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

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Release rates of salicylamide from single-core ethyl cellulose (EC) coated microcapsules were measured as a function of wall thickness and core particle size. Whereas up to ca 50% release zero order kinetics were observed, the overall reaction fitted the first order and Higuchi matrix treatment. These were distinguished by the differential rate treatment, which showed that the overall release in fact followed the first order pattern. For investigating whether the process was membrane-controlled, the experimental rate constants were transformed into effective permeability constants (P_0 and P_1) with the aid of the microcapsule dimensional parameters needed in the relevant equations and compared with the salicylamide permeability constant for planar ethyl cellulose membranes (P), measured experimentally. P_0 and P_1 values obtained for a given microcapsule preparation were not identical: P_0 was of the same order as P, P_1 being much lower. While membrane-controlled release is evident, it is apparently accompanied by a first order concentration gradient change inside the microcapsule.

We have previously shown (Benita & Donbrow 1982a,b) that theophylline release from ethyl cellulose (EC) microcapsules unequivocally follows a first order pattern even though the experimental results also appeared to conform with the Higuchi equation for release from matrix dispersions. The correct kinetic pattern was identified by use of the differential forms of the respective equations for the two mechanisms (Schwartz et al 1968), a procedure which, though established for matrix dispersions, had not hitherto been applied to microcapsules.

The present report examines the in vitro release kinetics of salicylamide from uniform-wall, single-core microcapsules prepared under differing conditions. Rates were studied as a function of wall thickness and particle size. In addition, the permeability constant of the EC wall material, calculated from the rate constants and the microcapsule size parameters, were compared with the permeability constant of the drug through planar EC membranes, measured in parallel diffusion experiments.

MATERIALS AND METHODS

Salicylamide conformed to B.P. 1973. The other materials are described by Benita & Donbrow (1982b) as are also the preparative and test methods used.

* Correspondence.

Salicylamide analysis was at 298 nm; the sink solution was water except in the experiments on the influence of pH on release, in which buffers were prepared according to the McIlvaine method (Donbrow 1966).

RESULTS AND DISCUSSION

Kinetics of release from microcapsules

Salicylamide release was studied using microcapsule samples prepared by varying the quantity of protective colloid or the particle size of the core material. The influence of these variables on the drug content and wall polymer loss has been reported by Benita & Donbrow (1982a).

A linear relation between drug concentration in the sink solution and square root of time, expected on the basis of the matrix model, was obtained experimentally (Fig. 1). However, the data also fit the first order equation, log amount retained in the microcapsules decreasing linearly with time (Fig. 2).

As both the above plots are acceptably linear and give correlation coefficients near to 1 (see examples in Table 1), a more stringent test was needed to distinguish between the mechanisms. The treatment, previously applied to theophylline microcapsules prepared under similar experimental conditions, was based upon the use of differential forms of the first order and square root time equations. For the matrix mechanism, the rate will be inversely proportional to

Table 1 Kinetics of salicylamide release from microcapsules prepared using different core particle sizes. Comparison of linearization parameters for (a) first order and matrix equations, (b) plots of release rate against reciprocal amount (1/Q') and amount (Q') of drug released. *Initial conditions:* Salicylamide (selected particle size) 5% w/w, * PIB 7% w/w, EC 5% w/w in cyclohexane, 300 rev min^{-1}.

		a		b	
				Correlation coefficients: Rate $\frac{dQ'}{dt}$	
Particle size mesh	Drug content %	k_1** 10^3 min^{-1}	k_H*** 10 mg $min^{-1/2}$	versus 1/Q'	versus Q'
40–60	89·3	2·13 (0·999)****	3·42 (0·996)	0·894	0·999
60–80	75·4	1·88 (0·999)	0·78 (0·998)	0·869	0·996
100–200	51·5	1·60 (0·999)	0·73 (0·999)	0·878	0·999
200–300	50·5	5·40 (0·999)	4·49 (0·998)***	0·838	0·998

* Systems were adjusted to 100 g total weight with cyclohexane.
** Calculated from first order equation, *** calculated from $Q' = k_H t^{1/2}$, **** correlation coefficients.

the total amount of drug released, Q', in accordance with equation 1:

$$\frac{dQ'}{dt} = \frac{k_H^2 S^2}{2Q'} \quad (1)$$

where $Q' = QS$ (S is the surface area of the microcapsules). The rate predicted by first-order kinetics (Schwartz et al 1968), however, is given by:

$$\frac{dQ'}{dt} = kW_0 - kQ' \quad (2)$$

In this case, the rate will be proportional rather than inversely proportional to Q'.

The rates 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 proving to be linear and the latter curving throughout the whole of the release period. This is a clear indication that the process follows the first order pattern for the microcapsules prepared using different protective colloid concentrations. The same treatment applied to microcapsules prepared from core material of differing particle size showed identical release behaviour (Table 1).

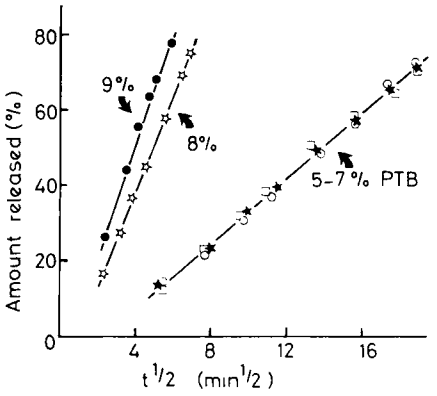

FIG. 1. Apparent diffusion-controlled salicylamide release profiles from EC microcapsules prepared using different PIB concentrations.

Even though the overall kinetic pattern was first order, a zero-order equation could nevertheless be fitted to the initial phase of release (up to 40–50%). The Q'-time plots were acceptably linear and gave correlation coefficients near to 1 (Table 2).

Zero order release would accord with the maintenance of a constant internal concentration gradient. Theoretically, sufficient drug was present to maintain saturation up to 60–70% release, assuming the full internal volume to be occupied by water. An apparent change of release kinetics after 40–50% could result from non-steady state factors only becoming significant at this stage. The apparent zero-order phase, if considered to be governed by an initial steady-state, can be treated by means of Fick's law in the form:

$$C = \frac{P_0 A C_s}{hV_2} t \quad (3)$$

where C is the drug concentration in the sink solution of volume V_2 at time t, C_s is the drug solubility in the permeating medium within the microcapsule, A is the microcapsule surface area, h is the wall thickness and P_0 is the permeability constant for the drug in the microcapsule wall. Apparent P_0 values were obtained using the experimental C/t plots, the remaining parameters required being measured or calculated.

Permeability constants and mechanism of release of drugs from microcapsules

The main processes involved in the release of core materials of low water solubility from microcapsules

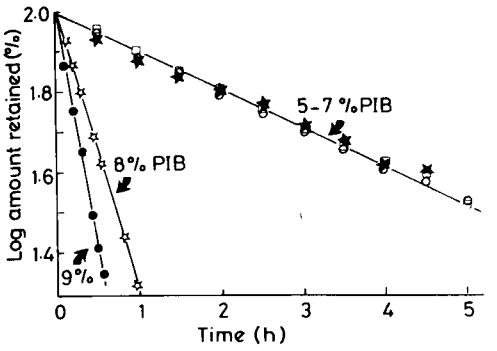

FIG. 2. Apparent first order salicylamide release profiles from microcapsules prepared using different PIB concentrations.

in which the wall polymer functions as a barrier layer have been described by Benita & Donbrow (1982b). To check the integrity of the wall polymer as a barrier under the experimental conditions, release rates were measured in sink solutions varying in pH between 1 and 9. Had the capillarity of the wall membrane been sufficient to allow penetration by the buffer, salicylamide solubility would have been greatly increased at pH 9 (Merck Index 1968) and release enhanced. In fact the release rates were constant at all pH values (Fig. 4).

For the purpose of determining whether drug permeation of the membrane was the rate-limiting process, effective permeability constants P_1 and P_0 of the EC microcapsule wall were calculated from the experimental first order and zero order release rate constants, utilizing the requisite microcapsule parameters needed, to enable comparison with the constants obtained in controlled zero order diffusion through planar EC films prepared by the standard plate method. (The theoretical background to the microcapsule release studies and the parallel planar membrane studies, including the equations used, has been presented fully by Benita & Donbrow 1982b). Similarity of values of the permeability constants in microcapsule release and film penetration would be evidence supporting membrane-controlled diffusion as the rate-determining step in the microcapsules.

P_0 and P_1 values obtained from the zero order and first order rate constants are listed in Tables 2 and 3. They are not identical, for a given microcapsule preparation, P_0 exceeding P_1. The P value measured for salicylamide diffusion through planar films was $0{\cdot}57{\cdot}10^{-8}$ cm^2 s^{-1}. This value reveals an important difference: whereas for most of the batches P_0 is somewhat larger than P (×4 to ×5) P_1 is very much smaller than P (×30).

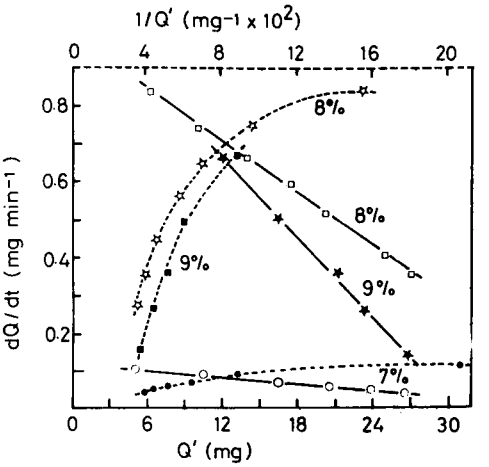

FIG. 3. Plots of release rate (dQ'/dt) of salicylamide against amount (Q') (—) and reciprocal of the amount (1/Q') (- - -) of drug released.

With regard to estimating the significance of the numerical differences between the P_0 and P values, at least two sources of error may be present. The planar films and microcapsule walls were produced by totally different techniques and the use of different solvents and condition known to affect the

Table 2. Mechanism of salicylamide release from microcapsules prepared using different core particle sizes: (a) Apparent zero order release rate constants (k_0) and r values up to 50% release, (b) Permeability constants of microcapsule walls (from zero and first order equations) and planar membranes. *Initial conditions:* as in Table 1.

Particle size mesh	Wall thickness μm	k_0* 10^2mg cm^{-2} min^{-1}	P_0** 10^8 cm^2 s^{-1}	P_1*** 10^{10} cm^2 s^{-1}
40–60	8·3	0·54 (0·995)****	1·88	3·79
60–80	13·3	0·49 (0·997)	2·73	3·41
100–200	17·0	0·42 (0·998)	2·99	1·94
200–300	9·8	0·63 (0·996)	2·59	2·01

* Calculated from $Q = k_0t$, ** calculated from eqn (3), *** calculated from eqn (7) in Benita & Donbrow 1982b, **** correlation coefficient (r).

The permeability constant value calculated from planar diffusion studies using EC membranes (thicknesses 15 and 30 μm) and 10^{-2} M salicylamide solution was $0{\cdot}57 \times 10^{-8}$ cm^2 s^{-1} (±5%, mean of 4 results).

Table 3. Mechanism of salicylamide release from microcapsules prepared using different polyisobutylene concentrations. (a) Apparent zero order release rate constants (k_0) and r values up to 50% release, (b) Permeability constants of microcapsule walls (from zero and first order equations) and planar membranes. *Initial conditions:* Salicylamide 5% (100–200 mesh), ethyl cellulose 5%, 300 rpm.

Polyisobutylene %	Wall thickness μm	k_0 10^2 mg cm^{-2} min^{-1}	P_0 10^8 cm^2 s^{-1}	P_1 10^{10} cm^2 s^{-1}
5	17·2	0·40 (0·998)	2·88	1·96
6	17·4	0·39 (0·996)	2·85	1·92
7	17·0	0·42 (0·997)	2·99	1·96
7·5	10·3	0·52 (0·995)	2·24	1·50
8	2·4	4·51 (0·998)	4·54	1·91
9	1·2	11·48 (0·997)	5·78	1·54

Key as Table 2.

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 more crystalline than that resulting from coacervation in cyclohexane at elevated temperatures. The PIB present may in fact function also as a plasticizer. These factors would account for the microcapsule P_0 values being higher than the P values. Such an effect was observed previously in mixed EC-polyethylene glycol (PEG) films in which P_0 values measured for salicylic acid and caffeine as a function of film composition were found to be linearly related to PEG concentration, provided the latter was low (Donbrow & Friedman 1975); however, the values for pure EC film were off the line and were unexpectedly low (Friedman 1973). By extrapolation of the line backwards to 0% PEG, a hypothetical P_0 value is obtained representing a pure EC film the permeability of which accords with films containing the second component (PEG). Such treatment of the data reported for salicylic acid yields P values elevated by a factor of 3 to 5 for a quasi-plasticized pure EC film formed under the influence of PEG using the same solvent and technique throughout. We would hardly expect the error to be less in the present system and this is in fact the order of the difference found between the P_0 and P values.

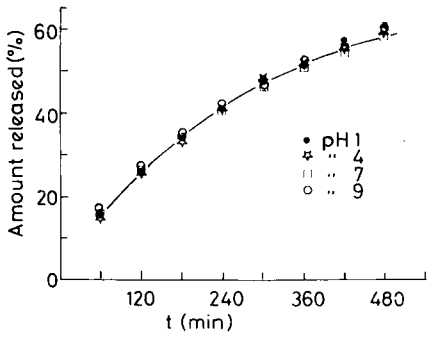

FIG. 4. Influence of variation of sink solution pH on salicylamide release from microcapsules. Preparation conditions: salicylamide 7% (60–80 mesh), EC 5%, PIB 5%, 300 rev min^{-1} (slow cooling).

Some consideration may also be given to convection or osmotic forces. After equilibration of wall material with solvent, the diffusion current of drug outwards should be accompanied by an equal and opposite diffusion current of water inwards (Jost 1960). Since the solid core material is impermeable to water, the incoming water must cause some convection of dissolved drug towards the membrane throughout the dissolution process. The magnitude of the effect may be estimated using Stefan's treatment (Jost 1960) and is found to be negligible for drugs the solubility of which is greatly below the water concentration at the reference surface in corresponding units, i.e. the barrier membrane surface in the present case. This type of effect should not be first order, in any case.

Returning to the question of the release mechanism, it would seem that the initial period (to 40–50% release) is effectively membrane-controlled, hence apparently zero-order, with P_0 comparable to P. However, the overall release is first-order, with P_1 significantly below P and relatively constant through the series covering microcapsule parameter variations (Tables 2 and 3).

It may be recalled that release from theophylline film-type microcapsules was also first order but that P_1 values were of the same order as P values and showed dependence on wall thickness (Benita & Donbrow 1982b).

A possible explanation is the presence of a time-variable boundary layer or non-steady state, introducing a concentration gradient changing on a first order basis. This would be similar to the boundary layer diffusion model of Roseman & Higuchi (1970) and Takenaka et al (1979) applicable in matrix delivery devices and spray dried drug-

hydrophilic binder granules or when stagnant layers are present, except that in the microcapsules the boundary layer would lie between the partly-dissolved core material and the inner wall of the microcapsule, constituting an additional gradient to that in the wall. On the other hand, in the matrix and granule systems, the boundary layer is present in the external solutions which in the case of granules are evidently in direct contact with the solid solute via the porous granule matrix. The source of the gradient would be the inability of the dissolution process under unstirred conditions to maintain saturation of the membrane. The thickness of the internal diffusion layer would in fact change quite slowly during the early stages of dissolution of the spherical core, and become significant only when the core diameter had decreased appreciably, at which time the first order k_1 values would be clearly established (Fig. 5).

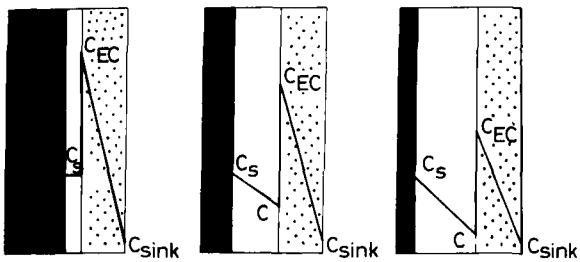

FIG. 5. Concentration gradient changes (schematic) in hypothetical internal layer and wall membrane of microcapsules at different phases of salicylamide release. Key: C_s is the salicylamide saturation concentration in water, C the aqueous concentration adjacent to the internal membrane surface, C_{EC} the corresponding equilibrium membrane concentration at the same surface and C_{sink} the aqueous concentration in the sink solution assuming absence of an external boundary layer.

The difference between the salicylamide and theophylline P_1/P ratios could then be an effect resulting from their different membrane-water partition coefficients S (S values EC/H_2O, salicylamide, 58·20, theophylline, 1·62; Benita & Donbrow, unpublished data). Salicylamide has a high S value, which is responsible for the more rapid transfer of this compound than theophylline through a planar film (P = DS according to Barrer 1939). This will also cause a greater reduction of salicylamide concentration gradient due to the high requirements of the membrane for saturation and the limited capability of the dissolution process to provide the required supply of solute. The involvement of two concentration gradients, liquid and film, (Fig. 5) would account for the drastic reduction in dissolution rate and the low P_1 value. In theophylline, the process will be similar but in this case less pronounced, due to the smaller S value, which enables the membrane to achieve a concentration gradient much closer to the saturation value.

To check whether a boundary diffusion layer could be detected by stirring rate variation, which does influence external unstirred layer thickness, release studies were performed at 50, 100, 250 and 500 rev min^{-1}. The release rate constants ($k_1 \times 10^4$ min^{-1}) for a selected batch (Initial conditions of preparation: salicylamide 7% (60–80 mesh), ethyl cellulose 5%, polyisobutylene 5%, 300 rev-min^{-1} (slow cooling)) were 6·05, 5·85, 5·90 and 5·58, respectively, the differences being insignificant. It may well be that internal gradients are not influenced under these conditions. Nevertheless, the unstirred internal solution together with the relatively large quantity of wall polymer present in the microcapsules, with its high capacity for solute uptake, provide a system in which the overall release rate is determined mainly by the polymer permeability but in which the dissolution process is of the non-steady state type yielding apparent first order kinetics.

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