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Dissolution from tablets prepared using ethyl cellulose microcapsules

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Microcapsules containing sodium phenobarbitone cores in ethyl cellulose have been used to prepare tablets at from 3·9 to 358·9 MPa compression pressures. The tensile strength of these tablets is related linearly to the core : wall ratio and to the microcapsule size. Dissolution of the drug from the microcapsules is also related to the core : wall ratio and microcapsule size, but except at low compression pressures is almost independent of the pressure used during preparation. The tablet matrix remains intact during the dissolution and the equations developed by Schwartz, Simonelli & Higuchi (1968) are followed. Large microcapsules of 1 : 2 core : wall ratio produce friable tablets with rapid release of contents.

The most frequently used dosage forms for microencapsulated products have until recently been suspensions and gels (Calanchi, 1976). Although tablets of microencapsulated acetyl salicylic acid have been prepared there have been few investigations into such formulations. One of the possible reasons is the belief that the thin microcapsule wall would be of poor mechanical strength and therefore destroyed during the compression. However, at least one claim has been made for the preparation of a sustained release tablet incorporating microcapsules (Estevenel, Thely & Coulon, 1975).

In the present work we have prepared tablets by the compression of ethyl cellulose microcapsules containing phenobarbitone sodium. The mechanical strength and *in vitro* release data from these tablets has been studied.

MATERIALS AND METHODS

Materials. All materials used were as described by Jalsenjak, Nicolaidou & Nixon, 1976.

Methods. Preparation, screening of microcapsules, and assay for sodium phenobarbitone were carried out as previously.

Preparation of tablets. Individual tablets were made using a hand operated compressor. Flat punches of 9·525 mm diameter were used and 250 mg of microcapsules fed into the die. Each tablet was made within an interval of 1 min, the last 30 s of which were used to keep the tablet under constant pressure. The pressure was then rapidly released and the tablet removed.

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Tensile strength measurements. The diametral compression test devised by Fell & Newton (1970) was used: the tensile strength, T, being given by the formula $T = \frac{2P}{\pi Dt}$ where P was the applied stress, D diameter of tablet and t the tablet thickness.

Dissolution procedure. The previously reported dissolution technique was modified in that one 250 mg tablet replaced the 500 mg of individual microcapsules as the sample.

RESULTS AND DISCUSSION

In recent years doubts have been expressed as to the advantage of using sustained release tablets but formulation work intended to improve both the safety and uniformity of release is proceeding. The use of suspended microcapsules can be shown to give a sustained release effect which could be controlled by the thickness and composition of the wall as well as by the core : wall ratio.

If it is possible to prepare tablets from the microcapsules then enhancement of sustained release would be expected. Watanabe & Hayashi (1976) have shown by electron photomicrographs that films of microcapsules under pressures of up to 19·6 MPa still retain many intact capsules although a liquid core was used. It is therefore probable that microcapsules with solid cores would withstand larger compression pressures before disintegrating. We investigated the effect of compression pressures between 3·9 and 358·9 MPa.

Tablets prepared from microcapsules of different mean diameter and core : wall ratio at a pressure of 156·1 MPa exhibited the physical properties shown in Fig. 1. It was found that with a core : wall ratio

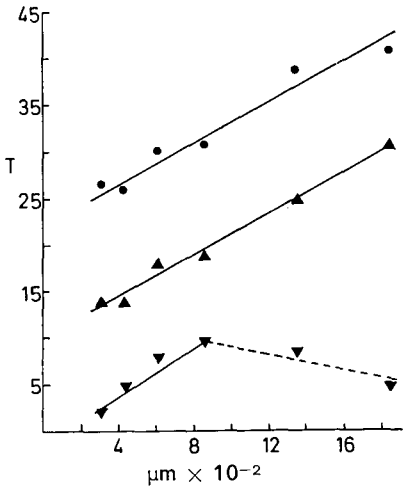

FIG. 1. Effect of microcapsule size ($\mu m \times 10^{-2}$) on the tensile strength (T) of tablets. Tablet weight 250 mg tablet diameter 9·5 mm, pressure 156 MPa Core: wall ratio ● 2:1; ▲ 1:1; ▼ 1:2.

of 2:1 and 1:1 that the tensile strength increased linearly with respect to microcapsule size and that the slope of the two lines was the same, but that tablets with a higher proportion of phenobarbitone sodium had a greater tensile strength. When a core:wall ratio of 1:2 was used for the microcapsules the same straight line relation between tensile strength and microcapsule diameter was found only up to the 855 μm size. With larger microcapsules the tensile strength decreased. If the thickness of these same tablets is compared, Fig. 2, it is found that there is a linear relation between the microcapsule diameter and thickness of tablet, but that the tablets containing proportionately the

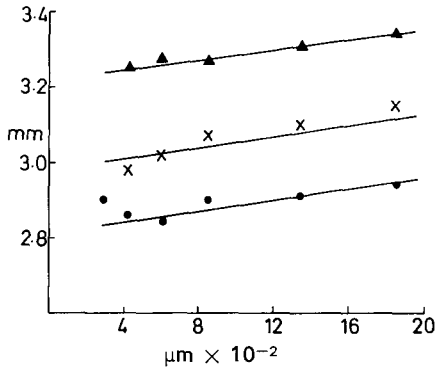

FIG. 2. Relation between tablet thickness (mm) and microcapsule diameters ($\mu m \times 10^{-2}$) weight of tablets 250 mg. Tablet diameter 9·5 mm, pressure 156 MPa. Core: wall ratio ▲ 1:2; × 1:1; ● 2:1.

largest amount of ethyl cellulose produce the thickest tablets and that there is no corresponding break to that shown in the tensile strength relations (Fig. 1). As expected, the thinner more compacted tablets (2:1 ratio) exhibited the highest tensile strength. It may also be noted that whilst for the 2:1 and 1:1 ratios the largest microcapsules produced tablets with the greatest tensile strength these same tablets had the greatest thickness within their respective series. Examination of the microcapsules of 1:2 ratio suggested that they were composed of aggregates producing an elongated effect. In many cases the individual microcapsules had merged during the liquid state of preparation in such a way that the crystalline core was spread in a linear manner similar to the bendrofluozide microcapsules noted by Matthews (1975). With the 2:1 and 1:1

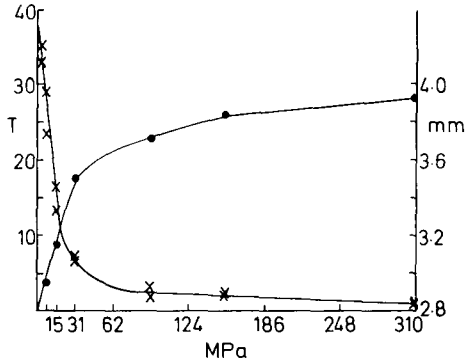

FIG. 3. Relation between tensile strength (T) and tablet thickness (mm) at different compression pressures (MPa). Microcapsule diameter 427·5 μm; Tablet weight 250 mg. Tablet diameter 9·5 mm, core: wall ratio 2:1, ● tensile strength, × tablet thickness.

ratios this did not occur. From the tensile strength results (Fig. 1), it would appear that these elongated microcapsules containing a larger proportion of ethyl cellulose do not bind together as strongly as those containing a smaller proportion of wall material and where the shape is more spherical.

The results obtained at 156 MPa pressure are qualitatively similar at pressures between 93·6 and 358·9 MPa; there being only a slight increase in the tensile strength at higher pressures and no further change in the tablet thickness (Fig. 3). At pressures below 93·6 MPa there is a rapid fall in the tensile strength of the tablets and a correspondingly rapid increase in the thickness of the tablets. It would appear that there is little advantage, from the point of view of tablet strength, in using pressures greatly in excess of 93·6 MPa.

The physical appearance of all the tablets was good, the faces being hard and shiny with no trace of powder. However the tablets prepared from 1:2 ratio microcapsules were slightly yellowish and this yellow colouration was also found in tablets made with high pressures 312·1 and 358·9 MPa using other core:wall ratio microcapsules.

The shape of the dissolution curves from tablets containing 2:1 and 1:1 ratios of core:wall material followed those from the corresponding microcapsules, which have been reported in detail (Jalsenjak & others, 1976), but with the drug release time significantly increased. Specimen release curves for the 2:1 ratio tablets made at 156·1 MPa pressure are shown in Fig. 4. With all microcapsule sizes there was a rapid release of approximately 20% of the drug but this then slowed and with large microcapsules 20% of the drug still remained to be released after 240 min. In all cases the release was proportionate to the microcapsule size used; the tablets containing smaller microcapsules releasing their contents more rapidly.

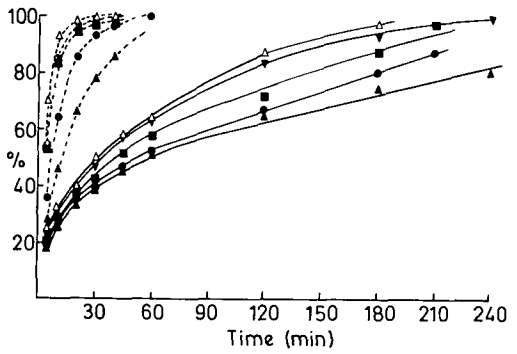

FIG. 4. Release of sodium phenobarbitone (%) from microcapsules (---) and tableted microcapsules (—). Tablet weight 250 mg, pressure 156 MPa, core:wall ratio 2:1, microcapsule size μm. △ 427·5, ▼ 605; ■ 855; ● 1350; ▲ 1850.

The time required to release 50% of the drug contents exhibits a straight line relation (Fig. 5). The tablets from larger microcapsules, which have a greater tensile strength, release at a slower rate. However, it should be noted that the effect of core:wall ratio is reversed in these dissolution curves and that tablets which have a higher proportion of drug release their contents faster than those with a 1:1 core:wall ratio, although the latter tablets have a lower tensile strength. Nor are the 50% release curves parallel as were the tensile strength curves, but they diverge as larger microcapsules were used in the preparation of the tablets. This more rapid release is in line with the results for dissolution from microcapsules and is most probably due to the relative thickness of the wall surrounding individual microcapsules. These walls probably remain intact during compression and the primary drug release from the tablets component microcapsules would therefore depend on diffusion of the dissolved drug through the ethyl cellulose wall which would be thicker or more dense in the case of the 1:1 ratio tablets.

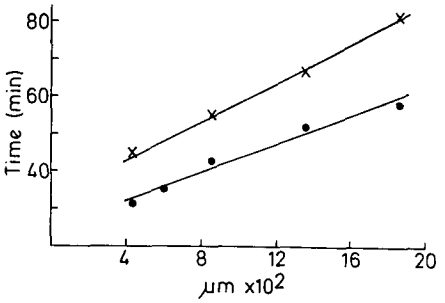

FIG. 5. Effect of microcapsule size (μm × 10^2) on the time for 50% release. Tablet weight 250 mg pressure 156 MPa; core:wall ratio; × 1:1, ● 2:1.

The release from tablets prepared with a 1:2 core:wall ratio also followed the tensile strength results. With tablets from small microcapsules the time for 50% release was slightly longer than those from the corresponding 1:1 ratio, e.g. microcapsule size 427 μm; 1:2 ratio 45 min; 1:1 ratio 43·5 min. However in those tablets which had low tensile strengths the time for release of 50% drug content was very low. With microcapsules of 1350 μm it was 23·5 min and for 1850 μm microcapsules 21 min. As these latter tablets did not disintegrate during the course of the dissolution their more friable structure must have contained more or wider tortuosity passages within the core; thus allowing more rapid release of the contents.

Whilst the tensile strength of the tablets never reached a constant value in relation to applied preparation pressure and in fact increased very rapidly at pressures up to 93·6 MPa the dissolution time for 50% release was almost independent of pressure down to 7·8 MPa (Fig. 6). At pressures below this the tablets became very friable and although they did not disintegrate during the dissolution experiment release was rapid. It is possible that the higher-compression pressures do not affect the walls of the component microcapsules, but only the tortuosity spacing between micro-

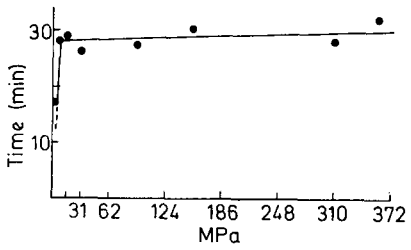

FIG. 6. Effect of compression pressure (MPa) on the time for 50% release. Tablet weight 250 mg. Microcapsule diameter 427·5 μm, core : wall ratio 2 : 1.

capsules within the tablet core. Thus, the rate of diffusion through the walls of a microcapsule of given size and core : wall ratio will be almost independent of applied pressure and will be the limiting factor in release from the tablet.

As with the release from individual microcapsules Higuchi plots showed a straight line relation up to a limit of 70% release. As the tablet matrix was intact at the end of the experiment, it is probable that dissolution follows a normal course of solution of the drug followed by diffusion through the microcapsule wall and removal from the tablet via tortuous passages between individual microcapsules. The skeletons of the tablets when 100% of the drug had dissoluted were dried in a dessicator to constant weight and in no case had more than 5% of the ethyl cellulose matrix been lost during the experiment.

It would appear that microcapsules with ethyl cellulose walls can be tableted and that the strength of such tablets is determined both by the applied compression pressure and the microcapsule size. The rate of dissolution from such tablets gives a useful sustained release effect and is dependent on both core : wall ratio and microcapsule size. Apart from very low compression pressures this factor in tablet preparation appears to play little part in determining the release rate.

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