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Microencapsulation of paracetamol using polyacrylate resins (Eudragit Retard), kinetics of drug release and evaluation of kinetic model

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Methacrylate copolymers were used for microencapsulation of paracetamol by phase separation from chloroform with polyisobutylene 6% in cyclohexane. With polyisobutylene as an anti-aggregating agent, high quality microcapsules were obtained. Drug release appeared to fit both first order and Higuchi matrix model kinetics. However, on application of the differential rate treatment, the evidence supported the first order description, which was further supported by computed simulations of the models. Variation of production conditions showed that increasing the proportion of core material raised the microcapsule drug content and the release rate. Reduction of core particle size correlated with reduced coating thickness and faster release rate. The rate constants correlated with the estimated surface areas and wall thicknesses of the various batches. The data were used to estimate an apparent permeability constant for paracetamol in Eudragit RS microcapsules, which was constant and comparable with values found single core, non-aggregated microcapsules containing other similar drugs and different wall materials.

Among the advantages of using microcapsules for controlled or slow release drug formulation are those of a drug delivery system of dispersed particle units which are associated with improved biopharmaceutical and safety characteristics (Lehman et al 1976) combined with a membrane of controllable permeability, in this case a polymethyl ethyl methacrylate (Eudragit Retard) hitherto used mainly as a tablet-additive material in sustained release. This polymer is inert to the digestive tract, pH-independent but capable of swelling and release of active ingredients by diffusion. Some polyacrylates have been applied in coating by spray drying (Lehman et al 1976) and interfacial polymerization techniques (Kreuter & Speiser 1976) but phase separation has not been used for them in microencapsulation. This method offers advantages, particularly increased uniformity of coating and formation of individually-coated core particles, if aggregation can be prevented, and it also enables microencapsulation of water-soluble drugs by use of organic solvents. Polyisobutylene (PIB) was used as an additive for preventing aggregation, with ethyl cellulose as wall material (Benita & Donbrow 1980; Samejima et al 1982), in initial studies on Eudragit Retard (Donbrow et al 1984). The presence of quaternary salt groups in that polymer would be expected to change its phase separation behaviour and aggregative tendencies compared with hydrophobic cellulosic polymers, and requires investigation. In the present study, production variables have been tested and the kinetic models of drug release examined for the purpose of defining conditions for the design and production of microcapsules of paracetamol having sustained-release properties.

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MATERIALS AND METHODS

Materials

Polyacrylate-polymethacrylate copolymers with low content of quaternary ammonium groups-Eudragit Retard-RS 100 and RL 100 (Röhm Pharma, GmbH, Darmstadt, West Germany). Polyisobutylene (Oppanol B50, BASF, Ludwigshafen, West Germany). Paracetamol conformed to the BP 1973.

Methods

Preparation of microcapsules

Formation. To a three-necked flask containing 20 g chloroformic solution of 6% w/w polyisobutylene (PIB) and Eudragit RS 8% w/w, 5 g of crystalline paracetamol of particle size 250–355 μm was added. The 'non solvent' solution (60 g of PIB 6% w/w in cyclohexane) was dropped into the flask at a constant rate of 0·9 g min^{-1} thereby gradually reducing the solubility of the Eudragit. A constant stirring rate (200 rev min^{-1}) and temperature (25 °C) were maintained throughout the production.

Separation. Two minutes after the formation process was completed, the microcapsules sank and were separated by decantation and rinsed twice with 100 ml portions of cyclohexane to remove any PIB adsorbed at the microcapsule interface and any empty wall polymer droplets. By means of an additional 50 ml of cyclohexane, they were transferred, vacuum filtered and solvent traces finally removed on paper at room temperature. All batches were duplicated.

The same processes were used with Eudragit RL.

Evaluation of the prepared microcapsules

The microcapsules were dissolved in methanol and assayed spectrophotometrically for paracetamol at 249 nm using a calibration curve based on standard solutions in methanol. Eudragit did not absorb in methanol at this wavelength.

The approximate wall thickness of the microcapsules was calculated from the particle size of the core material, the relative densities of the wall and core material (d core/d wall) and the drug content in the microcapsules (F) using the same equation as in Benita & Donbrow (1982a).

Optical and scanning electron microscopy were used to evaluate the quality of coating obtained under the various conditions used.

The kinetics of drug release from the microcapsules were determined as was described by Benita & Donbrow (1982a).

Density. The densities were: paracetamol, 1·316, coating polymer, 1·176 (pycnometrically).

RESULTS AND DISCUSSION

From preliminary work it became clear that a suitable additive had to be used in this 'non-solvent' addition method to prevent aggregation. The additive PIB stabilized the individual microcapsules during the production, since in its absence a large sticky mass had been obtained. The preferred PIB concentration was found to be 6% w/w, aggregation still occurring in more dilute solutions (e.g. 4% w/w). Higher concentrations (e.g. 8% w/w) were too viscous (Benita et al 1984).

Table 1 gives the properties of microcapsules produced at different PIB concentrations. Using the optimum concentration and conditions, all core particles were individually and completely coated, there were no multiple core microcapsules and the coatings simulated the shapes of the core particles, suggesting uniformity of thickness around the cores

Table 1. Properties of microcapsules produced using different PIB concentrations.

PIB concn* (% w/w)	Drug content (% w/w)	Rate constant ($min^{-1} \times 10^{-3}$)	Correl. coeff.
8	78·7	2·1	0·999
	79·7	2·2	0·997
6	79·3	3·2	0·999
	79·9	3·3	0·998
4	74·5	1·6	0·999
	74·5	1·5	0·999

* 0 aggregation to form a matrix.

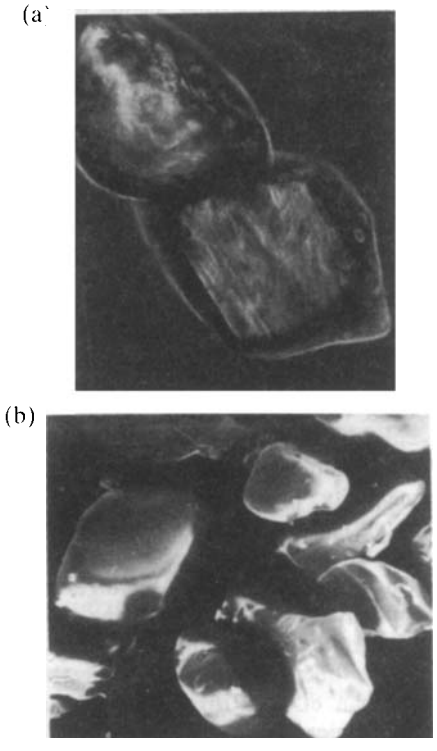

FIG. 1. Microcapsules of paracetamol in Eudragit RS. (a) Optical microscope (×100), (b) scanning electron microscope (SEM) (×55).

(Fig. 1). Furthermore, there was no rupture of the wall after drug release (Fig. 2).

Eudragit RS and RL were satisfactory as potential slow release coatings for microcapsule formulation, a lower release rate being attained with RS, the less hydrophilic of the two polymers, which was selected for more detailed study of variables.

Drug release kinetics

The dissolution time of paracetamol is very much shorter than the time needed for the release of the

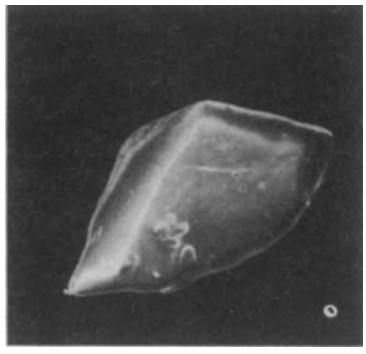

FIG. 2. As Fig. 1. SEM of microcapsule (×90) after release of paracetamol in water. (No ruptured walls detected.)

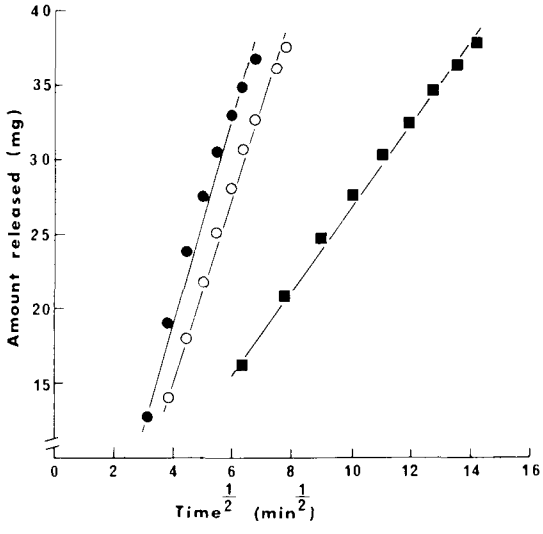

FIG. 3. The release of paracetamol from microcapsules produced at different 'non-solvent' addition rates treated according to the matrix model. Key: Rate of non-solvent addition (9 min^{-1}) ■ 0·9, ○ 5·1, ● 10·2.

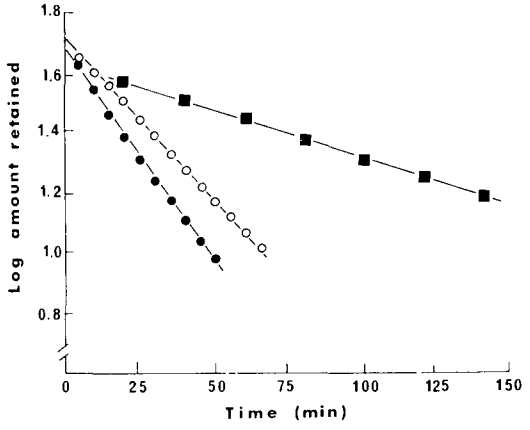

FIG. 4. The release of paracetamol from microcapsules produced at different 'non-solvent' addition rates treated according to the first order model. Key as in Fig. 3.

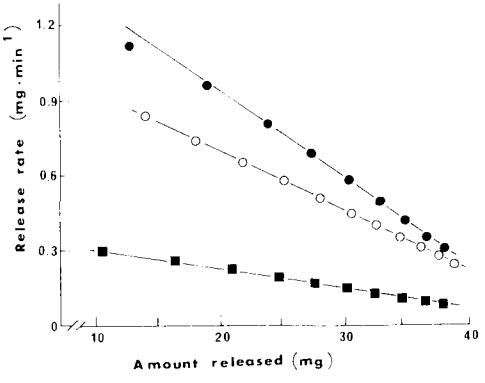

FIG. 5. Release rate (dQ′/dt) plotted against amount released (Q′) for release of microencapsulated paracetamol. Key as in Fig. 3.

paracetamol from its microcapsules under similar conditions, hence it is evident that the mechanism of release is determined by the membrane.

The main models which have been suggested to describe drug release kinetics from microcapsules are the matrix model, the first order model and the zero order model. These models have been discussed in previous publications and the linear model appears to fit some microencapsulation release data (Madan et al 1976; Donbrow & Benita 1982). Since release was non-linear, the zero order model was inapplicable. However, both matrix and first order models fit the data acceptably (Figs 3, 4). When first order and square root of time plots are acceptably linear a more stringent test is needed to distinguish between the mechanisms. Rate equations corresponding to matrix and first order equations were used for matrix products (Schwartz et al 1968) and more recently on microcapsules (Benita & Donbrow 1982; Donbrow & Benita 1982). For the matrix mechanism, the rate will be inversely proportional to 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; Q is the amount released per unit area) (Fig. 5). The rate predicted by the first order kinetics is given by equation 2:

$$\frac{dQ'}{dt} = k_1 w_0 - k_1 Q' \quad (2)$$

where $w = w_0 - Q'$. In the latter case, the rate is proportional rather than inversely proportional to Q'. The release rates have to be determined from Q' – time curves by measurement on a point to point basis.

The two mechanisms are clearly differentiated by the plots since the rate is linearly related only to Q' (equation 2) indicating that the process follows a first order release pattern in these systems (Fig. 5).

To confirm this, a computerized method was applied to find the best first order and matrix model constants describing the experimental release pattern and using the Chi-square statistics test to evaluate the degree of correlation between the experimental and calculated values (Benita 1984).

The results support the first order model. The values used for the kinetic model determination are of microcapsules which were produced by three different rates of non-solvent addition. The effect of the addition rate upon drug release rate from microcapsules has already been described (Donbrow et al 1984).

Core-wall ratio

Use of different amounts of core material of constant particle size in a narrow range with a fixed amount of coating material changed the experimental core-wall ratio of the microcapsules. Clearly, increased ratio gives thinner coating, as shown in Table 2, and consequently faster release rate properties. With thicker coatings, the efficiency of the microencapsulation process is reduced. Evidently, since there are fewer particles to be coated, part of the coating polymer is not taken up by the core surface and separates as empty coacervate shells, as shown in Fig. 6, and there is a wastage of polymer in the production. The approximate mean thickness of the microcapsule polymer coating was calculated on the basis that the paracetamol crystals are approximately spherical (Figs 1, 2, Table 2) using an equation

Table 2. The influence of core-wall ratio on the microcapsules produced.

Core material (g)*	Core material content Found (% w/w)	Core material content Theor (% w/w)	Wall thickness (μm)	1° rate constant ($min^{-1} \times 10^{-3}$)	Correl. coeff.
10	86·0	86·2	6·2	4·1	0·995
	86·1			4·1	0·999
5	79·3	75·7	9·4	3·2	1·000
	79·9			3·3	0·998
2·5	68·4	61·0	16·6	1·5	0·993
	66·6			1·7	0·996

* Per 1·6 g Eudragit polymer (see methods). Core particles 250–355 μm.

FIG. 6. Microcapsules of paracetamol showing attached aggregates of empty Eudragit RS shells formed at low core/wall ratios. SEM (×45).

Table 3. Effect of core material particle size on microcapsule properties.

Particle size (μm)	Core material content (% w/w)	Wall thickness (approx) (μm)	Half-time ($t_{\frac{1}{2}}$) (min)	1° rate constant ($min^{-1} \times 10^{-3}$)	Correl. coeff.
90–125	78·0	5·2	16	22·1	0·999
($\bar{d}$ = 108)	78·0			21·4	0·999
180–250	77·7	10·5	50	5·7	0·999
($\bar{d}$ = 303)	77·4			5·8	1·000
250–355	79·3	13·2	75	3·2	1·000
($\bar{d}$ = 303)	79·9			3·3	0·998
425–500	79·0	20·8	140	2·3	0·998
($\bar{d}$ = 463)	79·2			2·3	1·000

developed in previous work (Benita & Donbrow 1982a). The release constants are linearly related to the wall thickness.

Particle size of core material

Paracetamol was fractionated into four narrow particle size ranges by means of a standard test sieve shaker (Endecott), and microencapsulated using constant conditions. There is a major decrease in release rate with increase in particle size (Table 3). The rise in release rate for the smaller particles is due to their larger surface area and thinner coating since the core/wall ratio is constant. The first order $t_{\frac{1}{2}}$ value for 50% release, which is a useful parameter for comparison of release from different batches, increases with core diameter. The apparent rate of permeation through membranes is directly related to the surface area of permeation (calculated from the mean particle radius) and inversely related to membrane thickness, under steady state zero sink conditions and high stirring rates sufficient to eliminate 'stationary layer' concentration gradients. The plot of k, against surface area/wall thickness is linear, as

expected from this argument, and shows the consistency in the release behaviour of the microcapsules of different particle size and wall thickness. The slope of the plot, $4{\cdot}0 \times 10^{-7}$ $cm^{-1}\,min^{-1}$ may be used to estimate an apparent permeability constant using the procedure and equations previously developed (Benita & Donbrow 1982). The internal volume of the microcapsules required for this calculation is $35{\cdot}8 \times 10^{-3}$ ml (for 60 mg of microcapsules of 78·5% average drug content used in release studies for the batches of Table 3). A value of $5{\cdot}5 \times 10^{-10}\,cm^2\,s^{-1}$ is obtained for the apparent permeability constant (P_l) of paracetamol in Eudragit RS-walled microcapsules. This is of the same order as observed with similar drugs in ethyl cellulose microcapsules; moreover, the constancy of P_l in the present work recalls the case of salicylamide in ethyl cellulose (Donbrow & Benita 1982) and differs from theophylline, in which P_l decreases as the wall thickness increases (Benita & Donbrow 1982).

It may therefore be concluded that the manufacturing process described for microencapsulation of paracetamol using Eudragit RS or RL polymers yields coatings of reproducible permeability character over a wide range of core particle sizes and wall thicknesses indicative of the suitability of these microcapsules for sustained release products on the basis of variation of these two parameters.

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