DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 4(2), 117-129 (1978)

RELEASE OF DRUGS FROM SUSPENDED AND TABLETTED MICROCAPSULES

Nixon, J.R., Jalsenjak, I., Nicolaidou, C.F. and Harris, M.

Pharmacy Department, Chelsea College, University of London, Manresa Road, London, SW3 6LX, Great Britain.

One of the principal uses suggested for the microencapsulation of pharmaceuticals has been the preparation of sustained release dosage forms. The techniques commercially available for microencapsulation are numerous and well documented (3) but the emphasis has tended to be towards the use of gelatin-acacia coacervates as the wall material and this has resulted in microcapsule cores which are water insoluble (5). The finished microcapsules have usually been presented in the form of suspensions or gels (1), but in order to obtain greater sustained release effect a non disintegrating tablet would be a better formulation. A

Presented at the 1st International Conference on Pharmaceutical Technology, Paris, 1977.

very few tablets containing microencapsulated material are available, e.g. microencapsulated acetyl salicylic acid tablets (2), but doubts as to the strength of the microcapsule wall during compression and the flow properties of the microcapsules appear to have held back the greater use of this technique for sustained release purposes.

Water soluble drugs in microcapsule form have been studied only to a very small extent (4) due to the greater difficulty of the microencapsulation technique. In the current work we have studied the in vitro release of sodium phenobarbitone from ethyl cellulose microcapsules. The microcapsules were presented both as a suspension and as compressed tablets.

The method of microencapsulation was to dissolve the ethyl cellulose in cyclohexane in a three-necked flask fitted with a reflux condensor and a P.T.F.E. two-bladed stirrer. The sodium phenobarbitone was added at a temperature of 70° and the temperature raised to 80° over a twenty minute period. After a further hour during which the stirring speed was maintained the temperature was allowed to fall gradually when the ethyl cellulose, separating initially in a liquid form, coated the distributed sodium phenobarbitone particles. By the time room temperature was reached the ethyl cellulose had solidified to give a smooth hard coating and form individual microcapsules of sodium

phenobarbitone. The size of the microcapsules could be controlled, within limits, by the stirring speed and the particle size of the core material. In general a stirring speed of 560 r.p.m. was used for this work which gave a range of microcapsules between 301.5 and 1850.0 μm. These were separated into batches by sieving. These microcapsules were larger than normal - this was considered necessary for the purposes of the tabletting studies, but higher stirring speeds could produce microcapsules closer in size to those normally found with both the simple and complex coacervation process. The yield in this process was extremely good being equivalent to 98% recovery and all the sodium phenobarbitone appeared to have been microencapsulated.

The tablets prepared from the microcapsule fractions used flat faced punches 9.525 mm diameter fitted into a single punch hand compressor. The microcapsules, 250 mg, were fed into the die and the tablet compressed over a 60-second period during the last 30 seconds of which the pressure was kept constant. The compression was then released rapidly and the tablet removed and examined for surface defects. The applied pressure varied between 0.39 and 35.89 x 10^4 kNm^{-2}.

Dissolution from both the suspended microcapsules and the tablets was studied using a flask and stirrer technique. The volume of dissolution medium was 2l and the temperature maintained at 37° ± 0.1°

throughout. A 500 mg microcapsule charge was stirred at 100 r.p.m. and samples removed, filtered through a Millipore filter and assayed for sodium phenobarbitone spectroscopically at 240 nm using a Cecil CE202 U.V. spectrophotometer. Before assay all solutions were adjusted to pH 9.3 at which the 240 nm peak obeyed Beer's law and had an $E^{1\%}_{1\,cm}$ of 37.95.

A study of the in vitro release for both the free and tabletted microcapsules showed basically the same pattern, but the time scale for the release being greatly extended in the case of the tabletted preparation (Figure 1). In triple distilled water at pH 6.5 approximately the first 50% of sodium phenobarbitone irrespective of microcapsule size or core: wall ratio, was released rapidly at a constant rate from the suspended microcapsules. As the thickness of the microcapsule wall was increased the release rate during this initial period was slower and, with microcapsules of constant core: wall ratio, the smaller microcapsules released their contents more rapidly than the larger ones.

After the 50% release of the microcapsule contents the rate of removal of the remaining core material becomes progressively slower and is not complete, in the case of the largest microcapsules until at least two hours from the commencement of the experiment.

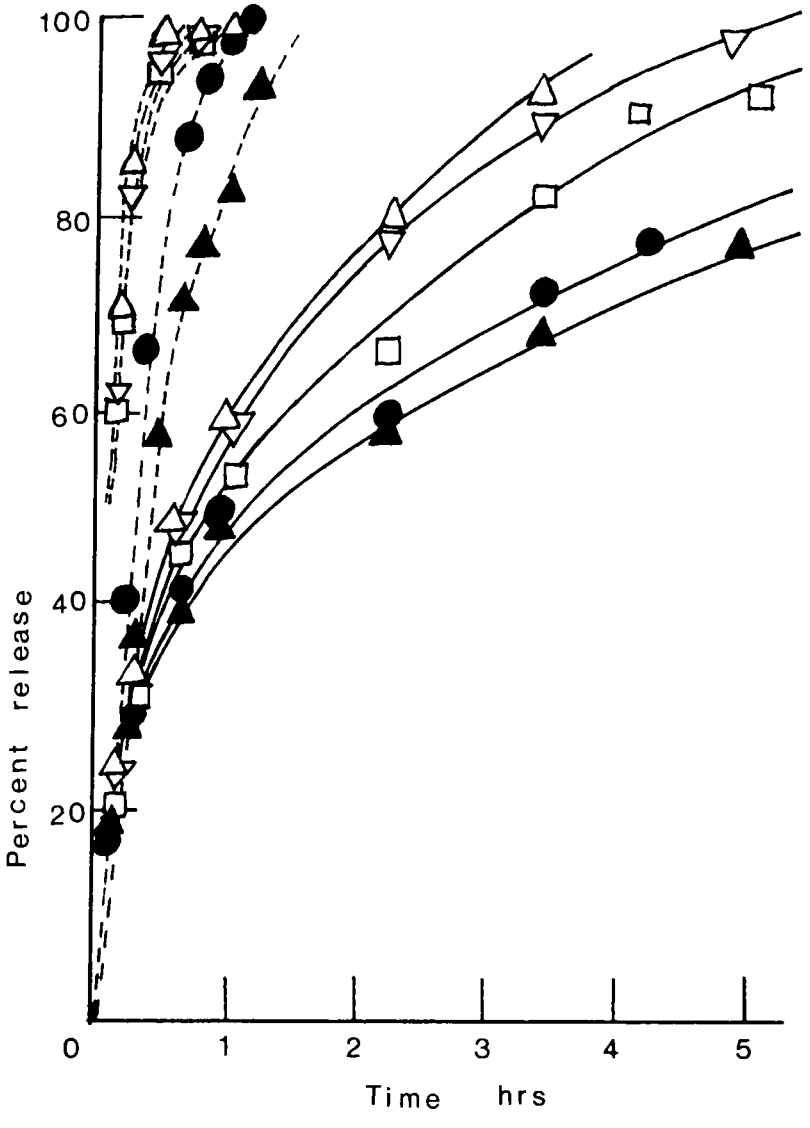

FIGURE 1 The release of sodium phenobarbitone from microcapsules and tabletted microcapsules.

Tablet wt 250 mg, Pressure 15.6×10^4 kNm^{-2},
core: wall ratio 2: 1. Temp. 37° ± 0.1°, pH 6.5.
Microcapsule size μm, Δ 427.5, ▽ 605.0,
□ 855.0, ● 1350.0, ▲ 1850.0.
- - - microcapsules, ——— tablets.

With the tabletted microcapsules only approximately 20% was released during the first ten minutes and after this the release rate slowed down considerably being complete in about four hours with the smaller microcapsules and in approximately seven hours with the 1850.0 μm microcapsules. In no case did the tablet disintegrate during the dissolution experiment.

The dissolution of the tabletted microcapsules is complicated by two important variables. The effect of compression pressure and the size of the microcapsules from which the tablets have been prepared both influence the release rate. As a consequence of these two parameters the tensile strength of the tablets will vary. It was found that tensile strength increased linearly with respect to microcapsule size and that tablets containing a higher proportion of sodium phenobarbitone exhibited higher tensile strength values. Exceptions to this generalisation were found when microcapsules greater than 855 μm were used to prepare tablets with a core wall ratio of 1: 2 at a compression pressure of 15.61×10^4 kNm^{-2}. The density of the microcapsules did not vary significantly being within the range 1.330 to 1.346 for all sizes and core: wall ratios except core: wall ratio 1: 2 and microcapsule size 1350 μm when it fell to 1.244. Whilst tablets containing proportionately more ethyl cellulose exhibited a greater thickness at a given pressure and it was found that a linear relationship

existed between microcapsule diameter and tablet thickness there was no break corresponding to that in the tensile strength values. Microscopic examination of the large microcapsules of core: wall ratio 1: 2 showed that they were aggregates with an elongated axis in one direction which did not occur with the other ratios and it is thought that this difference results in a lower tensile strength on compression.

The time required for 50% release of the sodium phenobarbitone from the tablets was measured and for a given core: wall ratio and microcapsule size was apparently independent of compression pressure until this fell below 0.8×10^4 kNm^{-2} (Figure 2). Such pressures produced very friable tablets which released their contents rapidly although they did not disintegrate.

On the other hand the time for 50% release at a given pressure did increase linearly with respect to the diameter of the microcapsules forming the tablets (Figure 3). Those with a higher proportion of drug release faster, probably because of the correspondingly thinner microcapsule walls, although the tensile strength results exhibit a reverse relationship.

The previous results were all obtained using a pH of 6.5. However if the microcapsules are administered orally the pH of the stomach contents will be far lower than this and therefore the release patterns were also studied throughout the pH range 1.3 to 9.6 which

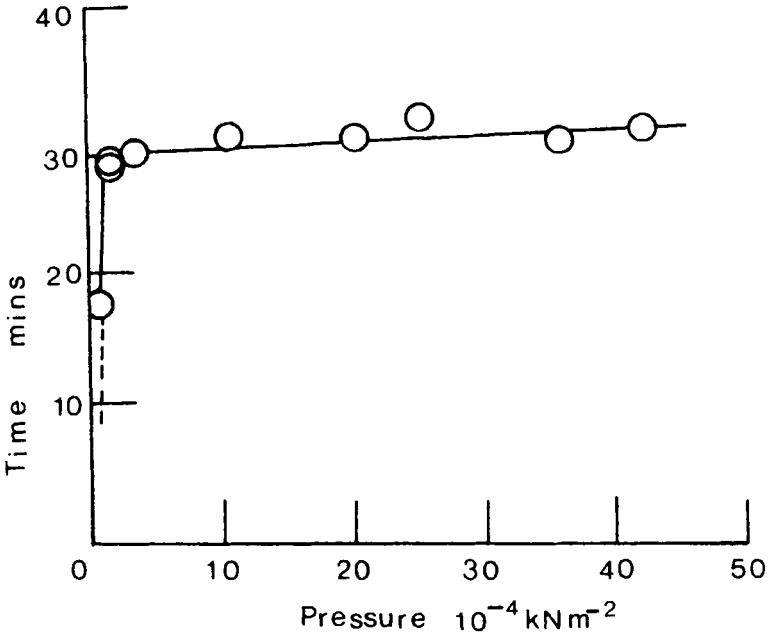

FIGURE 2 The effect of compression pressure on the time for 50% release of core contents.
Tablet wt 250mg, microcapsule diameter 427.5 μm.
Core: wall ratio 2: 1. Temp. 37° ± 0.1°, pH 6.5.

approximately corresponds to the conditions met with in vivo. Adjustments of pH in the dissolution media were made by adding HCl or NaOH and no attempt was made to simulate artificial gastro intestinal media to prevent added complications.

The effect of pHs between 9.6 and 3.1 on the suspended microcapsules was small and insignificant within the limits of experimental

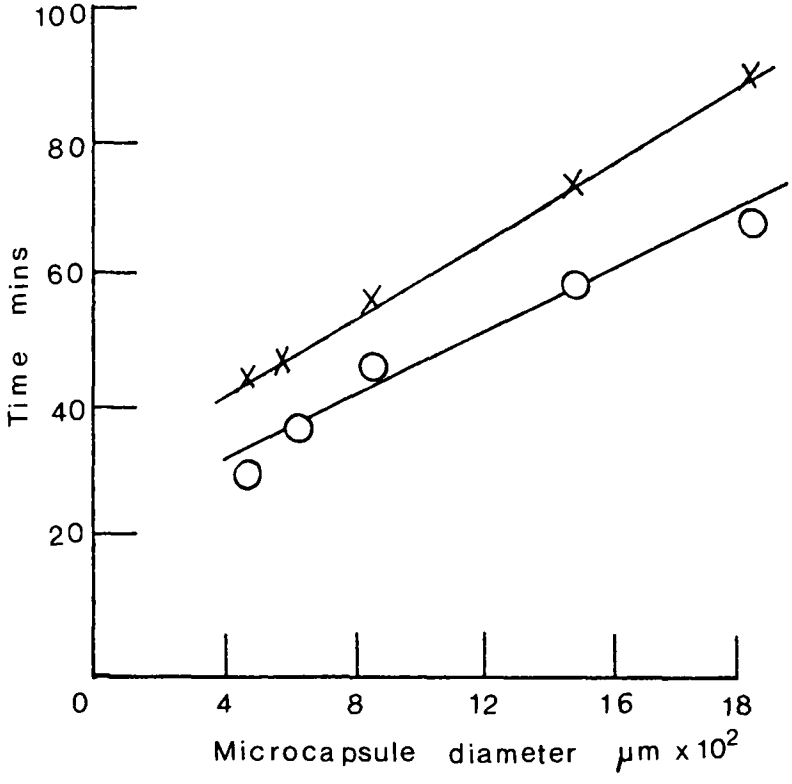

FIGURE 3 The effect of microcapsule size on the time for 50% release of core contents.
Tablet wt 250 mg, pressure 15.6×10^4 kNm^{-2}.
Core: wall ratio X, 1: 1; 0,2: 1., Temp. 37° ± 0.1°, pH 6.5.

error. When the pH was reduced to 1.3 a slower release was evident; 50% in seven minutes and 100% in 140 minutes using 427.5 μm diameter microcapsules at a core: wall ratio of 2: 1 (Figure 4).

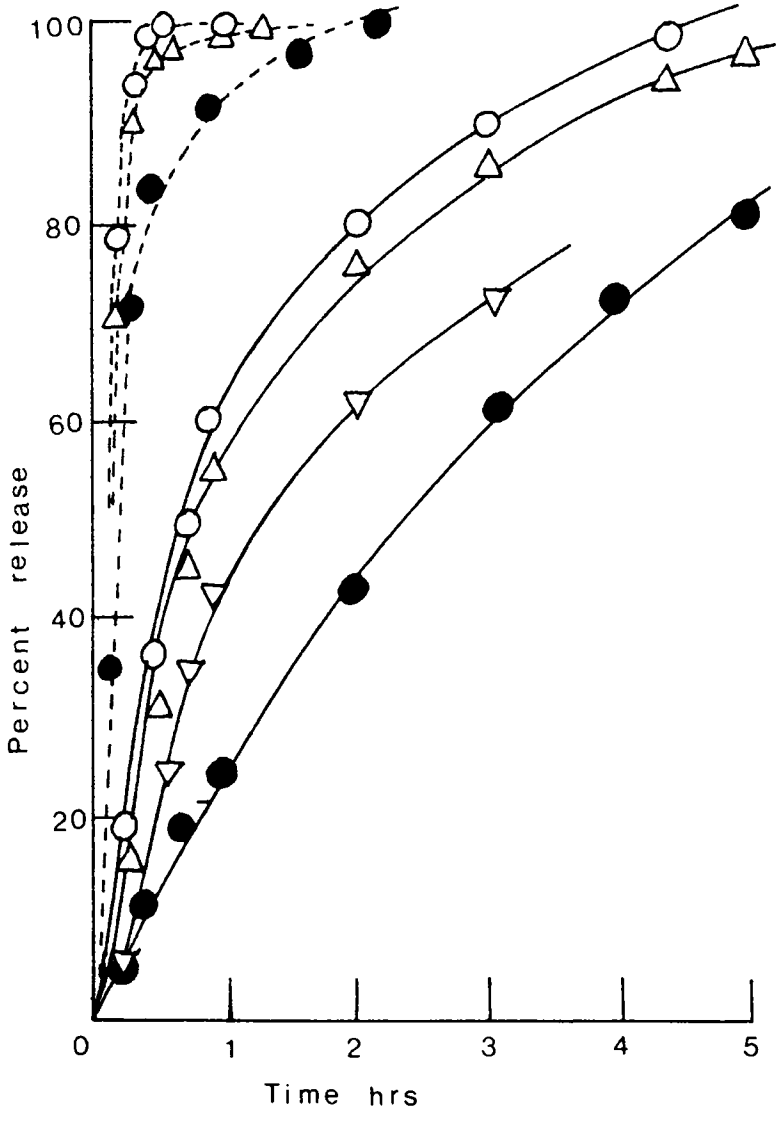

FIGURE 4 The effect of pH on the release of sodium phenobarbitone from microcapsules and tabletted microcapsules.
Tablet wt 250 mg, Pressure 15.6×10^{4} kNm^{-2},
Core: wall ratio 2: 1, Temp. 37° ± 0.1°,
Microcapsule diameter 427.5 μm. pH ○ 9.6, △3.1,
▽ 2.1, ● 1.3, --- microcapsules, —— tablets.

The result with the corresponding tabletted microcapsules at a compression pressure of 15.61×10^{4} kNm^{-2} was more significant. Again there was little difference in release pattern until the pH fell below 3.1 although because of the extended delay times with these sustained release tablets the time for 50% release at pH 9.6, 30 minutes, had increased to 43 minutes at pH 3.1. The corresponding times for 100% release were 206 minutes and 250 minutes.

At pHs below 3.1 the dissolution time is greatly extended in an exponential relationship and the time for complete release becomes progressively longer (Figure 5). Core: wall ratios of 1: 1 give slower release than 2: 1 ratios and when larger microcapsules are used in preparing the tablets they again slow down the release rate, but in the case of both variables the pattern is similar except that there is a tendency for the release rate at very low pH to become constant whatever the tabletting conditions. The effect of the microcapsule size, either calculated as diameter or surface area, used in preparing tablets at constant pressure characteristics is very small, although the increase tends to be linear. At pH 1.3 microcapsule size had no effect on release rate.

At these low pHs it is probable that the sodium phenobarbitone is converted into the far less soluble phenobarbitone and that this

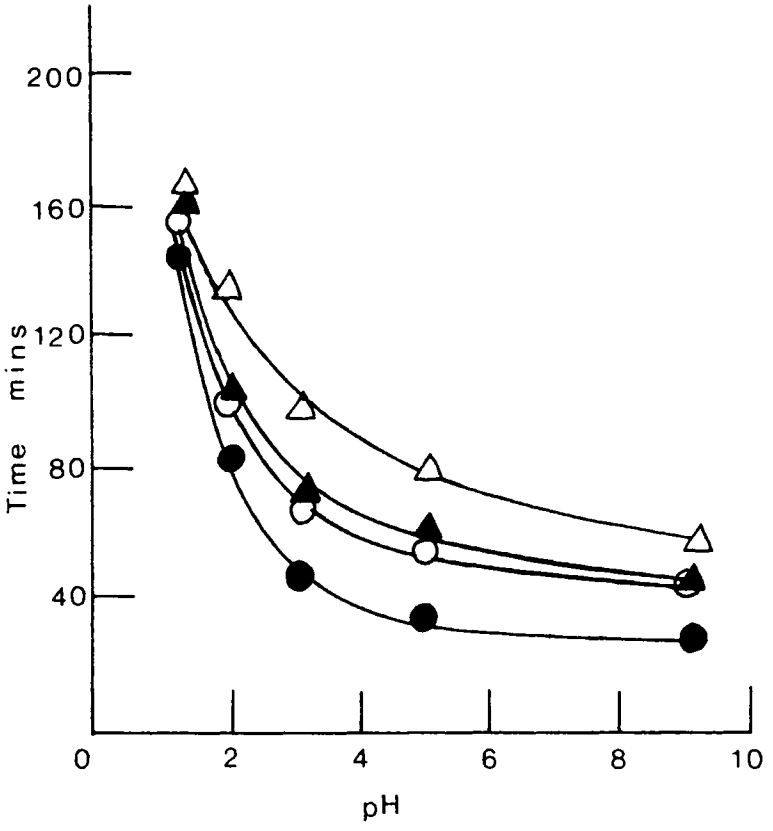

FIGURE 5 The effect of pH on the time for 50% release of core contents.
Tablet wt 250mg, Pressure $15.6 \times 10^4 kNm^{-2}$
Core: wall ratio 2 : 1, ● ▲ 1 : 1 △ ○
Temperature 37° ± 0.1°, microcapsule diameter μm
427.5 ○ ●, 1350.0 △ ▲

accounts for the slower release. If this conversion took place after dissolution it would not be expected to significantly slow down the release pattern, but as the dissolution media must diffuse into the microcapsule or tablet then the reaction will take place there and

at these low pHs it is the rate of release of phenobarbitone rather than phenobarbitone sodium which is taking place.

REFERENCES

1. Calanchi, M., (1976), 'Microencapsulation', Ed. J. R. Nixon, pp. 93 - 101, Marcel Dekker Inc., N.Y.

2. De Sabata, V., (1976), 'Microencapsulation', Ed. J. R. Nixon, pp. 155 - 156, Marcel Dekker Inc., N.Y.

3. Gutcho, M., (1972), 'Capsule technology and Microencapsulation', Noyes Data Corp. U.S.A.

4. Jalsenjak, I., Nicolaidou, C.F., and Nixon, J.R., (1976), J. Pharm. Pharmac., 28, 912 - 914.

5. Luzzi, L.A., (1970), J. Pharm. Sci., 59, 1367 - 1376.