J. Pharm. Pharmac., 1977, 29, 82–85 Received August 13, 1976

The properties of tablets containing microcrystalline cellulose

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Tablets have been prepared from mixtures of microcrystalline cellulose (Avicel) and spray dried lactose. Tests on these showed that a maximum value of dissolution rate occurred as the percentage of the cellulose increased. This maximum was at 4% w/w for mixtures containing Avicel PH 101 and coincided with the point of maximum liquid penetration rate. With grade PH 105 this maximum was at 2% w/w and corresponded to the optimum balance between the opposing factors of disintegration and liquid penetration rate. Addition of up to 2% w/w magnesium stearate to the formulation containing 4% w/w PH 101 grade had little effect on pore structure, but decreased the dissolution rate by retarding water penetration. Similar concentrations of Carbowax 4000 caused no such decrease.

Addition of microcrystalline cellulose (Avicel) to other tableting excipients has been shown to modify their behaviour. One effect appears to be an increase in the stability of certain drugs in tablet form (Fox, Richman & others, 1963; Lee, De Kay & Banker, 1965; Richman, Fox & Shangraw, 1965). The product has also been shown to increase the hardness of tablets and lower ejection forces (Fox & others, 1963). These results were explained in terms of the 'non-adherent' properties of the cellulose.

It has very good disintegrating powers, although somewhat inferior to those of starch (Fox & others, 1963), and has been included in studies of disintegrants in direct compression systems (Bergmann & Bandelin, 1965; Duvall, Koshy & Dashiell, 1965). Although the disintegration properties of tablets containing it have been well studied, the dissolution of soluble components from within these tablets has received little attention. Khan & Rhodes (1972) showed that the dissolution efficiency for tablets composed of the grade PH 101 with a small percentage of magnesium stearate decreased as compaction pressure increased. Dissolution studies from tablets containing the cellulose (Shah, Pytelewski & others, 1974; Needham, Luzzi & Mason, 1974) have not been concerned with its effect on their dissolution.

The logical extension to previous investigations (Marshall & Sixsmith, 1974; Sixsmith, 1975) would appear to be an assessment of the effect of addition of microcrystalline cellulose to other tableting excipients particularly those that might constitute the base for formulations containing a small proportion of active ingredients and intended for direct compression. I now report on such an investigation.

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MATERIALS AND METHODS

Materials

The excipient chosen was spray dried lactose U.S.P., median Stokes diameter 174 μm (Peebles Products Ltd., Canada) because of its wide usage as a direct compression excipient. Avicel PH 101, median Stokes diameter 37 μm, and PH 105, median Stokes diameter 25 μm (F.M.C. Corpn., Marcus Hook, U.S.A.) were used to prepare Avicel-spray dried lactose mixtures. Magnesium stearate B.P. (Hopkins & Williams) was used as a non-water soluble lubricant and Carbowax 4000 (Hopkins & Williams) as a water soluble lubricant.

Methods

Mixtures were prepared containing varying proportions of the grades PH 101 or PH 105 by mixing in a motor driven bowl mixer using a doubling up technique. Amaranth, which had previously been sieved through a 20 μm sieve, was incorporated into the powder mixtures at approx 1% w/w to enable dissolution from the mixtures to be studied.

The magnesium stearate and Carbowax 4000 were first sieved through a 150 μm sieve before mixing in a bowl mixer with the cellulose-spray dried lactose mixture, using a doubling up technique and a mixing time of 4 min after the final addition of material. The mixture chosen for testing was that containing 4% w/w of the PH 101 grade as this had the best compaction and dissolution characteristics of the various combinations tested.

The mixtures were conditioned at a humidity of

35–40% R.H. for several days before compaction. The tablets were prepared to constant overall porosity on an instrumented Manesty E2 tablet machine (Marshall, 1970), and stored at 35–40% R.H. for 24 h before testing. These tablets were subjected to a disintegration test according to the B.P. 1973, except that 10 tablets were tested individually so that individual disintegration times could be determined. The disintegration test was also carried out in a modified form by using a 355 μm mesh at the base of the sample tube instead of the 1680 μm mesh specified in the official test.

Dissolution studies were carried out using a flow through apparatus similar to that of Marshall & Brook (1969), except that during this investigation a cylindrical dissolution cell was used. The dissolution medium after passage through the dissolution cell was analysed at a wavelength of 525 nm using a spectrophotometer, allowing a continuous record of concentration within the system to be obtained.

The tablets were subjected to liquid penetration tests using an apparatus similar to that of Ganderton & Selkirk (1970). The liquid used was isopropanol as this did not cause disintegration of the tablets. The interparticulate pore structure was also studied using a high pressure mercury porosimeter (Model 905–1, Coulter Electronics Ltd., Luton).

RESULTS AND DISCUSSION

The disintegration times of all the tablets are shown in Fig. 1. Both types of tablet show an initial decrease in disintegration time as the percentage of the cellulose increases. The disintegration time of spray dried lactose tablets is largely dependent on the rate at which this component will dissolve in the test liquid causing breakdown of the tablet. The addition of the celluloses causes a more rapid uptake of water leading to a more rapid breakdown of the tablet structure. The effect continues until a continuous matrix of cellulose is formed, at which point the behaviour of the mixtures begins to differ. The disintegration time of tablets prepared from mixtures containing the PH 101 grade continue to decrease while those containing the PH 105 grade, show a marked increase. This difference is caused by the fact that tablets containing 100% of the PH 101 grade disintegrate very rapidly, whereas similar tablets of PH 105 are virtually non-disintegrating (Sixsmith, 1975) and those containing a continuous matrix of celluloses tend to behave as tablets composed entirely of cellulose.

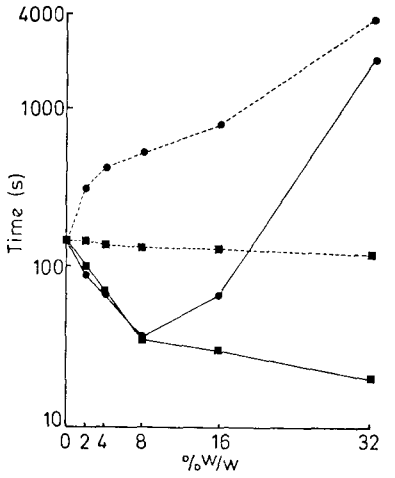

FIG. 1. The effect of two grades of Avicel (% w/w) on the disintegration time (s) of cellulose-spray dried lactose tablets. ■——■ PH 101 grade official test. ■- - - ■ PH 101 grade modified test. ●——● PH 105 grade official test. ●- - - ● PH 105 modified test.

The initial interparticulate pore structure, as shown by mercury porosimetry (Figs 2 and 3) is narrow with a modal radius of about 2·1 μm.

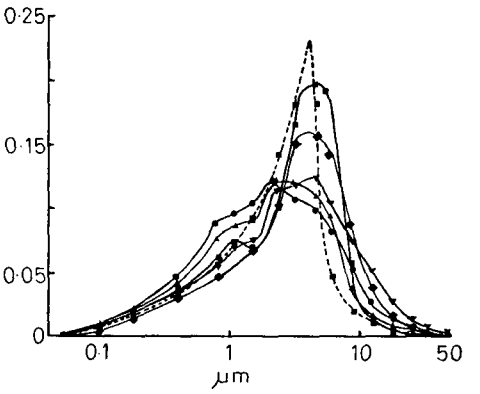

FIG. 2. Interparticulate pore size (μm) distribution of PH 101 grade–spray dried lactose tablets. Percentage w/w PH 101 - - ■ - - 0; —■—2; ▼ 4; ▲ 8; ● 16; ◆ 32. y-axis—Relative frequency.

Addition of either grade of the cellulose, widens this distribution. This would be expected as the pores can now be formed between particles of spray dried lactose themselves and additionally spray dried lactose–cellulose particles and cellulose–cellulose particles. As the concentration of cellulose increases, the tablets tend towards the pore size distribution of tablets of cellulose alone, again to be expected from the particle/particle contacts forming the pores.

This change in the character of the pore size distribution has a marked effect on the penetration rate of liquids into the tablets, as seen in Fig. 4. With both grades the rate of penetration increases up to a maximum value and then decreases as the

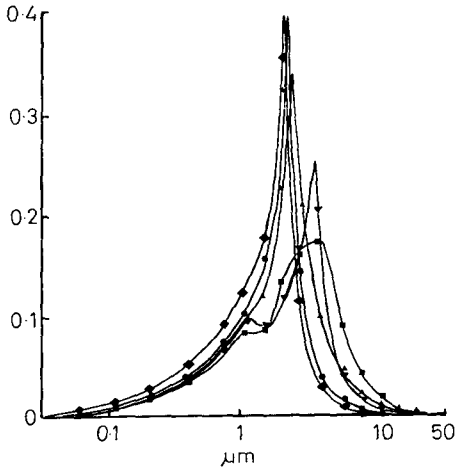

FIG. 3. Interparticulate pore size distribution of PH 105 grade–spray dried lactose tablets. Percentage w/w PH 105 ■ 2; ▼ 4; ▲ 8; ● 16; ◆ 32. y axis—Relative frequency.

cellulose concentration increases. The pore structure of the tablets at low concentrations of either grade is composed of a wide range of relatively large pores which allow rapid penetration of liquid. As the concentration of cellulose increases the pore size distribution becomes narrower, i.e. the pores are more uniform and the penetration rate decreases.

Fig. 5 shows that the dissolution rate increases to a maximum value at 2% w/w for PH 105 grade and 4% w/w for PH 101 grade, and then decreases as the concentration of cellulose increases. These maxima can be explained in terms of the type of aggregates formed on disintegration of the tablets. It can be

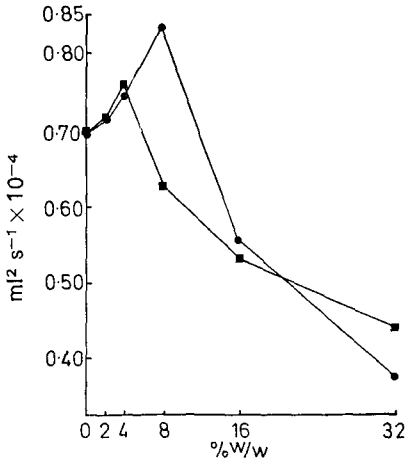

FIG. 4. The effect of two grades of cellulose (% w/w) on the penetration index ($ml^2 s^{-1} \times 10^{-4}$) of cellulose-spray dried lactose tablets. ■ PH 101. ● PH 105.

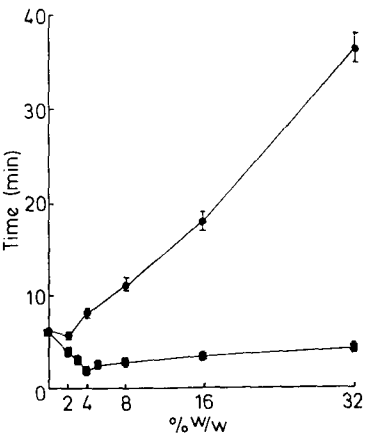

FIG. 5. The effect of two grades of cellulose (% w/w) on the dissolution of amaranth from cellulose-spray dried lactose tablets. ■ PH 101. ● PH 105. y axis—Time taken for 50% total amaranth liberation (min).

seen from Fig. 1 that mixtures containing the PH 101 grade show a decrease in disintegration time, for both the official and modified tests, throughout the range studied, although very much more slowly for the modified test. This implies that although large aggregates of particles may be formed initially by disintegration of the tablets they break up quickly and would, therefore, release their drug content reasonably efficiently. Mixtures containing the PH 105 grade, however, show a rapid decrease in disintegration rate, in the modified test, as the concentration of cellulose increases, whilst the reverse effect is seen in the official test, although at higher concentrations the rate does decrease. This suggests that with these mixtures, aggregates are formed which only slowly disintegrate.

The modified disintegration times of mixtures containing grade PH 101 indicate that the time taken for disintegration will not affect the relative dissolution rates of these mixtures. The penetration rate will, therefore, be the deciding factor in determining the dissolution rate.

In the case of mixtures containing the PH 105 grade the modified disintegration times imply that the initial aggregate size is gradually increasing as the concentration of cellulose increases. The penetration rate, however, increases to a maximum and then decreases. The dissolution rate will be determined by the balance between these two opposing factors.

The effect of the addition of a third material to the spray dried lactose 4% w/w PH 101 grade system is shown in Table 1. Addition of magnesium stearate has a marked effect on the disintegration time of the

Table 1. *Effect of addition of a lubricant on the disintegration time (DT) and dissolution rate of 4% w/w PH 101 grade cellulose-spray dried lactose tablets. (AL=50% amaranth liberation)*

	Magnesium stearate		Carbowax 4000	
% Lubricant	DT(s)	AL(min)	DT(s)	AL(min)
0	70	1·87	70	1·87
0·25	870	9·7	—	—
0·50	1260	25·9	85	2·08
1·00	2070	26·5	90	2·11
2·00	3840	31·0	85	2·10
4·00	—	—	140	2·14

tablets which increases dramatically as the concentration of magnesium stearate increases. This does not occur with Carbowax 4000.

The interparticulate pore structure of the tablets, shown in Fig. 6, is altered very little by the addition of the lubricant. The magnesium stearate causes a slight narrowing of the distribution but the modal pore radius remained in the range 2–3·5 μm, whilst the compacts containing Carbowax 4000 showed similar distributions at all the concentrations studied.

The penetration of isopropanol into these tablets, given in Table 2, remains essentially constant with only minor variations as the concentration of

Table 2. *The effect of addition of a lubricant on the penetration index of 4% w/w PH 101 grade cellulose-spray dried lactose tablets.*

	Penetration index ($ml^2\ s^{-1}$) × 10^{-4}			
	Magnesium stearate		Carbowax 4000	
% Lubricant	Water	Isopropanol	Water	Isopropanol
0	2·8273*	0·7575	2·8273*	0·7575
0·25	0·0045	0·7250	—	—
0·50	0·0024	0·7392	2·7872*	0·7098
1·00	0·0019	0·7692	—	0·7575
2·00	0·0018	0·5717	—	0·8080
4·00	—	—	2·6563*	0·7098

* Some disintegration occurred with these samples and the result may not accurately reflect the penetration index, although the uptake of water was at a significantly faster rate than with the remaining samples.

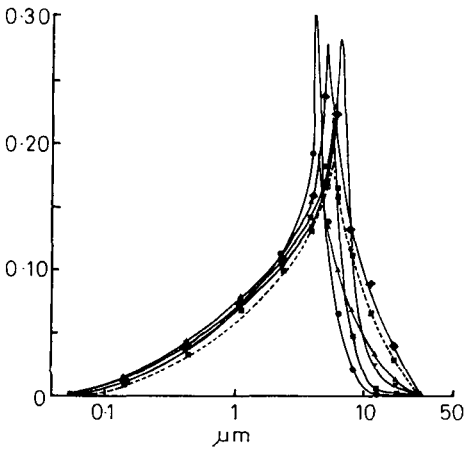

FIG. 6. The effect of a lubricant on the interparticulate pore size (μm) distribution of 4% w/w PH 101 grade-spray dried lactose tablets. Percentage w/w lubricant: Magnesium stearate ▲ 0·25; —■—0·50; ▼ 1·0; ● 2. Carbowax 4000 - - ■ - - 0·50; ◆ 1, 2 and 4. y axis—Relative frequency.

lubricant is increased indicating that the effect of the pore system within the compact is virtually constant. Penetration of water into the tablets containing magnesium stearate is, however, drastically reduced showing that increase in disintegration time is caused, not by change in the tablet pore structure, but by the inability of the water to penetrate the tablet, in agreement with Ganderton's (1969) results.

Similarly, the dissolution rate from the tablets decreases rapidly as the concentration of magnesium stearate increases, again because of the inability of the water to penetrate the tablet.

Acknowledgements

I am very grateful for the advice and guidance given by Dr K. Marshall and I thank the F.M.C. Corporation, Marcus Hook, U.S.A. for samples of Avicel.

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