The effect of preparative technique on the particle size of thiabendazole microcapsules

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The size distribution of microcapsules used as a method of prolonging the release, or of protecting the drug, will be one of the most important factors to be considered when attempting to control these properties. Previous studies dealing with microencapsulation have mentioned the effect of changes in preparative stirring speed (Koishi et al 1969; Nixon & Nouh 1977), and formaldehyde solution (Nouh 1978) without studying these factors in detail. The present paper examines the effect of these and other preparative variables on the size of thiabendazole microcapsules.

Materials. Thiabendazole (Merck Sharp & Dohme) was micromilled and had a mean particle size of 3·57 μm. Gelatin (Richard Hodgson & Sons, Ltd.), was acid processed, 250 Bloom. Acacia (BDH Ltd) complied with British Pharmacopoeial requirements. Isopropanol, formaldehyde solution, dilute HCl (BDH Ltd) were standard laboratory reagent grades.

Preparation of microcapsules. A standard complex coacervate gelatin : acacia technique was used with 2% of each of the colloids, a temperature of 40° ± 0·1 °C and a pH of 4·0. The thiabendazole was added to the gelatin solution. For hardened microcapsules formaldehyde solution was added before cooling to 5 °C and extracting by filtration, washing with isopropanol, and air drying. Stirring was continuous until the filtration stage. Variations in the core : colloid ratio (1 : 2, 1 : 3, 1 : 4) and the effect of a final adjustment to pH 9·2 were studied.

Water mounted spherical microcapsules were measured using a projection microscope. More than 300 microcapsules were measured.

Results and discussion. Stirring speeds of preparations between 200 and 900 revolutions min^{-1}, increasing in increments of 100 rev min^{-1}, were used. As the stirring speed increased the size of the microcapsules became smaller (Fig. 1) and 900 rev min^{-1} was a limiting value above which no separate microcapsules could be recovered, a gelatinous mass being produced.

The faster stirring speeds produced smaller coacervate droplets which, having engulfed a thiabendazole particle, tended not to aggregate to form larger microcapsules. At stirring speeds below 500 rev min^{-1} the initial coacervate droplets were larger, engulfed multiple core particles, and because they could be in contact with one another for longer periods, aggregated to form large microcapsules. Thus the range of microcapsule size was much wider at the slower preparative stirring speeds.

Hardening with formaldehyde produced slightly larger microcapsules and a wider size distribution (Fig. 2). The non-hardened samples show few very large or small microcapsules. The formaldehyde effect is probably due to the cross linking of the gelatin producing a more rigid wall which does not reduce in thickness during the dehydration stage of preparation. The effect of core : colloid ratio on the mean size of hardened microcapsules showed no significant variation for a given stirring speed above 400 rev min^{-1} but for unhardened microcapsules there was a gradual increase in the mean size as the core : colloid ratio varied from 1 : 2 to 1 : 4. At a stirring speed of 500 rev min^{-1} hardened microcapsules at all core : colloid ratios had a mean size of 39·0 μm whilst at the same stirring speed the mean diameter for unhardened microcapsules was 32·1, 34·9 and 37·8 μm at core : colloid ratios of 1 : 2, 1 : 3 and 1 : 4 respectively. Similar observations occur at other preparative stirring speeds with the size difference at varying core : colloid ratios becoming greater at lower preparative stirring speeds. At these lower speeds a colloid concentration effect also begins to become evident with the hardened microcapsules. Thus at 100 rev min^{-1} preparative stirring speed the mean size of hardened microcapsules is 81·3, 84·7 and 88·1 μm at core : colloid ratios of 1 : 2, 1 : 3 and 1 : 4. The values for the unhardened microcapsules under the same conditions are 78·4, 80·6 and 86·9 μm respectively. Stirring speed could therefore account for the observation of Luu Si Nang (1973) that the size of coacervate microcapsules was independent of colloid concentration. The present results show that this may occur under certain preparative conditions.

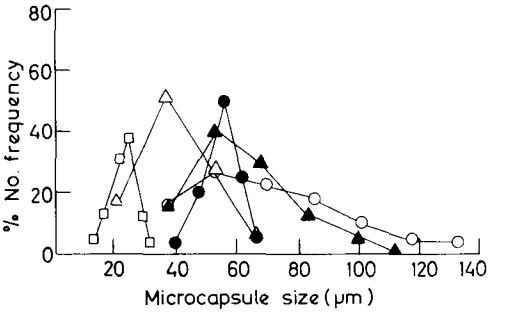

FIG. 1. The effect of preparative stirring speed on the size distribution of formalin-hardened thiabendazole microcapsules. Core : colloid ratio, 1 : 4, preparative stirring speed (rev min^{-1}), 200 ○, 300 ▲, 400 ●, 500 △, 900 □.

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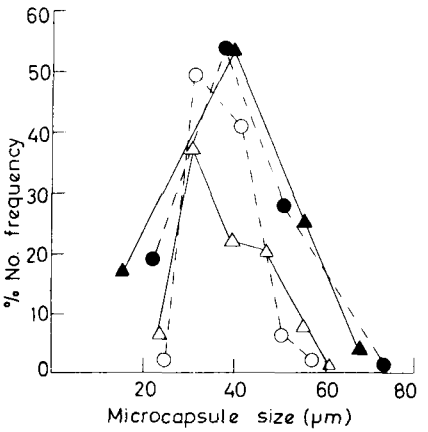

FIG. 2. The effect of formalin-hardening on the size distribution of thiabendazole microcapsules. Core: colloid ratio, 1:3 ●○, 1:4 ▲△, formalin hardened samples ● ▲, unhardened samples ○ △, preparative stirring speed 500 rev. min^{-1}.

The influence of a final adjustment to pH 9·2 with 20% sodium hydroxide solution was determined. Both hardened and unhardened microcapsules showed an increase in mean size, the effect being greater with the unhardened samples. Thus at 500 rev min^{-1} and a core: colloid ratio of 1:4 a batch of unhardened microcapsules showed a mean size increase from 39 to 45 μm and a corresponding batch of hardened microcapsules an increase from 42 to 56 μm. These changes are probably due to uncoacervated colloid present in the equilibrium liquid being deposited on the microcapsules as a result of the pH change.

The size distribution of microcapsules from various batches prepared under similar conditions were found to show no significant variations in their size distribution.

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The effect of tableting on the dissolution behaviour of thiabendazole microcapsules

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Levy & Gumtow (1963) found that hydrophobic lubricants retard the dissolution of drugs from tablets and that water soluble materials such as sodium lauryl sulphate enhanced the release of salicylic acid. However, sodium lauryl sulphate, whilst accelerating the release of phenobarbitone from granules, was found by Finholt et al (1966) to have little effect on dissolution from tablets. Similar contradictory observations have been made for the effect of other tablet additives. Whilst many reports have been published regarding the effect of additives on the tableting of granules there is no information regarding their effect on tablets prepared from, or containing, microcapsules. It has been reported that the release rate of sodium pentobarbitone was inversely proportional to tablet hardness (Luzzi et al 1970) and that tableting slowed down the release of sodium phenobarbitone from ethyl cellulose microcapsules (Jalsenjak et al 1977). The present work investigates the effect of additives on the release of thiabendazole from compressed microcapsules.

Materials. Thiabendazole (Merck Sharp & Dohme) micromilled with a mean particle size of 3·57 μm. Gelatin (Richard Hodgson & Sons, Ltd.) acid processed 250 Bloom. Acacia, chalk, formaldehyde solution, sodium stearate, stearic acid and wheat starch (BDH) were all of B.P. quality where appropriate.

Preparation of microcapsules. A suspension of thiabendazole in 2% gelatin solution was stirred at 300 rev min^{-1} and 40 °C with an equal volume of 2% acacia solution, the pH being adjusted to 4·0. 10 ml of formaldehyde solution was added and the temperature reduced to 5 °C with continued stirring. After filtration the microcapsules were washed with three portions of isopropanol and air dried.

Tablet preparation. A charge of 500 mg of microcapsules either alone or with additives was placed in a 8·0 mm dye. Compression was gradually applied over 1 min up to a limit of 5000 kg, held for a further 1 min, and gradually released over 30 s.

Dissolution studies. A flask and stirrer technique using two litres of pH 2 buffered water was used. The buffer consisted of 119 ml 0·2 M HCl and 881 ml 0·2 M KCl in the two litres. Samples were analysed by u.v. at 303 nm after first filtering. The filter paper and a suitable volume of fluid were replaced in the dissolution vessel.

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