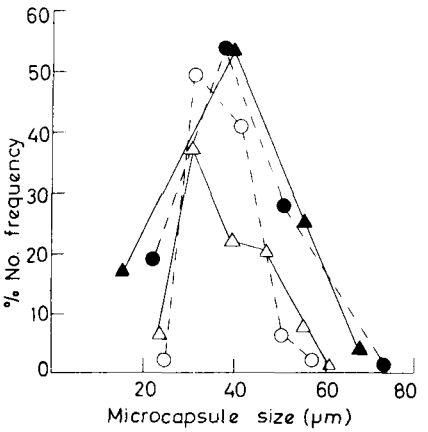

FIG. 2. The effect of formalin-hardening on the size distribution of thiabendazole microcapsules. Core: colloid ratio, 1:3 ●○, 1:4 ▲△, formalin hardened samples ● ▲, unhardened samples ○ △, preparative stirring speed 500 rev. min^{-1}.

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.

* Correspondence.

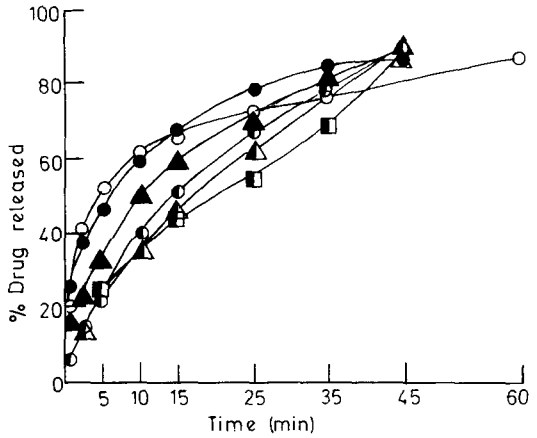

FIG. 1. The effect of compression pressure on the release of thiabendazole from 1:2 core to colloid microcapsules. Buffer pH 2·0, stirring speed 100 rev min^{-1}, temperature 37 °C. Compression pressure zero ○, 250 kg ●, 500 kg ▲, 1000 kg ◐, 3000 kg ◭, 5000 kg ◧.

Results and discussion. The effect of compressing the thiabendazole microcapsules is shown in Fig. 1. Higher compression pressures produced a slower initial release rate, but after 45 min approximately 90% of the thiabendazole had been released at all the pressures studied. However, whilst the initial rate of release from uncompressed microcapsules was faster, they showed a rapid fall in release rate and after 15 min the release rate was approximately constant resulting in less thiabendazole (85%) being released after 45 min. It is possible that damage may occur to the microcapsule wall during compression, but none was visible. The slower initial rates as compression increased is probably due to an increased difficulty of fluid penetration into the compressed mass. However, after approximately 10 min the tablets had disintegrated. If compression does produce microcapsule wall damage then the higher compressions are likely to have produced more damage and result in a faster release once disintegration into microcapsules has taken place. Superimposed on this effect will be the effect normally found when diffusion is from a depot and, as the depot approaches exhaustion, there is a slowing of release. In the present instance this will be coupled by build up of a drug-saturated layer round the microcapsule, which produces further slowing. Neither for microcapsules nor tableted microcapsules was a non-sink condition approached so this was not a cause of the fall in release rate.

The effect of adding stearic acid to the microcapsules before compression was to increase the time taken for disintegration. Thus 5% stearic acid had little effect and disintegration still occurred in approximately 10 min, but at the same compression pressure (5000 kg) the inclusion of 30% of stearic acid increased the disintegration time to 35 min. The effect of stearic acid was to produce a slower dissolution rate (Fig. 2) with no break in the curve corresponding to the disintegration of the tablet.

The effect of sodium stearate was to slow the release of the thiabendazole to a greater extent than did the

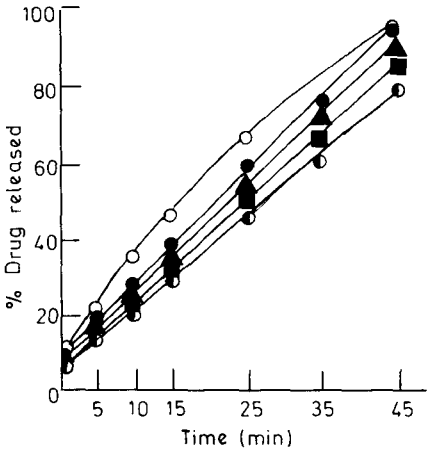

FIG. 2. The effect of varying percentages of stearic acid added before compression to 1:2 core to colloid thiabendazole microcapsules on their release in buffer of pH 2·0. Stirring speed 100 rev min^{-1}, temperature 37 °C. Compression pressure 5000 kg. No additive ○, 5% stearic acid ●, 10% stearic acid ▲, 20% stearic acid ■, 30% stearic acid ◐.

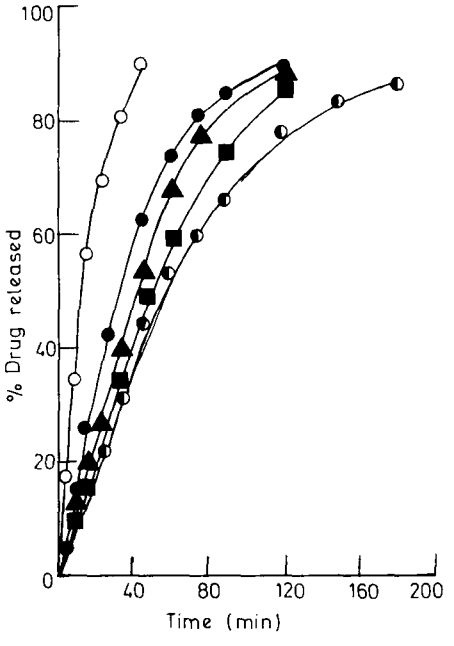

FIG. 3. The effect of varying percentages of sodium stearate added before compression to 1:2 core to colloid microcapsules on their release in buffer of pH 2·0, stirring speed 100 rev min^{-1}, temperature 37 °C. Compression pressure 5000 kg. No additives ○, 5% sodium stearate ●, 10% sodium stearate ▲, 20% sodium stearate ■, 30% sodium stearate ◐.

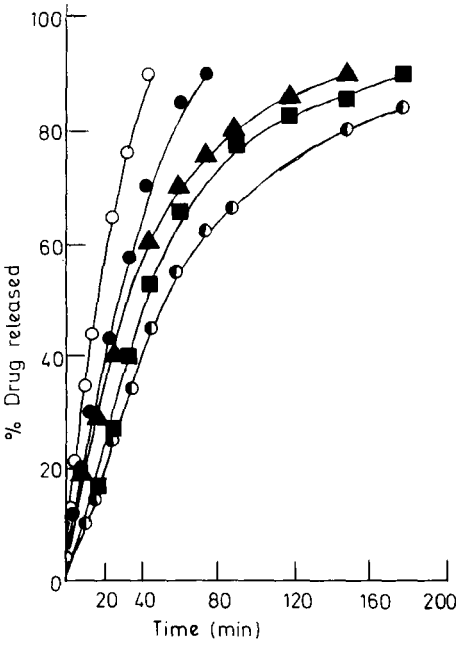

FIG. 4. The effect of varying percentages of chalk added before compression to 1:2 core to colloid thiabendazole microcapsules in the presence of sodium stearate on their release in pH 2·0 buffer. Stirring speed 100 rev min^{-1}, temperature 37 °C. Compression pressure 5000 kg. 30% chalk only ○, 30% sodium stearate only ◐, 25% chalk + 5% sodium stearate ●, 20% chalk + 10% sodium stearate ▲, 10% chalk + 20% sodium stearate ■.

stearic acid (Fig. 3). This was possibly a reflection on the greatly extended time required to cause tablet disintegration. A 5% addition of sodium stearate produced a disintegration time of 15 min, but 10% produced a time of 50 min whilst a 30% addition required 62 min for disintegration. Whilst no break in the dissolution profile corresponded to these disintegration times, there was a gradual slowing of the dissolution rate as the drug in the system was depleted and this appeared in the later stages to be independent of the sodium stearate concentration.

Starch is used as a disintegrant in tablet formulations and irrespective of the presence of stearic acid caused a rapid disintegration of the tablets. Even in the presence of 20% stearic acid, 10% starch caused complete breakdown into microcapsules within 20 min. Because of the rapid disintegration of the tablets, drug dissolution rates showed little variation with starch concentration and were similar to uncompressed microcapsules, although there was a very slight slowing of release reflecting the presence of increasing concentrations of stearic acid or sodium stearate.

A third inclusion in tablet formulations is a non-binding filler, such as chalk. In the absence of other additives the presence of chalk (up to 30%) caused very little change in either the disintegration time of compressed thiabendazole microcapsules or the dissolution of the drug. Combinations of chalk and sodium stearate showed a gradual decrease in dissolution rate as the sodium stearate increased (Fig. 4) corresponding to an increased difficulty of dissolution medium penetration and a lengthening of disintegration time.

The effect of the various additives used in the formulation of compressed tablets on the dissolution of microencapsulated drugs appears to be complex and interrelated. Because of the non-binding nature of most microcapsule walls it will probably be necessary to use additives during tableting and their effect on the drug release should be determined in each case.

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