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Release kinetics of sparingly soluble drugs from ethyl cellulose-walled microcapsules: theophylline microcapsules

S. BENITA AND M. DONBROW*

Department of Pharmacy, School of Pharmacy, Hebrew University of Jerusalem, Jerusalem, P.O.B. 12065, Israel

Release rates of theophylline from ethyl cellulose-coated microcapsules were measured as a function of wall thickness and core particle size. The kinetic data conformed with first order release and also the Higuchi matrix model. However, application of the differential rate treatment, hitherto applied only to drug matrix dispersions, showed that release from the microcapsules definitely followed the first order equation. For the purpose of confirming that the release process was membrane-controlled, the experimental rate constants were transformed into effective permeability constants (P_1) with the aid of the microcapsule dimensional parameters needed in the relevant equations and compared with the permeability constant (P) of theophylline measured experimentally using planar ethyl cellulose membranes. P_1 values decreased linearly to a moderate extent with wall thickness, probably due to decrease in porosity during wall-formation. P_1 values of the thicker-walled microcapsules were found to be of the same order as the membrane P value, supporting a release mechanism of membrane control under non-steady state conditions.

An application of microencapsulation is in the preparation of controlled-release products (Herbig 1967; Luzzi et al 1970; Feinstein & Sciarra 1975; Scheu et al 1977). The release rate would be expected to vary with the thickness, porosity and capillarity of the coat and also the particle size of the core, parameters which will be determined by the experimental conditions used. An insufficiently defined factor in release studies is the dispersion state; for example, products may contain dispersed microparticles of core material, or may be agglomerates of partially or completely coated microcapsules. Different release kinetic patterns have been obtained from ethyl cellulose (EC) microcapsules coacervated in the presence or absence of a protective colloid. In the latter case, a matrix diffusion equation similar to that describing release from particles dispersed in an insoluble matrix was applicable (Salib et al 1976; Jalsenjak et al 1976; Deasy et al 1980). On the other hand, first order release has also been reported and, in this case, a protective colloid had been employed (John et al 1979; Donbrow & Benita 1977). It may be that these different release patterns reflect different types of microcapsule structure, produced under different preparative conditions.

We have recently reported on the importance of a protective colloid, polyisobutylene (PIB), in forming individually film-coated core particles as opposed to aggregates (Benita & Donbrow 1980, 1981). The present work is an examination of the in vitro release kinetics of drugs sparingly soluble in water from such microcapsules.

Release rates have been studied as a function of wall thickness and particle size and, in addition, the permeability constant of the EC wall material, calculated from release rate constants and microcapsule size parameters, have been compared with the permeability constant obtained in parallel diffusion experiments performed using planar EC membranes.

MATERIALS AND METHODS

Materials

Ethyl cellulose (N-type) had an ethoxyl content of 47·5–49·0%. The viscosity of a 5% w/w solution in toluene–ethanol (80 : 20 w/w) was 100 cps (Hercules, Wilmington, Delaware). Polyisobutylene had a mol. wt of 380 000 (Oppanol B50, BASF, Ludwigshafen, West Germany). Theophylline conforms to B.P. 1973.

Methods

Microcapsule preparation. Details of the cooling method of EC coacervation used in microcapsule preparation and the methods of evaluation have been described (Benita & Donbrow 1981). The composition and properties of the theophylline micro-

* Correspondence.

capsules of which the release kinetics is discussed here (including the method of determination of release rates) were described by Benita & Donbrow (1981).

Wall thickness determination. The wall thickness of the microcapsules was calculated from the drug content, particle size of the core material and the relative densities of the wall material and core material. Quantitative expression of the relationship requires use of a shape factor, and since particle shape and size vary widely, even within batches of a single core material, it is generally assumed that the core particles are spherical and the capsule wall uniform.* This enables the use of a simplified model in which the microcapsule is considered to be composed of two spheres, and using the appropriate relationship (Herbig 1967) re-expressed in terms of fractional drug content, a mean spherical wall thickness is estimated:

$$r_2 - r_1 = \left\{\left[\frac{d_c}{d_{EC}}\left(\frac{1}{F} - 1\right) + 1\right]^{1/3} - 1\right\} r_1$$

where r_1, r_2 are the mean radii of the microcapsules and the core particles and d_{EC}, d_c are the densities of ethyl cellulose and the core materials. The densities of the microcapsules and the core and wall materials were determined in cyclohexane using a pycnometer. Dried materials were used and volume adjustment was completed in a few seconds to avoid imbibition and swelling. The results duplicated exactly and were within 2% of literature values.

Planar film preparation. The films were cast from a chloroform solution containing 10% w/w EC on glass plates using the techniques of Kanig & Goodman (1962). The solvent was allowed to evaporate for 24 h. The films were removed from the plates after immersion in water for 10 min and were air-dried on large sheets of filter paper for 24 h at ambient temperature. Selected fault-free portions were used in permeation studies, mounted with the upper film surface (air-exposed during formation) towards the drug solution.

Determination of film thickness. Dry film thickness was measured in ten different places by means of a micrometer (Tesa, Switzerland). Variation was not more than 5% over the film surface.

* In the present work, it was shown that the microcapsules were (a) composed of single-core particles, (b) unaggregated, (c) uniformly coated, as judged by photomicrographs of the solvated product during formation and in cyclohexane after 'hardening', and, again, by the shape and smoothness of SE Micrographs (Benita & Donbrow 1981).

Determination of film permeation rate. Permeation rates were determined using dissembling diffusion cells in which the film was clamped centrally between the compartments, forming a hermetic seal between them. One size of chamber was found convenient, holding a volume of 50 ml of liquid in each compartment, the effective area of the film being 12·55 cm^2 in all this work. The exact volumes of distilled water and drug solution, both previously warmed to 37 °C, were added to the respective compartments and both were stirred from the moment addition was completed by utilizing two channels of a multi-channel polystaltic pump (Buchler Instruments, Fort Lee, N.J.) operated at a flow rate of 20 ml min^{-1}. The sink solution flow was monitored spectrophotometrically (Unicam SP 1800, Cambridge, England) by use of a 10 mm flow cell in the channel and the diffusion cell was maintained thermostatically at 37 °C. Experiments were duplicated and measurements continued for 24 h. Theophylline was measured at 272 nm. Concentrations in the sink solutions were negligably low and in the permeating drug solutions essentially unchanged, so that the concentration gradient was virtually constant.

The solubility of theophylline were determined in water at 37 °C.

THEORETICAL

I. *Microcapsule release kinetics*

Various workers (Madan et al 1974; Voellmy et al 1977; Palmieri 1977) have considered the Higuchi equation for diffusion from a heterogenous matrix to be applicable to drug release from microcapsules. The amount of drug, Q, liberated per unit surface area of matrix into the external medium in time t, assuming a process of leaching by entry of the solvents, was then given by the equation:

$$Q = k_H t^{\frac{1}{2}} \quad .. \quad .. \quad (1)$$

$$\text{where } k_H = \left[\frac{\epsilon}{\tau} D(2C_0 - \epsilon C_S)C_S\right]^{\frac{1}{2}} \quad .. \quad (2)$$

where C_0 is the initial drug concentration in the microcapsule, C_S is the solubility, D is the diffusion coefficient of the drug in the leaching medium, ϵ is the porosity, and τ is the tortuosity of the polymer. Equation (1) would also be applicable if the polymer were non-leachable by the solvent, furnishing a homogeneous matrix system.

On the other hand, other authors (Nixon & Walker 1971; John et al 1979) have considered the release pattern to follow classical first-order behaviour, in which:

$$\log W = \log W_0 - \frac{k_1 t}{2{\cdot}303} \quad .. \quad (3)$$

where W is the quantity of drug remaining in the microcapsule at time t, W_0 is the initial quantity of the drug in the microcapsule and k_1 is the first order release constant.

In this study, the applicability of the two models is investigated for theophylline released from EC walled microcapsules. However, the simplified equation (3) cannot indicate if the core material release from the microcapsules is membrane- or dissolution rate-controlled. For the purpose of comparing the membrane permeability in EC walled microcapsules and planar EC films, a treatment was required by which the permeability constant could be extracted.

In the case of spherical diffusion through a thin membrane from a nonconstant source, as in the present microcapsules, where the values of the radii are close together and the wall thickness much smaller than the core radius, the membrane may be considered as planar and the equations governing the release under changing concentration gradient then has the form (Rogers 1977):

$$W = \frac{W_0}{V_1 + V_2}\left\{V_2 \exp\left[-\frac{P_1 A(V_1 + V_2)\, t}{h\, V_1 V_2}\right] + V_1\right\} \quad (4)$$

where P_1 is the permeability constant of the drug through the microcapsule wall, A is the surface area of the microcapsules, h is the wall thickness, W_0 is the initial amount of drug, V_1 is the internal volume of the microcapsules and V_2 is the sink solution volume. Since $V_2 \gg V_1$, this equation simplifies to

$$W = W_0 \exp - \frac{P_1 A t}{h V_1} \quad .. \quad .. \quad (5)$$

$$\text{or} \quad \log W = \log W_0 - \frac{P_1 A t}{2{\cdot}303 h V_1} \quad .. \quad (6)$$

This equation has the same form as equation (3) and permits evaluation of P_1 from the experimentally determined constant k_1 using the relation:

$$P_1 = \frac{2{\cdot}303 k_1 h V_1}{A} \quad .. \quad .. \quad (7)$$

All the parameters are measurable or calculable from experimental data.

II. *Permeation studies using planar EC membranes*

The permeation of thin membranes for linear flow under steady state conditions is characterized by means of Fick's law (Jost 1960). This may be expressed in the form:

$$\frac{dQ_1}{dt} = PA \frac{C_2 - C_1}{x} \quad .. \quad .. \quad (8)$$

Q_1 is the number of moles of drug penetrating in time t through a surface of area A, and C_2, C_1 are the concentrations of the drug in the permeating and sink solutions respectively, x is the thickness of the membrane and P is the permeability constant. P is a measure of the transfer rate of a specific drug from bulk solution on one side of the membrane to bulk solution on the other side, through unit thickness and area of the specific membrane.

Under the experimental conditions used, $C_2 \gg C_1$, when integration of equation (8) gives:

$$Q_1 = \frac{PAC_2 t}{x} \quad .. \quad .. \quad (9)$$

For a plot of concentration of drug transferred against time, the permeation rate is given by the slope dc/dt in accordance with the equation:

$$\frac{dc}{dt} = \frac{PAC_2}{xV_2} \quad .. \quad .. \quad (10)$$

where V_2 is the volume of the sink solution. It follows that

$$P = \frac{(dc/dt)\, xV_2}{AC_2} \quad .. \quad (11)$$

Slopes for permeation rate experiments were calculated by the least squares method and the other parameters of the equation were known. The very low final sink concentrations and the constancy of the P values accord with the use of the simplified steady state treatment.

RESULTS AND DISCUSSION

I. *Microcapsule release studies*

Release of theophylline was studied using microcapsules the preparation and properties of which have been described earlier. Treatment of the data on the basis of the matrix model yielded a linear relation between drug concentration in the sink solution and square root of time (Fig. 1). However, the data also fit the first order release pattern, since the log of the amount remaining in the microcapsules decreased linearly with time (Fig. 2).

As both first-order and square root of time plots are acceptably linear, a more stringent test was needed to distinguish between the mechanisms. Rate equations corresponding to equations 1 and 3 were

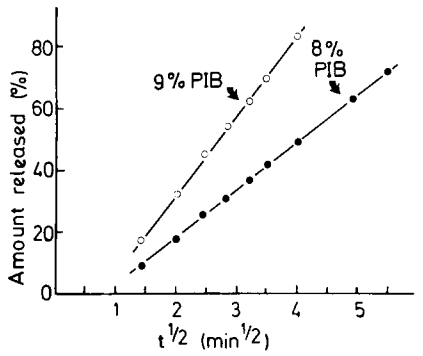

FIG. 1. Apparent diffusion-controlled theophylline release profiles from EC microcapsules prepared using different PIB concentrations.

used as the basis. This treatment has hitherto been applied only to drug dispersions designed and prepared as matrix products (Schwartz et al 1968) and not to microcapsules. For the matrix mechanism, the rate will be inversely proportional to the total amount of drug released Q′, in accordance with equation 12:

$$\frac{dQ'}{dt} = \frac{k_H^2 S^2}{2Q'} \quad .. \quad .. \quad (12)$$

where Q′ = QS (S is the surface area of the microcapsules). The rate predicted by first-order kinetics however is given by:

$$\frac{dQ'}{dt} = kW_0 - kQ' \quad .. \quad (13)$$

where $W = W_0 - Q'$. This indicates that the rate is proportional rather than inversely proportional to Q′.

The rates of release were determined from the Q′-time curves by measurement on a point to point basis. The two mechanisms were clearly differentiated by plots of rates as functions of Q′ and of 1/Q′ (Fig. 3). The former proved to be linear whereas the plots of rate vs 1/Q′ curved throughout the whole of the release period, indicating that the process definitely follows a first order release pattern in these systems. The same tendency and behaviour was also observed in all the other systems (Tables 1 and 2).

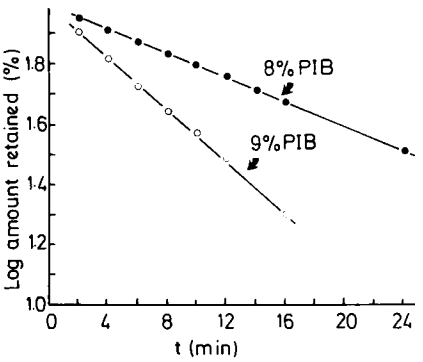

Fig. 2. Apparent first order theophylline release profiles from microcapsules prepared using different PIB concentrations.

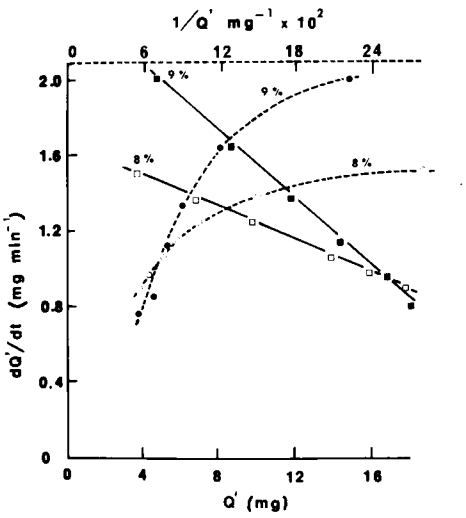

FIG. 3. Plots of release rate (dQ′/dt) of theophylline against amount (Q′) (—□■—) and reciprocal of the amount (1/Q′) (- - -○●- - -) of drug released.

II. *Permeability constants and mechanism of release of drugs from microcapsules*

The main processes involved in the initial release of materials of low water solubility from microcapsules in which the wall polymer functions as a barrier layer comprise:

1. Permeation of the polymer by water.
2. Dissolution of the wetted core material at the inner face of the wall.
3. Permeation of the membrane by the drug.
4. Diffusion into the bulk phase.

After the initial lag phase, when steady state is achieved, the rate is a function of the parameters determining the slowest step controlling the transfer. Considering the various stages, EC membranes are known to be readily permeable to water (the permeability constant P is at least 10^6 times greater than those of drugs in use (Eskilson et al 1976). Furthermore as the diffusion coefficient of the drug in H_2O is high (ca 10^{-5} cm^2 s^{-1}) it is anticipated that the dissolution rate is rapid. Turning next to stage 4, the use of sink conditions and an efficiently stirred

apparatus eliminates boundary layer-formation. Nevertheless, in order to exclude the possibility that a stationary layer effect at the outer wall of the microcapsules was involved, release rate was measured as a function of external agitation rate using 50, 100, 250 and 500 rev min^{-1}. The values of $k_1 \times 10^3$ min^{-1} for a typical batch (the first in Table 1) were 0·52, 0·57, 0·54 and 0·57, respectively, indicating that there is no dependence.

It would therefore appear that stage 3 was the rate-limiting process. For the purpose of confirming this, the effective permeability constants for the microcapsules were calculated from the experimental release rate constants utilizing the requisite parameters needed in equation 7 describing the membrane diffusion process. This enabled comparison with the corresponding constants obtained for controlled zero order diffusion through planar EC films prepared by the standard plate method. Similarity of P values in microcapsule wall and film penetration would be evidence favouring membrane-controlled diffusion as the rate-determining step in the microcapsules. P_1 values obtained from first order rate constants are listed in Tables 1 and 2. They are not identical throughout the series in which two parameters of microcapsule preparation, PIB concentration and particle size, were changed. In fact there is an apparent linear dependence on wall thickness (Fig. 4), which is unexpected. A possible explanation could be that the capillarity of EC coacervate membranes is sufficient to be significant in the transport of substances of relatively low membrane solubility, such as theophylline, in thin membranes. In such a case, the rate of transport of solutes should be a function of the porosity of the walls, so that the dependence of P on thickness could result from increase in porosity with decrease in wall thickness during the microencapsulation process.

Table 1. Mechanism of theophylline release from microcapsules prepared using different polyisobutylene concentrations. (A) Comparison between linearization of release rate data by first order and matrix equations, (B) comparison of parameters of linearity obtained from plots of release rate against the reciprocal amount ($1/Q'$) and the amount (Q') of drug released, (C) Comparison of permeability constants evaluated for microcapsule walls and planar membranes. Initial conditions: theophylline 5%, EC 5%, 100–200 mesh particle size at 250 rev min^{-1} in cyclohexane. Agitation rate in sink solution 100 rev min^{-1}.

Polyisobutylene %	A k_1* 10^3 min^{-1} ****	A k_H** 10 mg $min^{-1/2}$	B Correlation coefficients of plots of rate-dQ′/dt versus $1/Q'$	B versus Q'	C P_1*** 10^{10} $cm^2 s^{-1}$
5	0·57 (0·999)	0·51 (0·999)	0·801	0·999	0·60
7	4·75 (0·999)	1·08 (0·998)	0·778	0·999	3·35
8	8·15 (0·999)	3·04 (0·998)	0·295	0·999	4·64
9	16·85 (0·999)	8·07 (0·999)	0·825	0·999	5·64

* Calculated from eqn (3), ** calculated from $Q' = k_H t^{1/2}$, *** calculated from eqn (7). The permeability constant value calculated from planar diffusion studies using EC membranes at thicknesses of 15 and 30 μm and 10^{-2} M theophylline solution was $0{\cdot}31 \times 10^{-10}$ $cm^2 s^{-1}$ (±5%, mean of 4 results), **** correlation coefficients.

Table 2. Mechanism of theophylline release from microcapsules prepared using drug of selected particle size. (A) Comparison between linearization of release rate data by first order and matrix equations, (B) comparison of parameters of linearity obtained from plots of release rate against the reciprocal amount ($1/Q'$) and the amount (Q') of drug released, (C) comparison of permeability constants evaluated for microcapsule walls and planar membranes. Initial conditions as in Table 1 except for particle size and use of 5% PIB. Agitation rate in sink solution 100 rev min^{-1}.

Particle size mesh	A k_1* 10^3 min^{-1} ****	A k_H** 10^3 mg $min^{-1/2}$	B Correlation coefficient of plots of rate dQ′/dt versus $1/Q'$	B versus Q'	C P_1*** 10^{10} $cm^2 s^{-1}$
60–80	0·50 (0·999)	4·82 (0·999)	0·799	0·999	0·87
80–100	0·55 (0·999)	4·90 (0·999)	0·784	0·999	0·81
100–200	0·58 (0·999)	5·12 (0·999)	0·801	0·999	0·60

Symbols as in Table 1.

The P value obtained by measurements on planar films was $0{\cdot}31 \times 10^{-10}$ $cm^2 s^{-1}$ which is smaller than the lowest P_1 values, obtained from the greatest wall thickness (Table 1).

With regard to the significance of the numerical differences between these P values, two major sources of error may be identified. In the first place, the use of different solvents and conditions is known to affect the crystallinity and penetrability of polymers (Anderson et al 1973; Amann et al 1974; Nadkarni et al 1975). It seems likely that EC formed by chloroform evaporation at low temperature is

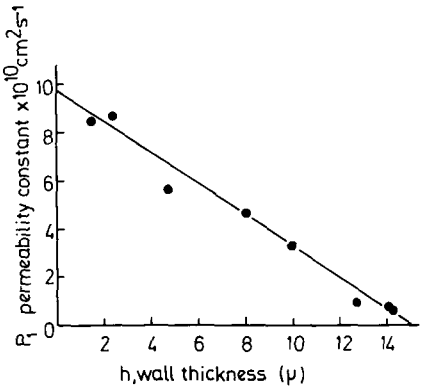

FIG. 4. Apparent linear dependence of permeability constants on wall thickness.

more crystalline than that resulting from coacervation in cyclohexane at elevated temperatures in the presence of PIB (which may in fact function also as a plasticizer) and this would account for P values being higher from the microcapsules. Planar membranes were prepared from pure EC in the present work because it was shown previously that the EC spheres isolated, after coacervation in the presence of PIB (used as protective colloid) and repeated rinsing with cyclohexane consisted essentially of pure EC (Benita & Donbrow 1980). The identical process was used in microencapsulation so that the products obtained after the final drying were composed of core material and EC coating free of PIB.

Coming now to the second source of error, the microcapsules were treated as spheres for the purpose of calculating the surface area and wall thickness, as the introduction of a more sophisticated treatment involving correction for shape factors and statistical estimation of specific surface was not justified at this stage of the investigation. A correction factor is probably needed in theophylline in which the crystals of the core material are in the form of needles and the elongated shape is maintained in the microencapsulated state (Benita & Donbrow 1981). The actual surface area per unit weight will therefore have been underestimated and the wall thickness overestimated. We therefore consider that the deviation in theophylline parameters at large wall thickness is acceptable and that the P_1 and P values are sufficiently close to be compatible with rate control by the membrane.

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