The *in vitro* dissolution of phenobarbitone sodium from ethyl cellulose microcapsules

I. JALSENJAK*, CONSTANTIA F. NICOLAIDOU AND J. R. NIXON†

Department of Pharmacy, Chelsea College, University of London, Manresa Road, London, SW3 6LX, U.K.

Microcapsules of sodium phenobarbitone, with a wall of ethyl cellulose, have been prepared. The size distribution was determined by use of standard sieves and the effect of core:wall ratio noted. Release of the drug into an aqueous medium was studied. The release pattern was found to have similar characteristics to the release of a drug from an insoluble porous matrix.

The development of microencapsulation as a technique for the preparation of sustained release dosage forms has progressed steadily with the emphasis mainly on the use of gelatin-acacia coacervates as a means of microencapsulating water-insoluble medicaments (Luzzi, 1970; Nixon, 1976). Other techniques have been investigated, particularly for microencapsulation of water-soluble materials (Gutcho, 1972). Many of these procedures are complicated and present difficulties in recovering a solid product. Amongst the simpler techniques is the separation of a polymer from a solvent due to temperature change (Miller, Fanger & Moniff, 1967), and this has been developed in the present study to investigate the release of a water soluble material, sodium phenobarbitone, from ethyl cellulose microcapsules.

MATERIALS AND METHODS

Materials

Sodium phenobarbitone B.P.: Evans Medical Ltd. Ethyl cellulose: BDH Laboratory Chemicals Division. Cyclohexane (May & Baker) not less than 95% distills between 80–81°. Purified water: distilled from an all glass still.

Methods

Preparation of microcapulses. The method of preparation was developed with modifications from the technique of Miller & others (1967). Into a 2 litre three necked flask, fitted with a P.T.F.E. two bladed stirrer and a reflux condenser, was placed 600 ml of cyclohexane. With a stirring rate of 560 rev min⁻¹ and a temperature of 50° ethyl cellulose was added and the temperature raised to 70° over 20 min. The core material, sodium phenobarbitone, was then

* Present address: Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Zagreb, Zagreb, Yugoslavia.
  † Correspondence.

added and over a period of 75 min the temperature was further raised to 80°. After being held constant for 1 h the system was allowed to cool slowly with continuous stirring and the hardened ethyl cellulose coated microcapsules filtered and air dried. The yield was greater than 98%. The quantity of ethyl cellulose and sodium phenobarbitone used varied depending on the core to wall ratio required. For a 2:1 ratio 6 g of sodium phenobarbitone and 3 g of ethyl cellulose was used in the above system.

Screening of microcapsules. The different sizes of microcapsules present in a batch were separated into suitable fractions by sieving on a mechanical shaker using a nest of standard sieves (250–2000 μm apertures) and a shaking time of four min.

Dissolution procedure. Dissolution of 500 mg of the microcapsule fractions into 2 litres of water at 37° $\pm$ 0·1° was studied. A round bottomed flask fitted with a PTFE stirrer and a syringe for extracting samples was used. A stirring speed of 100 rev min⁻¹ was maintained as a constant in all experiments. Timing commenced on the introduction of the microcapsules into the flask and was subject to an initial error due to transfer of not more than 3 s. Five ml samples were removed at intervals and filtered through a Millipore filter HAO. 45 μm Swinex-25 before assay by ultraviolet spectrometry. An equivalent quantity of purified water was returned to the dissolution system immediately after each sample was removed.

Assay of sodium phenobarbitone. Measurements of the transmittance at a wavelength of 240 nm were made using 1 cm matched silica cells. A suitable dilution of the original sample was made and the pH adjusted to 9·3 with dilute KOH. The F (1 %, 1 cm) at this pH was 37·97 and the peak obeyed Beer's law. At pHs below 7 no peak was obtained.

Table 1. *Size distribution of microcapsules.*

Size range μm	Mean size d μm	% fraction for a given core:wall ratio		
		2:1	1:2	1:1
250–355	302·5	11·65	19·27	1·92
355–500	427·5	29·50	26·77	7·66
500–710	605·0	28·57	26·12	17·62
710–1000	855·0	15·53	12·85	23·95
1000–1700	1350·0	10·87	11·78	33·52
1700–2000	1850·0	3·88	3·21	15·32

RESULTS AND DISCUSSION

The technique of polymer separation as a means of coating solid particles to form microcapsules is apparently easy, but slight changes in the procedure produce a marked variation in the final product. This variation is shown by the gross appearance of the microcapsules and also in their size distribution. The most obvious factor influencing the size of the microcapsules was the stirring rate. At slow speeds very large smooth ethyl cellulose coated beads were obtained. A second important variable was the rate of cooling. If this was rapid then the phenobarbitone was unevenly coated with small particles of the ethyl cellulose and the surface presented a rough appearance with the probability of pores extending through the wall to the surface of the encapsulated sodium phenobarbitone. The technique adopted produced microcapsules with a smooth outer wall and a size distribution which was approximately reproducible from batch to batch (Table 1). However, slight changes in geometry of the reaction vessel, e.g. size of paddle in relation to size of flask, could produce a difference in the relative size distribution although the overall size range remained constant. This is shown by the 1:1 ratio system in Table 1, where the stirring rate was reduced to 400 rev min^{-1}.

Although the performance of microencapsulated drugs *in vivo* is difficult to correlate with their *in vitro* dissolution rates, studies of the latter parameter do allow a comparison to be made between different microcapsule fractions and an assessment of their relative efficiencies as delayed release dosage forms. Fig. 1 shows the release of sodium phenobarbitone from microcapsule fractions with differing core to wall ratios. In all cases, there is a similar pattern of release, with approximately 50% of the core dissolving from the microcapsules at a constant rate, which then begin to slow down. The effect of microcapsule size at the different core ratios also follows a similar pattern. At a constant core: wall ratio, the smaller microcapsules released their
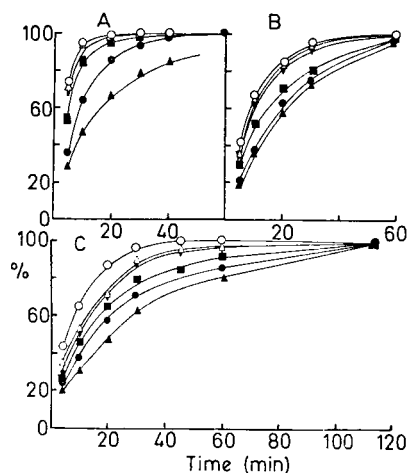

FIG. 1. Dissolution (%) of phenobarbitone sodium from microcapsules. Core:wall ratio: A 2:1, B 1:1, C 1:2. Mean microcapsule size, μm: ○ 302·5, △ 427·5, ▼ 605·0, ■ 855·0, ● 1350·0, ▲ 1850·0. Temperature 37 ±0·1°.

contents the most rapidly. As the core:wall ratio decreases it is reasonable to expect thicker walls and correspondingly greater delays in the release rate and this is also illustrated in Fig. 1. If the microcapsule batch has a predomenance of smaller capsules then the release will be influenced by these far more than the smaller percentage of large capsules. However, the overall release pattern is always intermediate between that of the largest and smallest fractions.

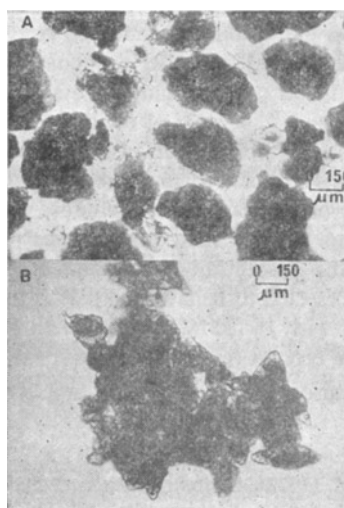Photographic evidence (Fig. 2) shows that in part

FIG. 2. Microcapsules of phenobarbitone sodium showing: A single microcapsules of mean size 427·5 μm and B compound microcapsules of mean size 1350·0 μm. Scale—0–150 μm.

the larger microcapsules are composed of aggregates of smaller capsules, rather than single capsules with thicker walls. This would appear to suggest that dissolution was confined to the outer surface, possibly due to incomplete wetting or the formation of static concentrated films of dissolved material towards the centre of the aggregate, which would lower the local concentration gradient and thus inhibit further release of core material from the centre of the aggregate. Because of the essential spherical nature of the microcapsules it is possible to calculate a mean surface area and a plot of this against the 50% release of sodium phenobarbitone is a straight line (Fig. 3).
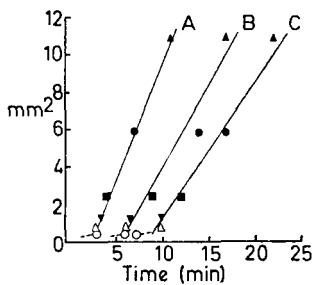

FIG. 3. Effect of mean surface area (mm²) and core: wall ratio of microcapsules on the time for 50% release (min). Core: wall ratio: A 2:1, B 1:1, C 1:2. Mean microcapsule size, μm: ○ 302·5, △ 427·5, ▼ 605·0, ■ 855·0, ● 1350·0, ▲ 1850·0. Temperature 37 ± 0·1°.

If the percentage of sodium phenobarbitone in a given size of microcapsule and at different core: wall ratios is compared with the time taken to release 50% of the drug then a straight line is obtained (Fig. 4). This implies that a uniform diffusion gradient is set up through the wall and that it should be possible to predict the 50% release time for microcapsules of known size and % content of the drug. This in turn should allow the preparation of micro-encapsulated dosage forms with a predictable release pattern.

The microcapsules of ethyl cellulose neither disintegrate nor change their surface area during the course of the dissolution experiments and therefore might be expected to behave like plastic matrices of the type studied by Schwartz, Simonelli & Higuchi (1968). The percent release from these was found to show a linear dependance on the √time. The sodium
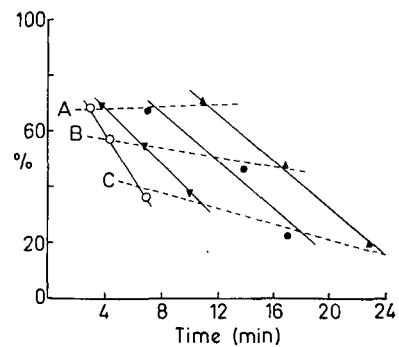

FIG. 4. Effect of % of phenobarbitone sodium content on the time for 50% release (min). Core: wall ratio: A 2:1, B 1:1, C 1:2. Mean microcapsule diameter, μm: ○ 302·5, ▼ 605·0, ● 1350·0, ▲ 1850·0. Temperature 37 ± 0·1°.

phenobarbitone-ethyl cellulose microcapsules show a similar straight line relationship (Fig. 5) which is further evidence that a diffusion process is responsible for the release of the drug.
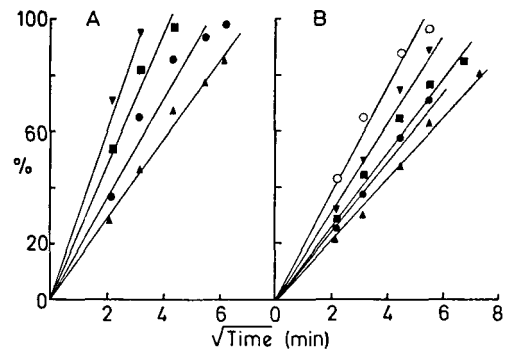

FIG. 5. The release of phenobarbitone sodium (%) as a function of √time. Core: wall ratio: A 2:1, B 1:2. Mean microcapsule size, μm. ○ 302·5, ▼ 605·0, ■ 855·0 ● 1350·0, ▲ 1850·0.

It would appear therefore that polymer separation can be used to prepare sustained release microcapsules of water soluble drugs and that the release of core material from these is a function both of the drug: wall material ratio and the overall microcapsule size. The release appears to proceed by a diffusion process as in the case of an insoluble polymer bead or a wax matrix.

REFERENCES

GUTCHO, M. (1972). *Capsule Technology and Microencapsulation*. Park Ridge, N.J., U.S.A.: Noyes Data Corp.
LUZZI, L. A. (1970). *J. pharm. Sci.*, **59**, 1367–1376.
MILLER, R. E., FANGER, G. O. & MONIFF, R. G. (1967). Union of South Africa, Patent 4211–66.
NIXON, J. R. (1976). *Microencapsulation, Drugs and the Pharmaceutical Sciences*, Vol. 3, New York: Marcel Dekker Inc.
SCHWARTZ, J. B., SIMONELLI, A. P. & HIGUCHI, W. I. (1968). *J. pharm. Sci.*, **57**, 274–277, 278–282.