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The effect of compression on some physical properties of microcrystalline cellulose powders

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Tablets have been prepared from previously characterized microcrystalline cellulose (Avicel) powders, using an instrumented single station tablet machine. The regenerated particle size was found to increase with increase in compaction pressure. Compaction caused a slight initial decrease in B.E.T. surface area, followed by an increase mainly as a result of elastic recovery of the particles. The intra-particulate pore size distribution showed no change throughout the range of compaction pressures studied, demonstrating that the internal pores did not collapse. Measurement of the interparticulate porosity by mercury porosimetry, liquid penetration techniques and scanning electron microscopy showed a decrease in this parameter with increase in compaction pressure. The dissolution behaviour from the compacts showed in general a decreased rate with increase in compaction pressure, that from the cellulose grade PH 105 being slower than from the remaining grades.

Wide interest has been shown in recent years in the use of materials that can be directly compressed on a manufacturing scale. These excipients have some or all of the desirable characteristics of a granular type of material, e.g. good flow and compaction and disintegration characteristics, without first having to undergo a granulation process. One of these excipients, a microcrystalline cellulose (Avicel) has been reported as having varied flow properties (Fox, Richman & others, 1963; Mendell, 1972; Bolhuis & Lerk, 1973) and good compaction and disintegration characteristics (Fox & others, 1963).

It was therefore decided to examine the pharmaceutical grades of Avicel. The work on the characterization of the powders has already been reported (Marshall & Sixsmith, 1974) and the present paper concerns the effect of compression on some of these previously measured characteristics.

MATERIALS AND METHODS

Materials

The powders used were four commercial pharmaceutical grades of microcrystalline cellulose, Avicel PH 101, PH 102, PH 103 and PH 105. They were conditioned for several days in an atmosphere of 30–40% relative humidity and a temperature of 18–20° before compaction but were otherwise as received from the manufacturer.

Methods

The tablets were prepared on a single station tablet machine (Manesty E2) which had been modified as described by Marshall (1970) except that insulation of the punches, necessary because of the nature of the previous investigation, was not now used.

For each tablet, the powder was fed into the die by hand as uniformity of weight could not otherwise be achieved because of the powder's poor flow properties. The tablets were produced at a standardized speed of the tablet machine and the responses of the instrumentation were recorded on a direct recording ultraviolet oscillograph (Southern Instruments, Mitcham).

Particle size distributions of compacts disintegrated by gentle agitation in distilled water, using a shaking reaction incubator (Gallenkamp, Widnes) at 20°, for 24 h were determined using a wide-angle scanning photosedimentometer (Microscal Ltd., London). No dispersing agent was necessary and the scanning facility of the instrument was not used.

The BET surface areas (Brunauer, Emmett & Teller, 1938) of the tablets were determined by nitrogen adsorption at liquid nitrogen temperature, −196°, using four tablets as the sample. The apparatus used was a standard gas adsorption apparatus, complying with British Standard Specification (Metric Units) 4359 Part I (1969).

The interparticulate pore structure of the tablets was studied using a high pressure mercury penetration porosimeter Model 905-1 (Coulter Electronics Ltd., Luton). A maximum penetration pressure of 280 MPa, corresponding to a pore radius of 2·2 nm, was used.

The pore structure was also studied using a liquid penetration apparatus based on that described by Ganderton & Selkirk (1970). The liquid used for these studies had to be one which wetted the powder

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but did not cause disintegration of the tablets. For this reason, isopropanol was chosen. The uptake was measured by time lapse photography using a 16 mm camera adapted to take single frames at accurately measured pre-determined time intervals.

A visual examination of the tablets was carried out using a scanning electron microscope at magnifications up to 500 times. The tablets were examined on the axial surface and along a transverse fracture surface formed by breaking the tablets manually. Before inspection they were coated with gold as the conducting material to a thickness of approximately 20 nm.

The dissolution of a water soluble tracer, amaranth, from the tablets was studied using a flow-through dissolution system similar to that described by Marshall & Brook (1969), except that, in this case, a cylindrical dissolution cell was used. The amaranth was ground, passed through a 20 μm sieve and then incorporated at a concentration of approximately 1% w/w. The dissolution medium, after passage through the dissolution cell, flowed through a spectrophotometer which allowed a continuous record of the concentration of the solution within the system to be made.

RESULTS AND DISCUSSION

Fig. 1 shows the results of the sedimentation analyses expressed graphically, the value for the median Stokes diameter being the mean of two determinations. The median Stokes diameter for all the regenerated powders increased as the compaction pressure increased. This effect was most noticeable with the PH 105 grade of cellulose which showed an increase of approximately 100% and least with PH 102 which had an increase of only 25%. This would be expected as the major factors influencing the interparticulate bonding process will be the extent of the external surface area of the particles, their geometry and the forces present on their surfaces. These forces have been shown to be of similar magnitude for all grades (Marshall & Sixsmith, 1974) and the bonding in this case will be influenced only by the extent of the external surface area. The smallest grade (PH 105) would therefore be expected to show the greatest increase in particle size and grade PH 102 the smallest increase.

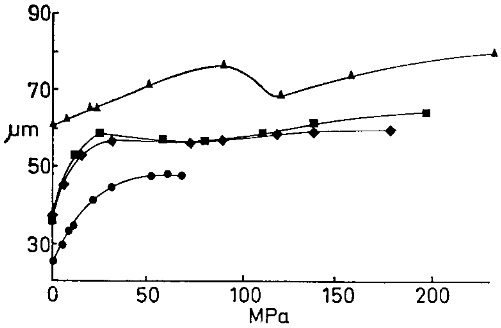

FIG. 1. Variation of median Stokes diameter (μm) of Avicel particles on consolidation. ■ PH 101. ▲ PH 102. ◆ PH 103. ● PH 105. x axis—Compaction pressure (MPa).

The surface area changes which the powders underwent when they were compacted are shown in Fig. 2. Grades PH 101, PH 102 and PH 103 show a gradual change throughout the range of compaction pressures studied. Most of the surface area of the Avicels has been shown to be in the form of internal pores (Marshall & Sixsmith, 1974) and unless the compaction process cuts off this internal surface to the adsorbing gas, the surface area changes caused by bonding of the external surface of the particles are likely to be small compared to the total surface area. The increase in surface above 125 MPa may be caused by particle crushing leading to an increased exposed surface. Or, more probably, by elastic recovery of the compact 'opening up' some of the closed intraparticulate pores since the increase in measured surface is greater than the total external surface area of the powder. The PH 105 grade, however, shows a rapid decrease in surface area at low compaction pressures, thought to be caused by aggregation of the particles, cutting off large portions of the internal surface to the adsorbing gas.

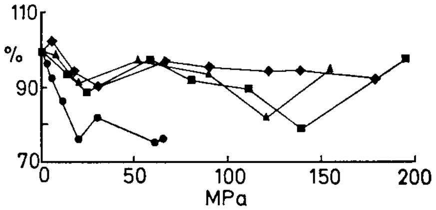

FIG. 2. Variation of B.E.T. surface area (% original) with maximum axial compaction pressure (MPa). Symbols as for Fig. 1.

The pore size distributions derived from the above isotherms using a mathematical model (Roberts, 1967) showed that the distributions did not alter on compaction, the modal pore radius remaining throughout the range of pressures studied at a value of approximately 2 nm, the same as that found for the uncompacted powder samples (Marshall & Sixsmith, 1974). The compaction process, at the pressures used in this investigation, does not therefore cause collapse of the particles with the resultant loss of intraparticulate porosity.

Compaction did, however, alter the interparticulate porosity, as shown in Fig. 3, the modal pore radius decreasing as the compaction pressure increased. The relation is virtually logarithmic and extrapolation of it suggests that for all grades zero porosity would be reached, theoretically, at a pressure of about 300 MPa.

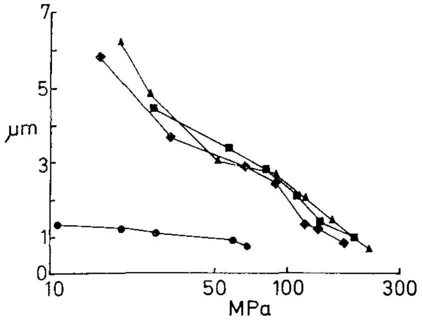

FIG. 3. The effect of maximum axial compaction pressure (MPa) on the modal interparticulate pore radius (μm) of Avicel tablets. Symbols as for Fig. 1.

Fig. 4 shows a graphical expression of Walker's equation (Walker, 1923) applied to the Avicels. Extrapolation of this graph for PH 101, PH 102 and PH 103 to zero porosity, i.e. a relative volume of unity, also suggests that a compaction pressure of about 300 MPa will theoretically create this condition.

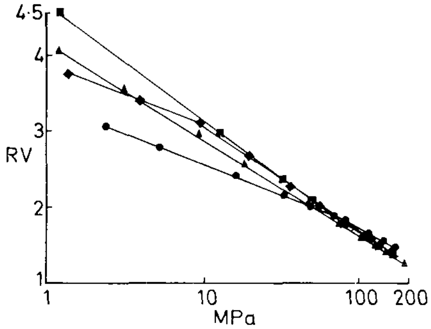

FIG. 4. Variation of relative volume (RV) of Avicel tablets with axial consolidating pressure (MPa). Symbols as for Fig. 1.

As expected, the penetration rate of isopropanol decreased as the compaction pressure increased, as seen in Fig. 5. Tablets of PH 105 grade cellulose do not disintegrate rapidly in water (Sixsmith, 1975) and this technique could therefore be applied to water penetration into these tablets. It can be seen that the uptake of water is more rapid than that of isopropanol. The penetration index/modal pore radius lines are parallel, indicating that the factor causing the different rates of penetration is constant and is likely to be the varying interfacial properties of the two systems.

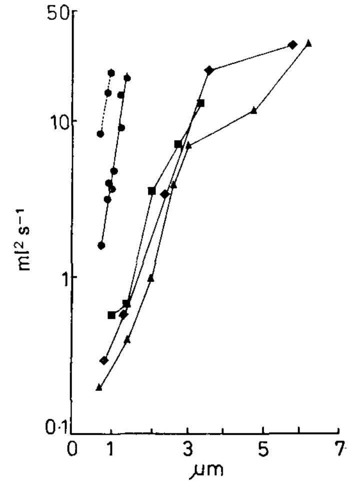

FIG. 5. The effect of compaction on the penetration index ($\text{ml}^2\ \text{s}^{-1}$ y axis) of Avicel tablets. Symbols as for Fig. 1. x axis—Modal pore radius (μm). Avicel PH 105 isopropanol penetration ———; water penetration – – –.

The decrease in penetration volume with increasing compaction pressure, shown in Fig. 6, followed a multistage process similar to the classical decrease in relative volume postulated by Seelig & Wulff (1956), Train (1956) and Marshall (1970) although an initial repacking stage was absent.

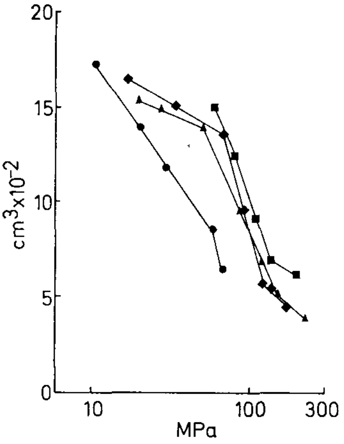

FIG. 6. The effect of consolidation on solvent penetration volume ($\text{cm}^3 \times 10^{-2}$) into Avicel tablets. Symbols as for Fig. 1. x axis—Maximum axial compaction pressure (MPa).

There was a change in the packing arrangement of the particles as the compaction pressure was increased. With increasing pressure the fracture surface shows a decrease in the interparticulate pore size confirming qualitatively the results found by mercury porosimetry. In compacts formed at pressures of 50 MPa and below there is little loss of particle identity whilst those formed at pressures in excess of 88 MPa show close packing and loss of particle identity.

In terms of disintegrating properties, there were two types of tablet present—disintegrating, i.e. those prepared from the PH 101, PH 102 and PH 103 grades and non-disintegrating, i.e. those prepared from PH 105 grade. This difference in character was reflected in the dissolution behaviour from the compacts as seen in Fig. 7.

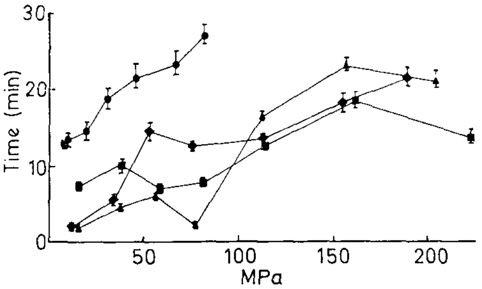

FIG. 7. The effect of maximum axial compaction pressure (MPa) on the dissolution of amaranth from Avicel tablets. Symbols as for Fig. 1. y axis—Time required for 50% of total amaranth to be liberated (min).

The tablets prepared from PH 101, PH 102 and PH 103 grade all disintegrated rapidly and therefore allowed the solvent to reach the amaranth rapidly. The tablets prepared from PH 105 grade did not disintegrate rapidly and the dissolution rate from them will be determined by the rate at which the solvent, water, can reach the drug molecule, i.e. the penetration rate into the tablet, and the transport of the dissolved drug out of the tablet. Once a solvent network has been set up and whilst solid amaranth is still present, the rate of transport from the tablet will remain approximately constant. The liquid penetration studies have shown that as the compaction pressure increases, the penetration rate decreases. The dissolution rate would therefore be expected to decrease with increase in compaction pressure.

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REFERENCES

BOLHUIS, G. K. & LERK, C. F. (1973). *Pharm. Weekblad*, **108**, 469–481.
BRUNAUER, S., EMMETT, P. H. & TELLER, E. (1938). *J. Am. chem. Soc.*, **60**, 309–319.
FOX, C. D., RICHMAN, M. D., REIER, G. E. & SHANGRAW, R. J. (1963). *Drug Cosmet. Ind.*, **92**, 161–164; 258–261.
GANDERTON, D. & SELKIRK, A. B. (1970). *J. Pharm. Pharmac.*, **22**, 345–353.
MARSHALL, K. (1970). Ph.D. Thesis, University of Bradford.
MARSHALL, K. & BROOK, D. B. (1969). *J. Pharm. Pharmac.*, **21**, 790–792.
MARSHALL, K. & SIXSMITH, D. G. (1974). *Drug Development Communications*, **1**, 51–71.
MENDELL, E. J. (1972). *Mfg Chem. Aerosol News*, **43**, 43–46.
ROBERTS, B. F. (1967). *J. Colloid Interface Sci.*, **23**, 266–273.
SEELIG, R. P. & WULFF, J. (1946). *Trans Am. Inst. Min. metall. Engrs*, **166**, 492–505.
SIXSMITH, D. G. (1975). Ph.D. Thesis, University of Bradford.
TRAIN, D. (1956). *J. Pharm. Pharmac.*, **8**, 745–761.
WALKER, E. E. (1923). *Trans. Faraday Soc.*, **19**, 73–89.