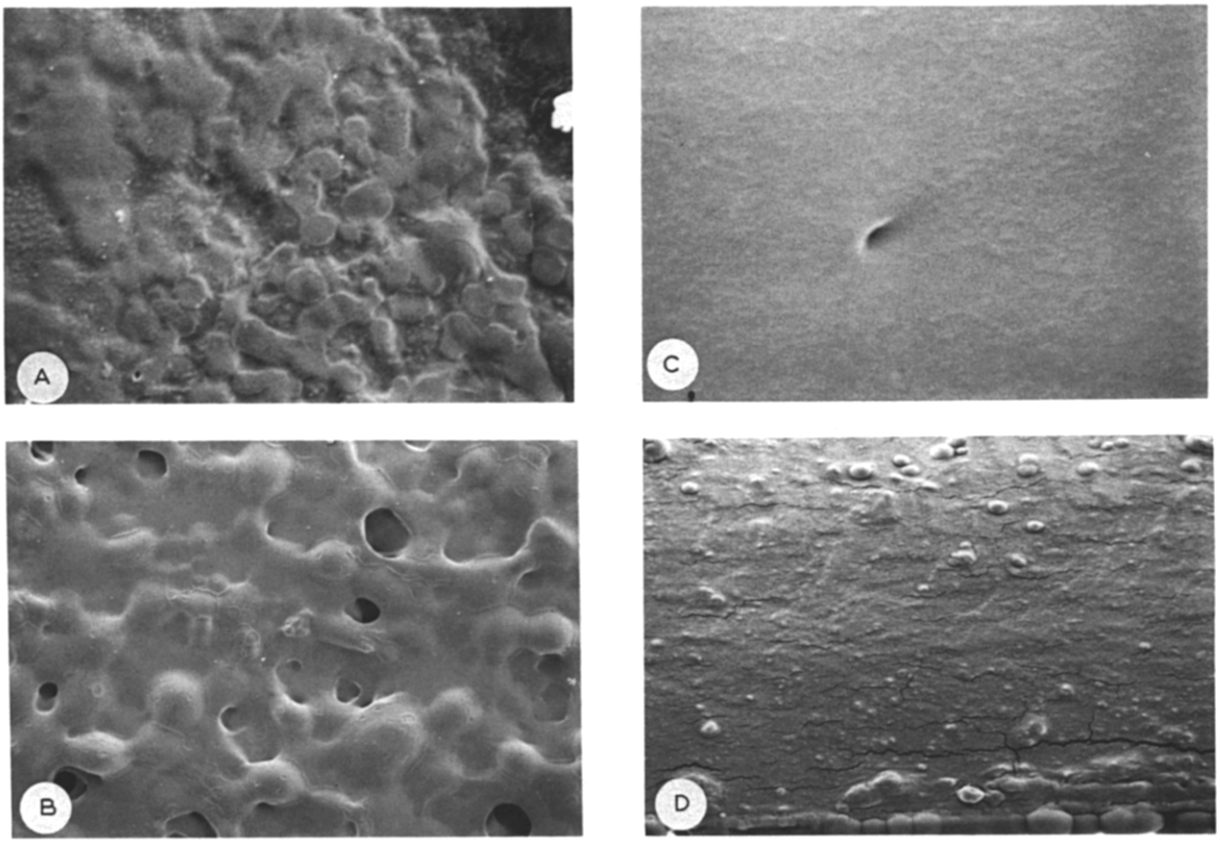

Fig. 2. Scanning electron micrographs of gelatin-acacia coacervate films prepared by different casting techniques. A: surface of film prepared by casting method 1. B: surface of film prepared by casting method 3. C: surface of film prepared by casting method 2. D: cross-section of film prepared by casting method 2.

high degree of hydration favourable to extensive swelling both in the film and in the corresponding microcapsules.

A simple two-compartment cell, in which the film was clamped between the two halves, was used to study diffusion, using Fick's first law to describe the relationship. The effect of the physicochemical properties of the permeant was demonstrable with a series of N-7-theophylline derivatives. It was found that both the thickness of the membrane and the partition coefficient of the permeant played part in controlling the transitions from membrane control to aqueous phase control of drug transport through coacervate film. The transport rate of N-7-theophylline derivatives increased exponentially with increasing partition coefficient reaching a critical value after which membrane resistance was no longer dominant and a static saturated concentration layer became the controlling factor (Fig. 5 and Table 1). The mathematics of this phenomenon have been discussed in detail by Flynn et al. (1972).

A positive correlation exists between the permeability and partition coefficient (Fig. 6) indicating the importance of the relative affinity of the solute towards the membrane or solvent phase during permeation.

The internal structure of the microcapsule is important in determining the release kinetics of these typical monolithic microcapsules. Both scanning electron and optical micrographs (Figs. 3c and 7) show the needle-shaped crystals of N-7-theophylline acetic acid,which is less aggregated when microencapsulated. With the more soluble drugs,

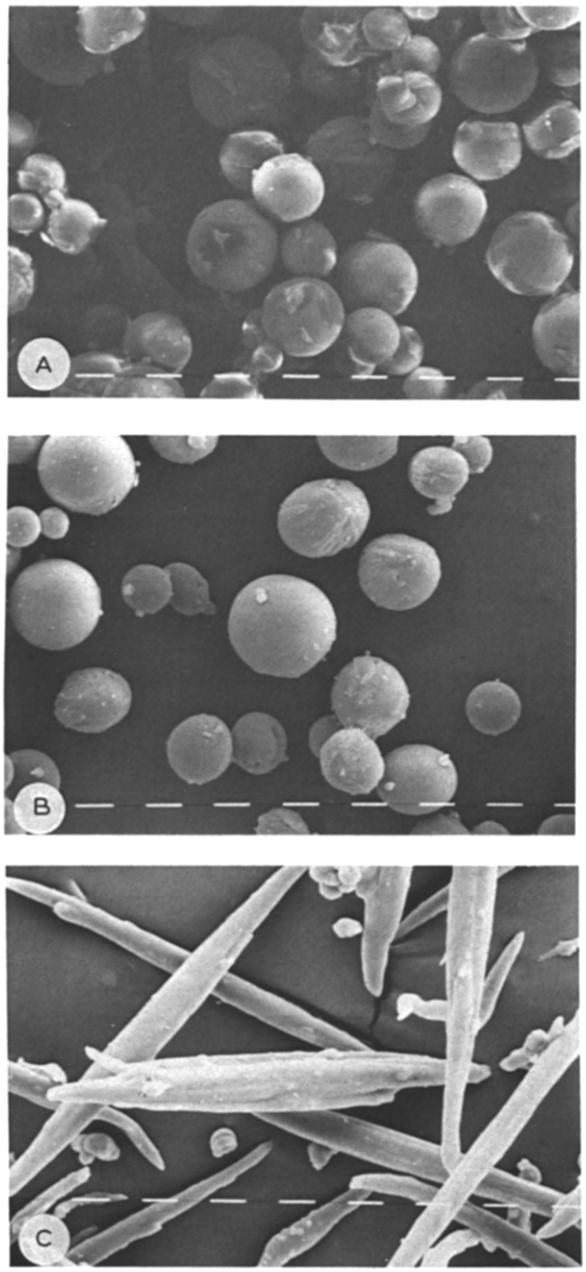

Fig. 3. Scanning electron micrographs of drug containing gelatin–acacia walled microcapsules: (A) theophylline; (B) caffeine; (C) N-7-theophylline acetic acid.

theophylline and caffeine, microencapsulation could only be achieved from a saturated solution in which excess drug was dispersed to give a solid

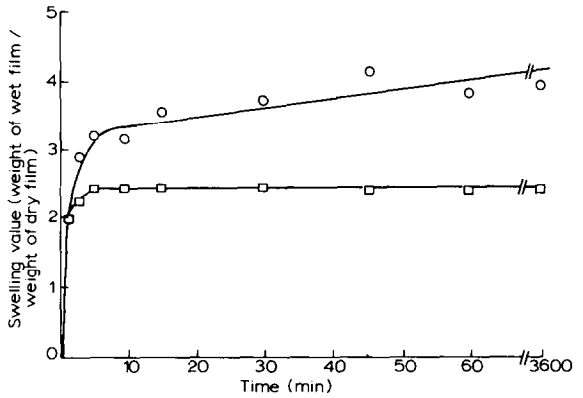

Fig. 4. The swelling behaviour of gelatin–acacia coacervate films in water at 20 °C. Method of casting = 2. ○, non cross-linked; □, cross-linked.

core. As shown in Figs. 3A and B, the resulting microcapsules were smooth-coated and spherical. Even using this technique, the washes with isopropanol removed significant portions of the solid core.

The mean size of the microcapsules as measured by the Coulter counter (Table 2) is larger than the corresponding value obtained from scanning electron microscopy (Fig. 3) due to hydration. The swollen hydrated state, providing a larger surface area and greater wall thickness than the dry powder, is closer to conditions encountered

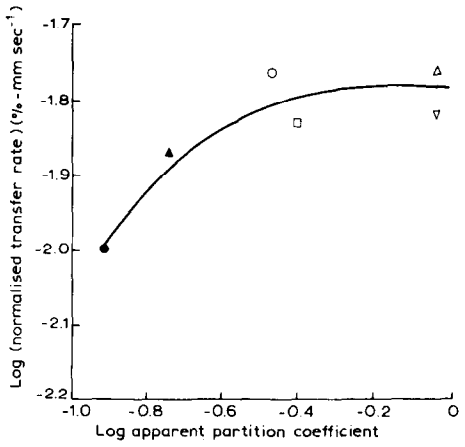

Fig. 5. Dependence of transfer rate of N-7-theophylline derivatives on partition coefficient. △, theophylline; ○, aminophylline; ▽, caffeine; □, etofylline; ▲, diprophylline; ●, N-7-theophylline acetic acid. Casting method = 2; temperature 37 °C.

TABLE 1

The effect of film thickness on membrane and aqueous phase resistance

Drug	Film thickness (cm)	Membrane resistance, R_M ($\times 10^{-4}$ s · cm^{-1})	Aqueous phase resistance, R_A ($\times 10^{-4}$ s · cm^{-1})	R_M/R_A
Theophylline	0.029	2.4	0.50	4.8
	0.012	0.99	0.50	2.0
Aminophylline	0.028	3.0	0.25	12
	0.015	1.6	0.25	6.4
Caffeine	0.032	2.6	0.95	2.7
	0.013	1.0	0.95	1.1
Etofylline	0.030	2.9	0.90	3.2
	0.015	1.4	0.90	1.6
Diprophylline	0.031	5.7	0.10	57
	0.015	2.8	0.10	28
N-7-theophylline acetic acid	0.037	8.0	0.25	32
	0.014	2.9	0.25	12

during release, which is a function of permeability to the dissolution media and the solubility of the core material. Release from spherical reservoir microcapsules can be considered as planar diffusion through a thin membrane.

Because of the small size, steady-state release from microcapsules is rapidly achieved, but is maintainable only for a short period before internal saturation no longer exists. Therefore the initial zero-order release will rapidly give way to first-order release kinetics. Zero-order permeabilities of caffeine, theophylline and N-7-theophylline acetic acid are 1.5×10^{-9}, 1.1×10^{-8} and 3.1×10^{-9} cm^2 · s^{-1} respectively, whilst the corresponding first-order permeabilities during the second stage release are 3.9×10^{-10}, 5.2×10^{-10} and 1.8×10^{-10} cm^2 · s^{-1}. In contrast, the permeability of the gelatin–acacia model film to the same 3 drugs

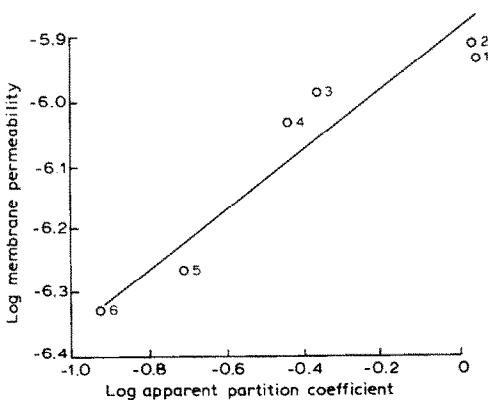

Fig. 6. Dependence of membrane permeability on the apparent partition coefficient at 37 °C. (1) Theophylline; (2) caffeine; (3) etofylline; (4) aminophylline; (5) diprophylline; (6) N-7-theophylline acetic acid.

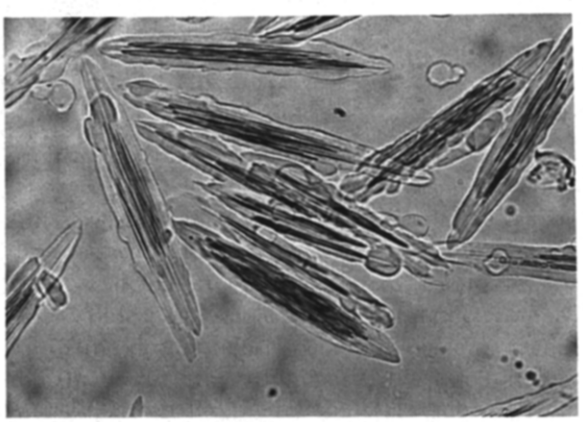

Fig. 7. Optical photomicrograph of N-7-theophylline acetic acid containing gelatin–acacia walled microcapsules.

TABLE 2

Estimated wall thickness and surface area of gelatin–acacia microcapsules with various drug cores

Drug	Mean diameter ± S.D. (μm)	Specific surface area ± S.D. ($\times 10\ m^2 \cdot g^{-1}$)	Estimated wall thickness (μm)
Caffeine	31.79 ± 1.36	1.43 ± 0.14	5.2 *
Theophylline	38.21 ± 0.61	1.24 ± 0.02	6.1 * 5.4 **
N-7 theophylline acetic acid	26.15 ± 3.58	1.83 ± 0.30	3.4 * 11.2 **

S.D. = standard deviation.
* Luu Si-Nang equation.
** Benita and Donbrow equation.

are 1.25×10^{-6}, 1.22×10^{-6} and $4.7 \times 10^{-7}\ cm^2 \cdot s^{-1}$ in the same order.

Thus the estimated membrane permeability of the microcapsule wall was approximately 10^2–10^4 less than with the film. This could be due to differences in the cross-linked density between the microcapsule wall and the cast film.

Mathematical models, such as those discussed by Reinhart et al. (1981) do not account for the aqueous phase boundary resistance, or the changes in size due to hydration, both of which influence drug release. Shape factors, as with the needle crystals of N-7-theophylline acetic acid, and the film casting substrate, may also contribute to divergence from a theoretical model. Bakan (1980) recognised some of these difficulties and suggested that the deposition of polymer onto a drug core produces inherent properties which may be difficult to simulate in a cast film.

In general it can be seen that gelatin–acacia coacervate does not materially slow the release of a drug core, and with N-7-theophylline acetic acid resulted in faster solution than with the unencapsulated drug. This phenomenon may parallel the enhanced bioavailability of poorly water-soluble drugs when prepared as molecular dispersions in water-soluble polymers (Chiou and Riegelman, 1971). The reduction in aggregation and the large increase in surface area attendant on microencapsulation act in the same way.

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