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Effect of Microcapsule Core–Wall Ratio and Aggregate Size on the Properties of Tableted Microcapsules

JOSEPH R. NIXON and GEORGE A. AGYILIRAH *x

Received February 23, 1982, from the *Department of Pharmacy, Chelsea College. London University, London SW3 6LX, England.* Accepted for publication October 21, 1982. *Present address: Department of Industrial and Physical Pharmacy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, IN 47907.

Abstract □ Microcapsules containing sodium phenobarbital cores and ethylcellulose walls have been tableted. The thickness of the tablets, the breaking strength, and the dissolution characteristics were studied and found to be affected by the microcapsule core–wall ratio and the size of the microcapsule aggregates.

Keyphrases □ Microcapsules—sodium phenobarbital and ethylcellulose, tablets, effect of core–wall ratio and aggregate size on dissolution □ Dissolution—tablets composed of microcapsules, sodium phenobarbital and ethylcellulose, effect of core–wall ratio and aggregate size □ Sustained-release formulations—tableted microcapsules, sodium phenobarbital and ethylcellulose, effect of core–wall ratio and aggregate size on dissolution

Microcapsules consist of a thin wall which can enclose a solid or liquid core material. One of the many important reasons for microencapsulating medicaments is to achieve sustained release. Good sustained release has been achieved by microencapsulating poorly water-soluble medicaments such as aspirin and phenobarbital (1). With very water-soluble substances such as sodium phenobarbital, the rate of release is slowed by microencapsulation, being controlled partly by the wall thickness. However, no satisfactory sustained release has been achieved with water-soluble substances (1–3). Tableting of microcapsules has been shown to slow the release significantly and provide a sustained- or prolonged-action release (4–6). The microcapsules which have been tableted appear to be mainly those with ethylcellulose walls prepared using a modification of the method described by Fanger *et al.* (7); in most cases, this technique has produced aggregates (2, 5, 7). This work studies the effect of the aggregate size and the core–wall ratio on the properties of the prepared tablets.

EXPERIMENTAL

Materials—Phenobarbital sodium[1] (99.4% pure), ethylcellulose[1] (viscosity 5% w/w solution in 80:20 toluene–ethanol mixture: 14.13 cP; degree of substitution: 2.50; ethoxy content: 47.5%), and cyclohexane[2] (99.5% pure, bp 80–81°C, fp 5.95°C; wt/mL at 20°C: 0.776) were purchased commercially.

Preparation of Microcapsules—The method used was a modification of an original technique by Fanger *et al.* (7) as further modified by Agyilirah and Nixon (5). This method involves deposition of polymeric wall-forming material onto dispersed particles of core by cooling below a critical liquid–liquid phase separation temperature. A typical example of microcapsule preparation was as follows. Ten grams of sodium phenobarbital and 5 g of ethylcellulose were dispersed in 500 mL of cyclohexane. The stainless steel stirrer was adjusted to the middle of the dispersion to obtain uniform stirring and a speed of 500 rpm was used. The temperature was raised slowly to 80°C over a period of 1 h after which it was allowed to reflux for 30 min. While continuing the stirring, the temperature was allowed to decline at a controlled rate. The ethylcellulose separated, first as a liquid, which was deposited round the core particles, and when the temperature had reached 25°C the stirring was stopped so that the microcapsules could be filtered and dried.

Preparation of Tablets—The tablets were made by compressing 250-mg quantities of the dried microcapsules. The die was fitted onto a 9.5-mm flat lower punch, and 250 mg of microcapsules was placed in it. The upper punch was carefully placed in position, making sure no microcapsules were lost. The punch and die arrangement was placed under the compression head, which was lowered onto the upper punch until the required compression pressure was attained. A compression pressure of 315 kg/cm^2 was maintained for 1 min and then quickly removed. Tablets were prepared from microcapsules of core–wall ratios 4:1, 1:1, 1:2, and 1:4 as well as from 2:1 core–wall ratio microcapsules sieved into sizes of 215, 302.5, 427.5, 605, and 855 μm using British Standard sieves.

Determination of Tablet Thickness and Breaking Strength—The thickness of the tablets was determined by means of a micrometer screw gauge. For each tablet five different measurements were taken at five

[1] B.D.H. Chemicals Ltd., Poole, England.
[2] Fisons Scientific Apparatus, Loughborough, Leicestershire, England.

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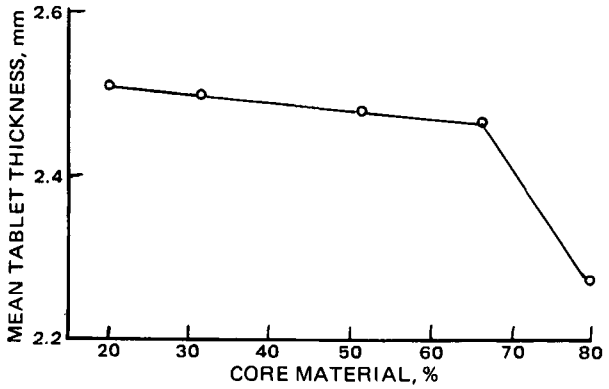

Figure 1—*Influence of microcapsule core–wall ratio on tablet thickness. Compression pressure: 315 kg/cm²; tablet weight: 250 mg; tablet diameter: 9.5 mm.*

different positions and the mean value recorded. Tablet breaking strength was determined by means of a hardness tester[3]. The tablet was pressed between platens across its diameter and the force increased until the tablet fractured. The force required to break the tablet was recorded as its breaking strength.

Dissolution Studies—The dissolution medium consisted of 2 L of distilled water in a 2500-mL flask at a temperature of 37°C. A stirring rate of 100 rpm was standardized using a 7-cm paddle. The dissolution flask was connected to the cells of a digital spectrophotometer[4] by an inlet tubing through which solution from the flask was continuously pumped through the 1-cm UV cells for assay. The solution once assayed returned to the flask *via* the outlet tubing. A wavelength of 240 nm was used and the instrument calibrated to give a direct reading of percent dissolved. One tablet was used for each dissolution.

RESULTS AND DISCUSSION

The effects of the microcapsule core–wall ratio and aggregate size on the thickness of the tablets are shown in Figs. 1 and 2, respectively. From Fig. 1 it can be seen that the thickness of the tablet decreased as the proportion of the core material increased. During the compression both the sodium phenobarbital and the ethylcellulose became compressed, with a greater elastic compression of the ethylcellulose wall due to its fibrous nature. On removal of the compression pressure there is a reexpansion of the ethylcellulose wall. The larger the amount of ethylcellulose present, the greater the expansion. This explains the reduction in the tablet thickness as the core–wall ratio increases, since the amount of ethylcellulose present becomes proportionately less under these conditions. The much smaller value for the 4:1 core–wall ratio (*i.e.*, 80% core) occurs because at this ratio the ethylcellulose wall is so thin that breakdown of the wall occurs during the compression. When wall destruction occurs, some sodium phenobarbital crystals penetrate the wall, making it impossible for any appreciable expansion on removal of the pressure.

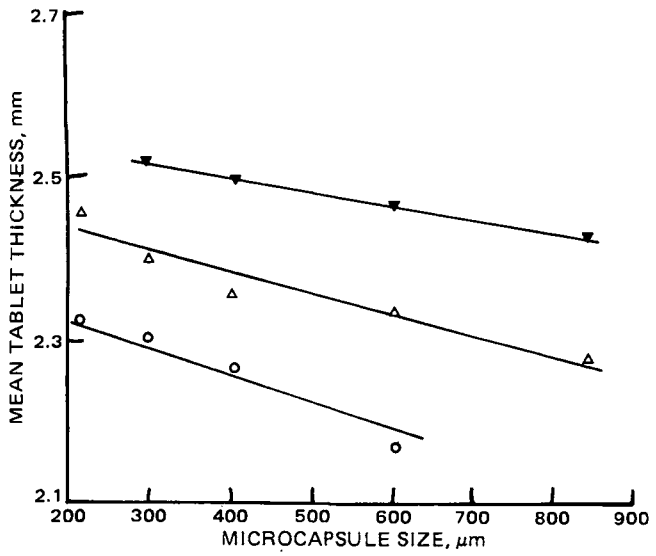

Figure 2—*Effect of microcapsule size on tablet thickness. Microcapsule core–wall ratios: (○) 4:1, (△) 2:1, (▼) 1:1. Compression pressure: 315 kg/cm²; tablet weight: 250 mg; tablet diameter: 9.5 mm.*

[3] Nottingham Engineering, Nottingham University, Notts, England.
[4] Cecil Instrument Co., Milton, Cambridgeshire, England.

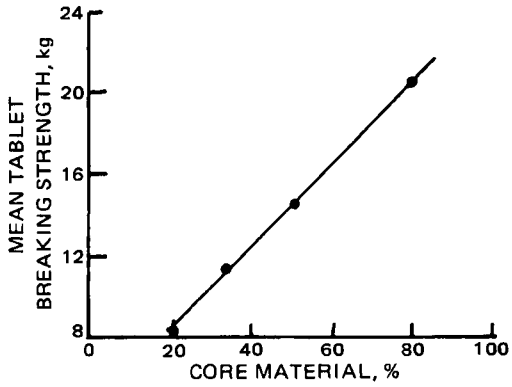

Figure 3—*Effect of the percent core material on the mean breaking strength of tablets prepared from 4:1, 1:1, 1:2, and 1:4 core–wall ratio microcapsules. Compression pressure: 315 kg/cm²; weight of tablet: 250 mg; tablet diameter: 9.5 mm.*

The decrease in the thickness with increasing microcapsule aggregate size is due to the breakdown of microcapsule aggregates during the compression. The smaller particles resulting from the breakdown would fill gaps between larger particles, thus producing a more compact mass.

The amount of sodium phenobarbital that resulted from assaying 100 mg of 1:1 core–wall ratio microcapsules of aggregate sizes 215, 302.5, 427.5, and 605 μm were 49.5, 51.0, 50.3, and 49.2 mg, respectively, showing that the amount of drug contained in a given amount of the same batch of microcapsules did not depend on the aggregate size. This finding is not surprising since the different aggregates are made up of microcapsules that existed as individual entities at one stage of their preparation and the different aggregate size only reflects the numbers of individual microcapsules in the aggregate.

Figures 3 and 4 show the relationship between the strength of the tablets, the core–wall ratio, and the microcapsule size. Figure 3 appears to complement the results shown in Fig. 1 in that when ethylcellulose expands after the removal of the compression pressure, the bonds formed during the compression are relaxed producing a less rigid tablet. This relaxation could explain the decrease found in the strength of the tablets as the core–wall ratio was reduced. The walls of the microcapsules also

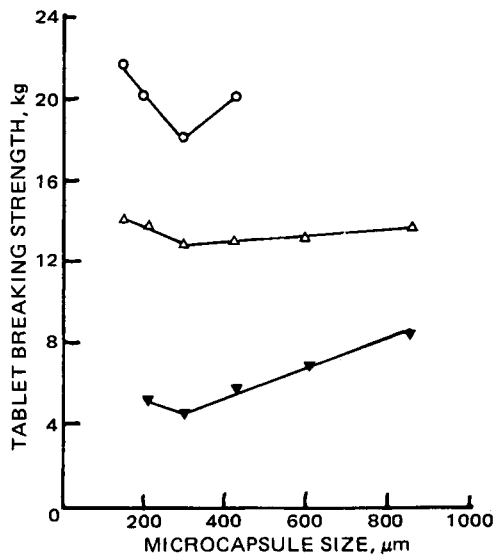

Figure 4—*Effect of microcapsule size on tablet breaking strength. Microcapsule core–wall ratio: (○) 4:1, (△) 2:1, (▼) 1:1. Compression pressure 315 kg/cm²; tablet diameter: 9.5 mm; tablet weight: 250 mg.*

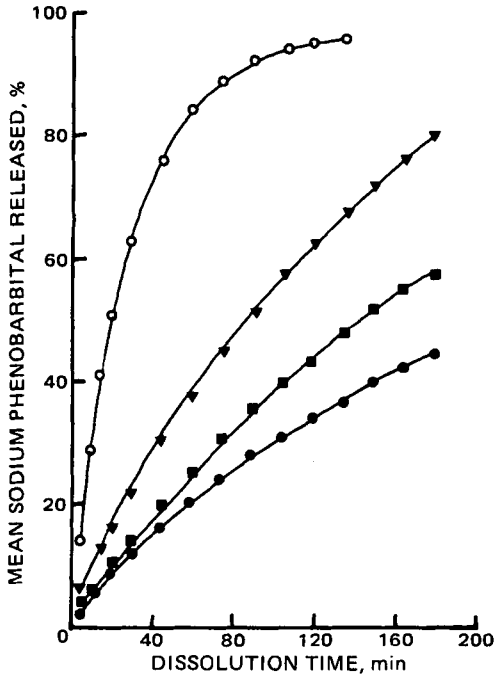

Figure 5—*Effect of microcapsule core–wall ratio on tablet dissolution. Core–wall ratio: (○) 4:1, (▼) 1:1, (■) 1:2, (●) 1:4. Dissolution medium: 2 L of distilled water (pH 5.4); dissolution temperature: 37°C; dissolution stirring rate: 100 rpm; compression pressure: 315 kg/cm²; tablet weight: 250 mg; tablet diameter: 9.5 mm.*

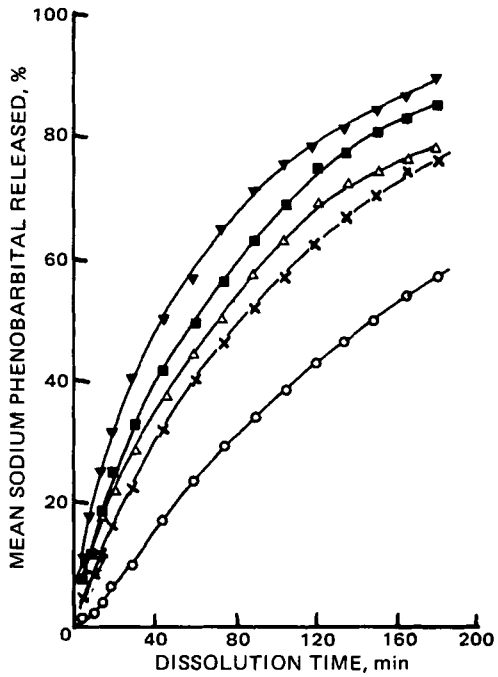

Figure 6—*Effect of microcapsule size on the dissolution from 2:1 core–wall ratio microcapsule tablets. Microcapsule size: (○) 215 μm, (×) 302.5 μm, (△) 427.5 μm, (■) 605 μm, (▼) 855 μm. Dissolution medium: 2 L of distilled water (pH 5.4); dissolution temperature: 37°C; dissolution stirring rate: 100 rpm; compression pressure: 315 kg/cm²; tablet weight: 250 mg; tablet diameter: 9.5 mm.*

became thinner with a decrease in the proportion of wall material. At higher core–wall ratios there is the possibility of wall breakage during the compression. When walls rupture, particles of core material are exposed and will interlock strongly, thus leading to stronger tablets.

An explanation of the effect of the microcapsule aggregate size on the tablet strength, as shown in Fig. 4, is that with the very small aggregates the large surface areas result in greater bonding. The strength of the tablet decreased as the aggregate size increased, and the surface area available for bonding decreased. A further rise in the size of the microcapsule aggregate brought about the breakdown of the aggregates and exposed fresh surfaces for bonding. The greater the aggregate size, the greater the extent of breakdown as found by Armstrong and Haines-Nutt (8) in the case of tablet granules. This would result in a larger fresh bonding surface being exposed and explain the second rise in the tablet strength curve at larger aggregate size.

Figures 5 and 6 show the release of sodium phenobarbital from these tablets. Dissolution was faster from the higher core–wall ratio microcapsules with greater strengths, although one would normally expect dissolution to be faster from a weaker tablet. When dissolution studies were conducted on untableted microcapsules, a faster release occurred from the higher core–wall microcapsules because these had thinner walls, making penetration of both the dissolution medium and the core solution through the walls easier. Also, because of the higher core–wall ratios, there were more core particles per microcapsule, resulting in a higher concentration gradient to boost dissolution.

These same considerations are controlling factors for dissolution from the tableted microcapsules since the microcapsule wall still has to be penetrated to release the core. The only difference is the compact nature of the tablet as compared with the corresponding microcapsules. Compacting the microcapsules results in a greatly reduced surface area being available for release. Even after release of core material from the individual microcapsules composing the tablet, the core solution has to permeate narrow channels prior to release between the compressed aggregates into the outside dissolution medium. The effect of reduced surface area and channel permeation results in a considerable slowing of the release from the tableted microcapsules compared with the untableted microcapsules.

The effects of microcapsule size on the dissolution from tablets are shown in Fig. 6. This illustration indicates that release was faster from tablets made from larger microcapsules. The increase in the release from tablets prepared using 215-μm microcapsules to those from 302.5-μm microcapsules followed the same pattern as the corresponding strength graph, which also showed a decrease. Beyond 302.5-μm microcapsule size, the tablet strength increased again; the corresponding increase in the release characteristic of the core material is in line with the explanation given for the increase in strength found in this region. The increase in strength found with microcapsules >302.5 μm was due to a breakdown of aggregates, possibly even to the breakdown of individual microcapsule walls, either of which conditions would expose fresh surfaces for dissolution. The breakdown would be greater the larger the initial microcapsule size, as confirmed by the dissolution results. We can conclude, therefore, that the aggregate size significantly affects the properties of the tablets and should be taken into consideration whenever one is designing a dosage form as it will affect the availability of the drug. Tablets made from different sized aggregates of the same preparation could give markedly different absorption rates because of the differences in drug release.

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