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The influence of moisture content on the preparation of spherical granules of barium sulphate and microcrystalline cellulose

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Summary

The influence of water content on the ability of mixtures of a range of proportions of barium sulphate and microcrystalline cellulose to form spherical granules by extrusion spheronisation has been assessed. Producing the extrudate by a ram extruder indicates that a range of steady state extrusion forces, which produce a satisfactory product, can be assigned to formulations. Below 2500 N, the extrudate is too wet and agglomerates, while above 10000 N the product is too dry and fails to round or cohere. The range of moisture contents over which successful products can be prepared is relatively wide for contents of barium sulphate from 20 to 60%. As this level is exceeded, the moisture content becomes more critical and once 80% of barium sulphate is reached, a critical moisture content is required. The quantity of water relative to the microcrystalline cellulose content, which was required to produce a consistent product in terms of particle size, was found to be proportional to the percentage of barium sulphate in the mixture. The ratio ranged from 1 : 1 for 20% barium sulphate to 1 : 1.5 for 80% barium sulphate.

Introduction

Devereux et al. (1990) have shown that the density of the pellets can influence their gastric emptying. Hence, the ability to control the density of the pellets could be a useful formulation variable. Devereux (1987) and Clarke (1989) have shown that it is possible to prepare pellets of different density by extrusion/spheronisation by the inclusion of barium sulphate, but their approach involved the ability to produce pellets rather than a detailed investigation of the preparation of pellets. Anderson and Newton (1990) found that, for mixtures containing equal parts of barium sulphate and microcrystalline cellulose, the particle size and water content did influence the rheology of the wet powder mass. Over the range of particle sizes (2.6–10.1 μm) and moisture contents (35.5–39.4% of final blend) it was, however, possible to produce spherical particles with appropriate properties.

The objective of the current study was to assess the ability of mixtures of varying proportions of barium sulphate and microcrystalline to produce spherical granules and to assess their sensitivity to the presence of water.

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Materials and Methods

Materials

The microcrystalline cellulose was grade PH101 (FMC Corp., U.S.A.), and the barium sulphate was from a single batch (Sachtleben Chemie GmbH, Germany) with a medium/median volumetric diameter of 2.6 μm (determined by laser light diffraction, Malvern 2600C, Malvern Instruments, U.K.). The water was freshly distilled water.

Methods

Mixtures of microcrystalline cellulose, barium sulphate (500 g of each) and water were prepared by a standardised procedure in a planetary mixer (Hobart Model A 200). The standard procedure involved dry blending at the lowest speed for 5 min followed by 10 min once the water had been added in one quantity. All mixtures were left for at least 12 h prior to extrusion in sealed polythene bags to allow the water to equilibrate throughout the mix. What is involved in this equilibrium process is not fully understood, but it has been shown to be necessary to obtain reproducible values for the steady state extrusion force.

Extrusion was undertaken in the ram extruder system described by Harrison et al. (1985) with a 1 mm diameter die of 4 mm length at a ram speed of 200 mm min^{-1}. The ram was driven by a physical testing instrument (J.J. Lloyd model MX50, U.K.). The force displacement curve was collected and retained via a computer system to allow measurement of the shape of the curve and the steady state extrusion force.

Spheronisation was undertaken by placing 200 g of extrudate from each blend, obtained during the steady state extrusion stage, onto the radial cut plate of a 20.32 cm diameter plate of a spheronizer (Caleva Ltd, U.K.) rotating at 1000 rpm. The sample was processed for 20 min. The pellets formed were collected and dried at 60°C for 30 min in a fluidised bed driver (PRL Engineering Ltd, Model No. FDBL 70, U.K.). A sample of 75 g of each preparation was taken by a spinning riffler (Microsal model TM1, U.K.) and subjected to sieving on a $\sqrt{2}$ progression of appropriate size sieves by mechanical agitation on a sieve shaker (Endicott Ltd, U.K.).

Results and Discussion

The blends of barium sulphate and microcrystalline cellulose ranged in proportion from 20 : 80 to 80 : 20. In view of the extended time necessary to form a flow rate/shear stress curve as described by Harrison et al. (1985) the ram extruder was used at a single ram velocity and with die of constant length to radius ratio. The quantity of water added to the system diverged from 1.2 times the weight of microcrystalline cellulose until the samples were too wet or too dry to form spheres. Once a ratio at each end of the scale had been achieved, experiments with the system were stopped. A preparation that was too dry was judged either by its inability to extrude under the maximum pressure available (20 kN) or when appreciable quantities of the mixture fell between the plate and the wall. A preparation was judged too wet when there was gross agglomeration on the plate to yield a grossly enlarged set of spheres.

Using these criteria it is possible to produce a graph of the steady state extrusion pressure as a function of water content for the various blends of barium sulphate and microcrystalline cellulose (Fig. 1). Here there is no judgment placed on the quality of the spheres in terms of particles, diameter and distribution of diameter. The limits are those of gross limits of performance in terms of the ability to produce spheres. It appears possible to identify steady state force limits over which a formulation can be further processed. Unless a force of approx. 2500 N is achieved, the extrudate

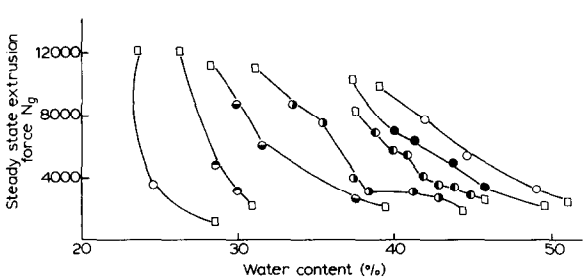

Fig. 1. Steady-state extrusion force for mixtures of microcrystalline cellulose and barium sulphate as a function of moisture content. Spheres not produced (□); barium sulphate content: 20% (○), 30% (●), 40% (◐), 50% (◑), 60% (◒), 70% (◓), 80% (○).

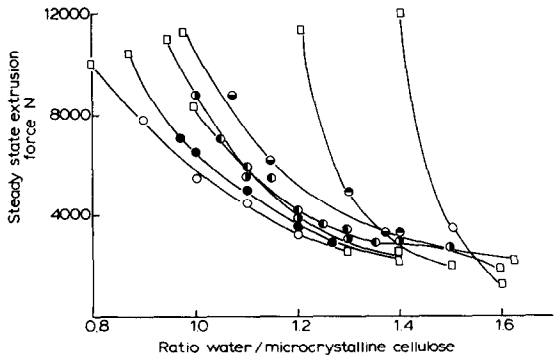

Fig. 2. Steady-state extrusion force for mixtures of microcrystalline cellulose and barium sulphate as a function of the ratio of microcrystalline cellulose to water. Symbols as for Fig. 1.

is too soft, due to excess water and can agglomerate into aggregates. Above a steady-state extrusion force of 10000 N, the extrudate is too hard and cannot be further moulded by the spheronisation process and hence fails to round or cohere.

The influence of microcrystalline cellulose on the distribution of water in these systems is critical. Microcrystalline cellulose appears to hold water in such a way that the extrudate has a consistency suitable for the process. Just what this consistency is and how the water is held have not yet been established. It is important to look at these results in terms not of the total water content, but as a function of the content relative to the quantity of microcrystalline cellulose (Fig. 2). It will be observed that between 20 and 60% of barium sulphate the quantity of water is not critical. At 70% barium sulphate the range is reduced and by the time a final level had reached 80%, there was only one formulation which would produce spheres. This can be further illustrated if the results are presented showing the range of water to microcrystalline cellulose ratios which can produce spherical granule products, as a function of barium sulphate content (Fig. 3).

The comments made so far have only indicated the ability to make spherical products as judged qualitatively. If a more critical evaluation of the

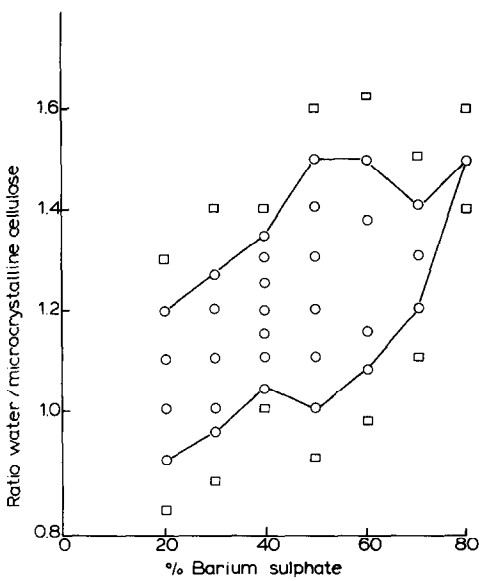

Fig. 3. Range of formulations from which spherical granules can be prepared from mixtures of microcrystalline cellulose, barium sulphate and water. (○) Spherical granules possible; (□) spherical granules not possible.

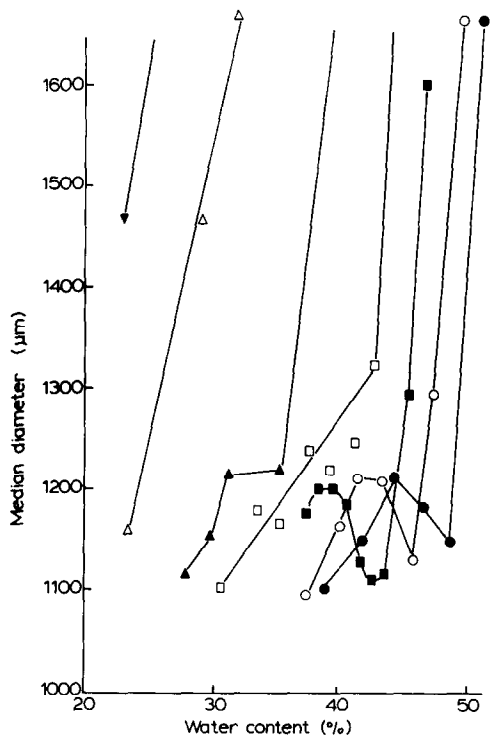

Fig. 4. Median diameter of spherical granules produced from mixtures of microcrystalline cellulose, barium sulphate and water. Barium sulphate content (%): 20 (●), 30 (○), 40 (■), 50 (□), 60 (▲), 70 (△), 80 (▼).

product is required, it is necessary to consider the size and range of sizes produced by the process. This is illustrated in Fig. 4, which clearly shows that although the mixtures produce satisfactory spheres, they are not all of equal median diameter. Further evidence of the quality of spheres can be obtained from their distribution of sizes. These are presented in Fig. 5 as the interquartile range. In most cases, there is a clear indication that for the good product the size range is limited, and only when the high water content is causing granule growth, is there also a wide range of sizes.

An interesting feature is how critical is the upper level of moisture content. Even before the quantity of water which is too wet is achieved, there is clear evidence of agglomeration of the product, hence it is possible to add to Fig. 3 an upper limit where agglomeration is already present, and therefore a restriction on formulation should be placed.

If the level of moisture content as a ratio of microcrystalline cellulose content which gives a

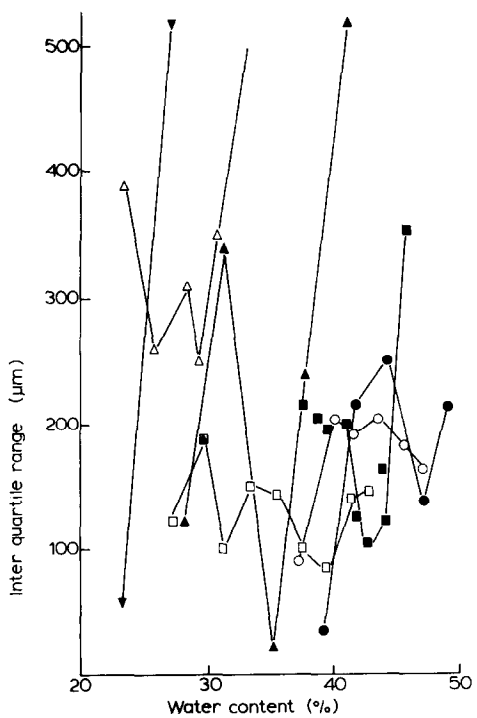

Fig. 5. Interquartile size range of spherical granules prepared from mixtures of microcrystalline cellulose, barium sulphate and water. Symbols as for Fig. 4.

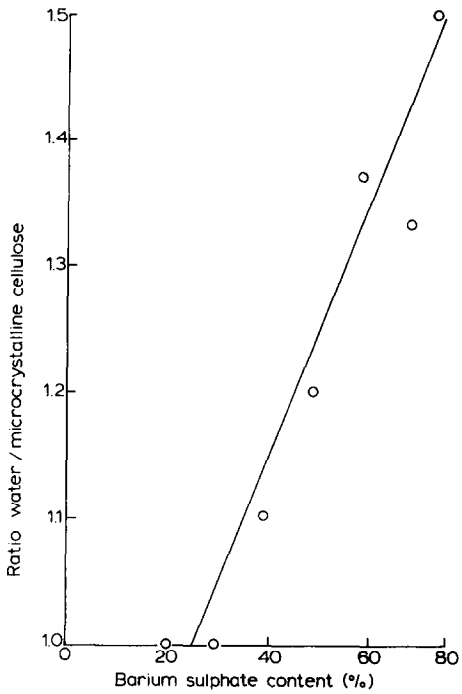

Fig. 6. The ratio of water to microcrystalline cellulose required to produce spherical granules within the size fraction 1180–1450 μm, as a function of barium sulphate content, for mixtures of microcrystalline cellulose, barium sulphate and water.

predominance (at least 75%) of particles in the size range 1180 to 1450 μm is selected and expressed as a function of barium sulphate content (Fig. 6), it will be observed that there is an approximately linear relationship. The ratio usually considered optimum (1 part microcrystalline cellulose to 1.2 parts water) is confirmed as a useful guide for equal parts of barium sulphate and microcrystalline cellulose. Above and below this ratio the quantity of water required should be increased or decreased as the quantity of barium sulphate is greater or less than equal parts. This is presumably associated with maintaining appropriate rheological properties of the mass to ensure that it has suitable characteristics which produce a standard product.

These findings clearly provide a guide to the formulation of spherical granules. These can probably be extrapolated to insoluble material of equivalent particle size, size distribution and shape to those associated with barium sulphate. Materi-

als with other properties, especially those which are highly water-soluble, will require further study and could be far more specific in their requirements, even if they can be spheronised.

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