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# The prolongation of the in vitro dissolution of a soluble drug (phenethicillin potassium) by microencapsulation with ethyl cellulose

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Microcapsules of phenethicillin potassium as a model water-soluble drug, coated with ethyl cellulose, have been prepared (core : wall ratios 1 : 1, 1 : 2 and 1 : 3) in which the taste has been masked, the odour almost eliminated and the release retarded. Sieve analysis showed that with decreasing core : wall ratios there was a trend towards increasing amounts of larger sized microcapsules. At constant core : wall ratios in vitro release of drug was generally greatest from the larger microcapsules. This result correlated with the surface areas of the microcapsules which became less as the asymmetry of the microcapsules diminished with decrease in microcapsule size. There was a linear relation between the amount of ethyl cellulose and the time for 60% release of drug, and the release pattern was analogous to that from insoluble porous matrices. Scanning electron micrographs showed the microcapsules to be irregularly shaped with circular surface pores, and they did not alter in shape or size during dissolution. Tableting of 1 : 1 core : wall ratio microcapsules significantly further retarded the dissolution.

Water soluble drugs may be formulated as sustained-release dosage forms by retarding their dissolution rates and various methods are employed for this purpose (Lee & Robinson 1978). Phenethicillin potassium constitutes a model drug for such studies since it is very soluble, has a rapid absorption rate and a short half-life ($t_{\frac{1}{2}}$ 30–50 min) (Martindale 1977; Pharm. Codex 1979). Also, it has a slightly sulphurous odour and a bitter taste which, for patient acceptance, might advantageously be minimized. Microencapsulation provides a possible method since odour and taste masking, and control or slowing of drug release so as to prolong the therapeutic activity, are some of the potential uses of microencapsulation techniques (Bakan & Anderson 1976). This paper reports the preparation of microcapsules, with ethyl cellulose at different core : wall ratios, their dissolution and the relationship between surface area and dissolution. The effect on dissolution of tableting the 1 : 1 core : wall ratio product is also examined.

## MATERIALS AND METHODS

### *Materials*

Phenethicillin potassium, Beecham Pharmaceuticals, sieved through a 120 $\mu$m mesh; ethyl cellulose, BDH Chemicals Ltd., viscosity 14 cP; cyclohexane, BDH Chemicals Ltd., not less than 99% distils between 80°–82 °C; purified water, prepared by distillation from an all glass still.

### *Methods*

Preparation of microcapsules: the method was based on those of Miller et al (1967) and Jalsenjak et al (1976). At a continuous stirring rate of 248 rev min$^{-1}$ and 50 °C, wall material (ethyl cellulose) in an amount depending on the core : wall ratio, was added to 600 ml of cyclohexane and the temperature raised to 70 °C over 20 min. Core material, phenethicillin potassium (6 g) was then added and the temperature raised to 80 °C over 1 h and held there for 1 h after which the system was allowed to cool to 35 °C. Cooling was then accelerated to 20–25 °C. The microcapsules were filtered off, washed with fresh cyclohexane, and allowed to dry in air. The yield was 87–96% and microcapsules with core : wall ratios of 1 : 1, 1 : 2 and 1 : 3 were prepared, the different sizes in a batch being separated by sieving using a range of standard sieves (355–2000 $\mu$m mesh) for 10 min.

*Dissolution test.* The procedure and apparatus were essentially those of the B.P. 1980. An amount of microcapsules containing 125 mg phenethicillin potassium, or a 250 mg tablet, was placed in a basket of aperture size 425 $\mu$m (75 $\mu$m for the 355–500 $\mu$m fraction) which was then immersed in 1 litre of water at 37 ± 0·1 °C. A stirring speed of 100 rev min$^{-1}$

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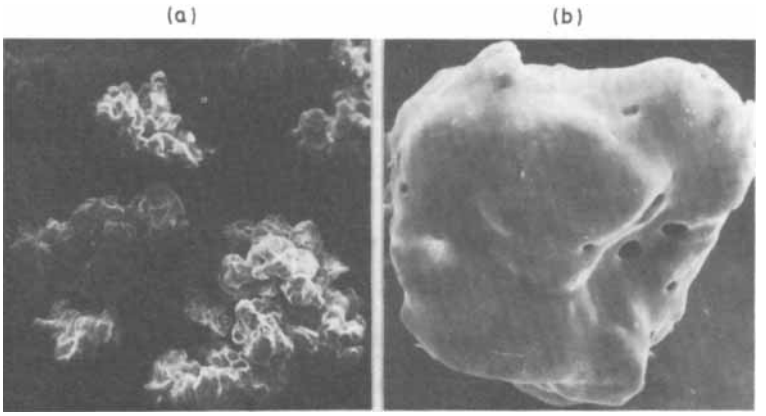


FIG. 1. Scanning electron micrographs of phenethicillin potassium microcapsules showing irregular aggregates (a) 1:2 core:wall ratio, mean size 1500 $\mu$m ($\times$20), (b) single microcapsule with surface pores, 1:3 core:wall ratio, mean size 427·5 $\mu$m ($\times$180).

was used. Timing commenced on the introduction of the basket into the water. 5 ml samples were removed at intervals and assayed. An equal volume of water was added to the dissolution vessel immediately after each sample was removed.

The antibiotic was assayed by measurement of the absorption at $\lambda$ max 268 nm using 1 cm matched silica cells. A linear standard curve for absorption against concentration up to 200 $\mu$g ml$^{-1}$ was obtained and the regression equation $y = 2{\cdot}289x + 0{\cdot}024$ was used to determine the concentration of phenethicillin potassium in the test samples.

*Surface area measurement.* This was carried out, in duplicate, with 1–1·5 g samples, by low-temperature nitrogen adsorption using a Ströhlein area-meter and the relevant procedure. The accuracy of the method was assessed using a National Physical Laboratory standard sample (Sterling FT-G 2700) of specific surface area $11{\cdot}1 \pm 0{\cdot}8$ m$^2$ g$^{-1}$. Duplicate results of 11·64 and 11·67 m$^2$ g$^{-1}$ were obtained.

For the preparation of tablets, 250 mg of 1:1 core:wall ratio microcapsules having a mean particle size of 605 $\mu$m were compressed with 11 mm diameter flat-faced punches at 160 MNm$^{-2}$.

## RESULTS AND DISCUSSION

Factors affecting the nature and yield of the microcapsules were the viscosity of the polymer, the degree of agitation, the time of addition of core and wall materials, and the rate of cooling. The stirring rate had the greatest effect. Speeds of 400, 510 and 800 rev min$^{-1}$ were rejected in favour of 248 rev min$^{-1}$ because at higher speeds a greater proportion of large microcapsules was obtained as a result of aggregation, and there was a lower percentage yield. Different stirring rates have been used, for example, Jalsenjak et al (1976) used 560 rev min$^{-1}$, Deasy et al (1980) used 750 rev min$^{-1}$, whereas Feinstein & Sciarra (1975) used 100 rev min$^{-1}$. The behaviour of the system probably depends on the materials as well as on the rate of stirring. The technique we adopted produced microcapsules with smooth surfaces and a size distribution (Table 1) which in replicate batches was reproducible within $\pm 15\%$ of the mean.

The microcapsules are irregularly shaped, the larger-sized consist of aggregates of smaller ones (Fig. 1a). The surfaces show the presence of a number of circular-shaped pores (Fig. 1b) which become fewer with decreasing core:wall ratios. These pores can act as points of entry for dissolution fluid. With decreasing core:wall ratios there is a trend in the size distribution towards increasing percentages of larger-sized microcapsules (Table 1).

Studies of the in vitro dissolution rates allow a comparison to be made between the different microcapsule size fractions and may give an indication of their relative efficiencies as potential delayed release dosage forms. Fig. 2 shows the release from microcapsule fractions with differing core:wall ratios. While it might be expected, within a constant

Table 1. Size distribution of microcapsules.

| Size range ($\mu$m) | Mean size d, $\mu$m | % sieve fraction for a given core : wall ratio 1 : 1 | 1 : 2 | 1 : 3 |
|---|---|---|---|---|
| −355 | <355 | 1·60 | 3·40 | 0·93 |
| 355–500 | 427·5 | 7·26 | 10·46 | 4·27 |
| 500–710 | 605·0 | 18·16 | 20·45 | 10·23 |
| 710–1000 | 855·0 | 28·99 | 28·61 | 16·81 |
| 1000–2000 | 1500·0 | 29·97 | 30·39 | 38·54 |
| +2000 | >2000 | 14·82 | 8·43 | 29·18 |

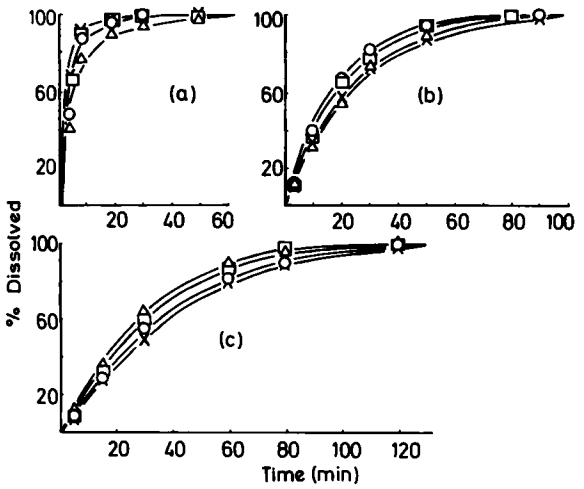


FIG. 2. Effect of core: wall ratio (a 1 : 1, b 1 : 2, and c 1 : 3) on the dissolution of phenethicillin potassium microcapsules. (Results are the mean of two experiments.) Mean microcapsule size, μm, ○ = 1500; □ = 855; × = 605; △ = 427·5

core: wall ratio, that the larger microcapsules would release more slowly, in fact they tended to release their contents more rapidly, there being a tendency to increasing dissolution rate with increasing microcapsule size, particularly with the 1 : 1 and 1 : 2 core: wall ratios. However, as the larger microcapsules consisted of aggregates of smaller microcapsules (Fig. 1a) dissolution could be influenced by the greater effective surface area arising from irregular shapes and surfaces, pores and pits which facilitate wettability. The surface area measurements (Table 2) showed for the 1 : 1 and 1 : 2 core: wall ratios that with decrease in the mean microcapsule size the surface areas also decreased, due to their diminishing asymmetric structure, with consequent decrease in dissolution rate. The thicker-walled 1 : 3 core: wall ratio microcapsules were the least asymmetric and their surface areas increased slightly with decreasing size, correlating with the trend towards increasing dissolution (Fig. 2). Between core: wall ratios, the surface areas decreased in the order 1 : 1, 1 : 2, 1 : 3 as the surfaces became smoother as a result of increasing wall thickness. There was a corresponding decrease in the release rate (Fig. 2) which may be attributed to the slower rate of diffusion of dissolution medium into the microcapsules. The intensity of surface pores decreased with decreasing core: wall ratios.

Table 2. Surface area of microcapsules ($m^2 g^{-1}$)[a]

| Core: wall ratio | Mean microcapsule size, μm 1500 | 855 | 605 | 427·5 |
|---|---|---|---|---|
| 1 : 1 | 7·22 | 7·37 | 6·07 | 4·74 |
| 1 : 2 | 4·10 | 3·83 | 3·50 | 3·27 |
| 1 : 3 | 3·06 | 3·30 | 3·01 | 3·46 |

[a] Determined in duplicate by Ströhlein area-meter. Results within <1·7% of the means.

There was a linear relationship between the time for 60% release (t60) and the amount of coating material (derived from the core: wall ratio) for the same size fractions (Fig. 3). Such data would permit the determination of the t60 for microcapsules of known size and core: wall ratios which in turn should allow the preparation of microencapsulated dosage forms with a predictable release pattern.

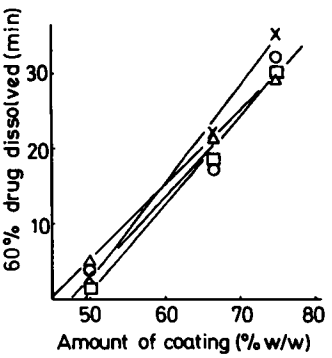


FIG. 3. Effect of increasing microcapsule wall material on the time for 60% release of phenethicillin potassium. (Symbols as in Fig. 2. Correlation coefficient = 0·97 for the 1500 μm mean size microcapsules, 0·997 for the others).

The microcapsules did not fragment or alter in shape or size during dissolution and no enlargement of the surface pores through which solution and diffusion occurs, was observed in contrast with the results of Deasy et al (1980). Release would, therefore, be expected to occur by a diffusion-controlled process as described by Higuchi (1963) and subsequently by others (e.g. Schwartz et al 1968) for the release of drug from insoluble porous matrices. A plot of release against time$^{\frac{1}{2}}$ shows the relationship to be linear up to about 80% (Fig. 4). The remainder is released more slowly presumably due to greater occlusion of drug by the insoluble ethyl cellulose matrix.

In addition to slowing release of drug the microencapsulation process masked its characteristic bitter taste and its odour was almost eliminated.

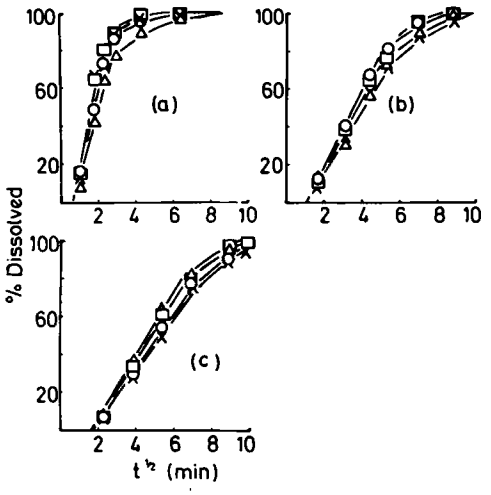


FIG. 4. Per cent dissolution-time½ plots for phenethicillin potassium microcapsules (details as in Fig. 2).

The effect of tableting the microcapsules was to prolong significantly the duration of release. Typical results are shown in Fig. 5 for the release of phenethicillin potassium from tabletted microcapsules of 1:1 core:wall ratio and 605 $\mu$m mean size. The t60 was 190 min (from Higuchi plots) in contrast to a t60 of 4 min for the untabletted microcapsules, indicating that the microcapsules did not fracture on compaction. The tablets exhibited good physical properties, had a crushing strength value of 19·5 Strong Cobb hardness units and did not disintegrate during the dissolution test.

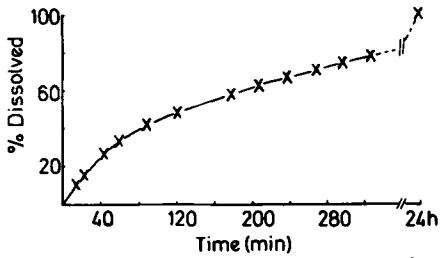


FIG. 5. Dissolution (mean of two results) of phenethicillin potassium from tablets of microcapsules (1:1 core:wall ratio, microcapsules of 605 $\mu$m mean size, compressed at 160 $MNm^{-2}$).

*Acknowledgement*

We thank Beecham Pharmaceuticals for the kind gift of phenethicillin potassium.

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