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The Effect of Lactose Particle Size on the Extrusion Properties of Microcrystalline Cellulose-Lactose Mixtures

K. E. FIELDEN†, J. M. NEWTON AND R. C. ROWE*

*The School of Pharmacy, University of London, Brunswick Square, London WC1N 1AX and *ICI Pharmaceuticals, Alderley Park, Macclesfield, Cheshire SK10 2TG, UK*

Abstract—Ram extrusion has been used to assess and compare the flow characteristics and quality of wet powder masses formed from mixtures of water with microcrystalline cellulose and two different particle size samples of lactose. The force-displacement profiles can reveal poor flow properties. Steady state flow was achieved for the mixture containing fine lactose which produced an extrudate of uniform moisture content at all extrusion rates except the lowest (5 cm min^{-1}). Increasing the lactose particle size significantly altered the extrusion properties of the formulation with forced flow predominating and high extrusion pressures observed. Formulations showing that type of extrusion are to be avoided as they produce poor quality extrudate which may be unsuitable for spheronization. Flow visualization studies showed that problems associated with such mixtures are caused by failure to maintain a constant angle of convergence during extrusion, which is essential for maintenance of steady state flow. With the mixture made with coarse lactose, the extrudate quality could be improved by extruding at high velocities, information that may be of significance in the development of formulations for large-scale production. Differences between formulations may be expressed quantitatively by plotting the apparent shear stress-shear rate relationship. The curves are modified by the particle size of lactose included in the mixtures. Such curves have implications in predicting the suitability of an extrudate, produced under particular experimental conditions, for spheronization.

Extrusion-spheronization is increasingly used to prepare spherical granules for multiparticulate oral dosage forms (Conine & Hadley 1970; Reynolds 1970; Rowe 1985). Preparation of satisfactory spheroids is largely dependent upon the achievement of an optimal formulation suited to extrusion, which is the preliminary stage in the process. The method of ram extrusion reported by Harrison et al (1985) may be used to characterize such wet powder masses intended for extrusion-spheronization. This technique has been applied to study the influence of the particle size of one component of the formulation on the extrusion process.

Materials and Methods

Two formulations containing microcrystalline cellulose (Avicel PH101-FMC Corporation) mixed in equal quantities with either fine grade lactose (regular grade, Dairy Crest), mean particle size 18·0 μm ± 3 μm (projected area diameter by Quantimet Image Analyser), or a coarse grade (crystalline grade, Dairy Crest) mean particle size 117·0 μm air jet sieve (Alpine), were blended in a planetary mixer (Hobart) with water to a moisture content of 37·5% w/w. The flow characteristics of the wet powder masses were studied by monitoring the force required to extrude them at different rates through 1·0 mm diameter dies of varying length-to-radius ratios using a ram extruder according to Harrison (1982). The wet powder mass was allowed to equilibrate for at least 12 h before extrusion measurements were made. Moisture contents of extrudates collected during steady state extrusion, and of the plugs of material in the ram extruder, were determined after both had been dried to constant weight. The values for moisture content given in Table 1 represent the average of three extrusions. Techniques adapted by Harrison et al (1985) from polymer extrusion (Tordella 1957; Bagley & Birks 1960) were used to visualize the flow of wet powder masses through the die. This method uses coloured material layered at regular intervals with the wet powder mass in a ram extruder. The coloured layers subsequently delineate the flow of material in the die entry region during extrusion. Here, the colour was produced by adding charcoal to the mixtures.

Correspondence to: J. M. Newton, The School of Pharmacy, University of London, 29-39 Brunswick Square, London WC1N 1AX, UK.

† Present address: The Wellcome Foundation Ltd, Temple Hill, Dartford, Kent, DA1 5AH, UK.

Results and Discussion

Force-displacement profiles

The force-displacement profiles for the mixtures containing the coarse and fine grades of lactose were compared at varying experimental conditions of die length, Fig. 1, and extrusion rate, Fig. 2, at constant moisture content (37·5% w/w) and die diameter (1·0 mm). The mixture containing fine lactose demonstrated optimal extrusion, progressing through three distinct stages: compression, steady state flow, and forced flow, as demonstrated by Harrison et al (1985). During the compression stage the volume of the material was reduced as it was compressed into a plug before flow. The extent of the consolidation, as indicated by the distance the piston descends before flow, was shown to be independent of the lactose particle size or extrusion conditions, and

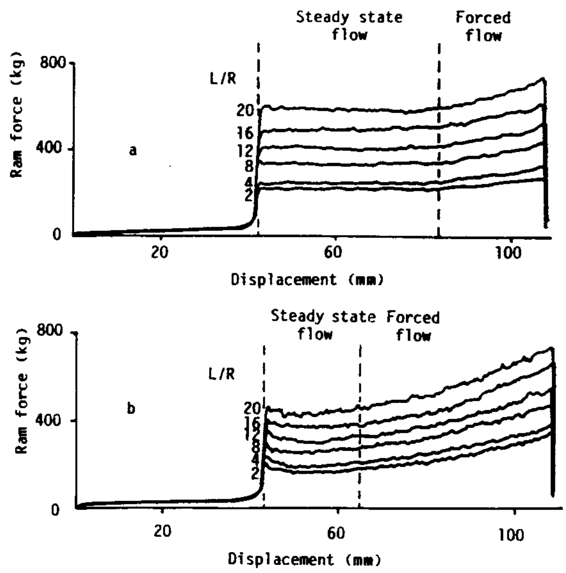

FIG. 1. The effect of length to radius ratio on the force-displacement profile for microcrystalline cellulose:lactose:water (5:5:6). Die diameter: 1·0 mm. Ram speed: 20 cm min^{-1}. (a) Fine lactose. (b) Coarse lactose.

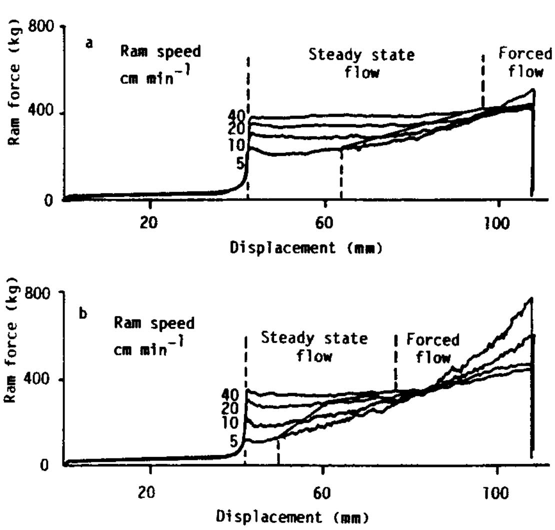

FIG. 2. The effect of ram speed on the force-displacement profile for microcrystalline cellulose:lactose:water (5:5:6). Die diameter: 1·5 mm. Length to radius ratio: 8. (a) Fine lactose. (b) Coarse lactose.

depended only on the moisture content of the particular mixture (Fielden 1987). Towards the end of the compression stage the pressure applied to the wet powder mass increased until it was sufficient to enable the material to yield and commence flow. This was followed by a period of steady state flow in which the force required to maintain the extrusion remained constant as the displacement increased. Harrison et al (1985) concluded that a high quality extrudate could only be prepared if steady state flow predominated; this is supported herein. In general, the duration of steady state flow for both formulations, containing fine and coarse lactose, was found to be independent of die length but was prolonged with increasing velocity of throughput. The steady state extrusion force generally increased with increasing die length and velocity of throughput. However, the period of steady state flow and the extrusion force, at any given experimental condition were consistently lower for the mixture containing coarse lactose. The more jagged appearance of the force-displacement profiles of the mixture containing coarse lactose was thought to be caused by a greater tendency for the material to slip at the die wall, as opposed to the ideal situation of flow through orifices where no slip at the die wall occurs. The extrusion rate was the factor which most influenced the duration of steady state flow in the mixture containing coarse lactose. Steady state flow was brief at low extrusion rates (5 cm min^{-1}) and it was only at rates above 20 cm min^{-1} that slippage at the die wall was significantly reduced and prolonged steady state flow achieved.

Forced flow occurs when steady state flow can no longer be maintained and is shown by a gradual rise in the extrusion force with displacement. With both formulations the duration of forced flow was found to be independent of the die length, but occurred at an earlier displacement at lower extrusion rates. This trend was more pronounced in the mixture containing coarse lactose where, particularly at low extrusion rates (5 cm min^{-1}), the force-displacement profiles showed forced flow occurring immediately after the compression stage, Fig. 2(b). Prolonged steady state flow only occurred at high extrusion rates—40 cm min^{-1}.

Variation in extrudate moisture content

Extrudate prepared with the fine lactose appeared uniform under varying experimental conditions, whereas that containing coarse lactose noticably varied during extrusion. The moisture content of extrudates and materials in the barrel determined during steady state flow were compared at varying ram speeds (Table 1). In general, both formulations developed a moisture gradient where there was a tendency for the water content of the extrudate to exceed that of the plug within the cylinder. The moisture imbalance increased as the extrusion rate was reduced, but was not significant at ram speeds above 5 cm min^{-1} for the mixture containing fine lactose. In contrast, the mean moisture content of the extrudate containing coarse lactose varied substantially with the ram speed, being 2–8% greater than that of the plug. Further investigation determined the change in moisture content of the latter formulation as extrusion progressed at various ram speeds (Table 2). Values referred to in the Table can be related to the piston displacement in the force-

Table 1. A comparison between the moisture content of the material in the barrel and the extrudate for the mixtures containing fine and coarse lactose. Microcrystalline cellulose-lactose-water (5:5:6).

Ram speed cm min^{-1}	Moisture content % w/w Extrudate	Moisture content % w/w Plug	Moisture content extrudate:plug % w/w
(A) Mixture containing fine lactose			
40	38·6	38·6	0
20	38·6	38·5	0·1
10	38·9	38·6	0·3
5	38·2	37·4	0·8
(B) Mixture containing coarse lactose			
40	38·8	36·7	2·1
20	39·1	36·2	2·9
10	39·7	35·7	4·0
5	41·1	33·2	7·9

Table 2. Variation in the moisture content of extrudate containing coarse lactose at various time intervals and displacement intervals relating to the force-displacement profile in Fig. 2b. Microcrystalline cellulose: lactose: water (5:5:6).

Time interval (s)	Piston displacement (mm)	Average extrusion force (kg)	Extrudate moisture content (% w/w)
(A) Ram speed 5 cm min^{-1}			
0-5	42-48	120	50·2
5-10	48-53	135	45·9
10-20	53-64	173	42·0
20-30	64-75	226	39·0
30-40	75-86	293	36·9
40-50	86-97	412	35·3
50-60	97-108	591	32·8
(B) Ram speed 20 cm min^{-1}			
0-5	42-64	273	38·4
5-10	64-86	315	36·9
10-15	86-108	392	34·5

displacement profiles shown in Fig. 2(b). The material emerging during the initial 50 mm displacement at a ram speed of 5 cm min^{-1} has a high water content (50% w/w) and resembled a slurry (Table 2(A)), implying that the wet powder mass containing coarse lactose was overwetted. This is because gradual consolidation allows excess free water in the system to move through the plug towards the die exit of the ram extruder. The pressure build-up immediately before extrusion squeezed this water out of the system as the pressure was relieved. The force-displacement profile indicated that extrusion thereafter proceeded by way of forced flow and the resultant pressure build-up caused increasing quantities of water to be pushed out of the plug. The extrudate then became progressively drier. Thus, the onset of forced flow can be identified as the point on the extrusion cycle at which a moisture gradient between extrudate and material in the barrel is developed. This moisture differential increased as extrusion progressed, and resulted in continual variation in extrudate moisture content. The above effects were minimized by increasing the extrusion rate to 20 cm min^{-1} whereupon the moisture content of the extrudate was approximately equivalent to that of the wet powder mass for the initial 90 mm displacement. The force-displacement profile, Fig. 2(b), showed that this period corresponded to the duration of the steady state flow region, which had lengthened as a result of the increased ram speed. Onset of forced flow at 90 mm displacement again resulted in variation in extrudate moisture content.

Flow visualization

The flow visualization study enabled the convergent flow patterns of the wet powder masses containing fine and coarse lactose to be compared during extrusion. The development of convergent flow patterns during steady state flow for the

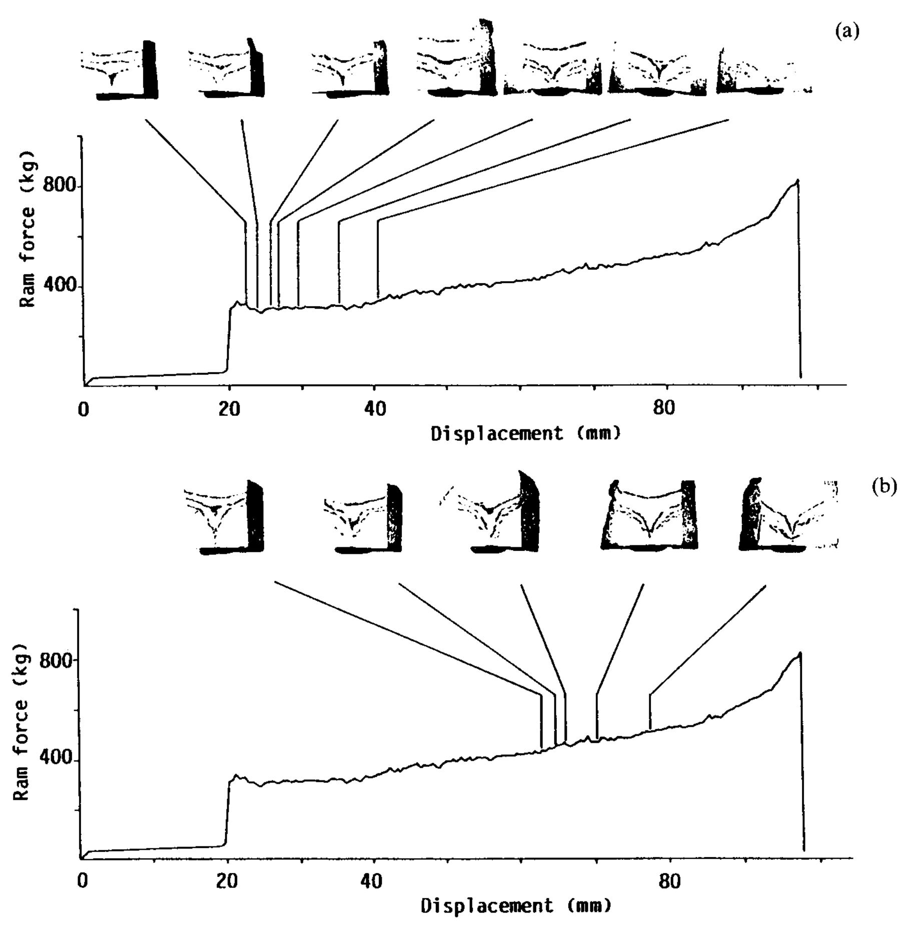

FIG. 3. A flow visualization study showing the development of convergent flow patterns into the die. Microcrystalline cellulose: lactose: water (5:5:6): fine lactose. Die diameter 1·0 mm., length 4 mm. (a) Steady state flow at 5 cm min^{-1}. (b) Forced flow at 5 cm min^{-1}.

mixture containing fine lactose is related to the force-displacement profile obtained at a ram speed of 5 cm min^{-1}, Fig. 3(a). The material can be seen to flow symmetrically through a vortex, allowing the natural angle of convergence (approximately 65°) to be repeatedly formed then dissipated by successive coloured layers. This type of pattern should ideally be maintained throughout extrusion and is an indicator of steady state flow conditions (Harrison et al 1984). The coloured bands which have not been extruded remain within a stagnant zone as discrete static layers and do not take part in flow through the capillary. Similarity may be drawn between the extrusion of metals and plasticine (Green 1951) in contrast to polymer extrusion where the material is known to circulate within the stagnant zone (Bagley & Birks 1960). The convergent flow patterns were altered at a greater displacement (60 mm) where the force-displacement profile indicated conditions of forced flow, Fig. 3(b). The flow patterns showed an increased stagnant area as the entrance angle was reduced to about 20°.

Very different flow patterns were obtained under identical experimental conditions for the mixture containing coarse lactose. The force-displacement profile indicated that the material passed from the compression stage directly into forced flow, Fig. 4(a). The coloured layers initially flowed asymmetrically, presumably because they were not accelerated symmetrically about the axis before entering the capillary. Hence the angle of convergence was displaced, and less clearly defined than for the mixture containing fine lactose. A similar phenomenon, also indicating abnormal flow, was reported by Tordella (1957) during polyethelene extrusion at a critical stress. At a greater displacement, 50 mm, the flow patterns became more severely disrupted implying a greater degree of turbulance at the die entrance (Fig. 4(b)). The resultant vortex area comprised largely static material while the angle of convergence narrowed to approximately 10°. Extrusion at a higher rate (20 cm min^{-1}) allowed a constant angle of convergence to be established throughout most of the extrusion cycle (Fig. 5). The type of flow depicted in Figs 4–5 may indicate the cause of variability in the moisture content of the resultant extrudate. Formation of a constant angle of convergence indicates that controlled extrusion, at constant pressure, is taking place. Analysis of the extrudate has indicated that such conditions of steady state flow produce a consistent extrudate of uniform moisture content (Table 1(A)). At high extrusion rates (20 cm min^{-1}) the formulations containing fine and coarse lactose sustained a constant angle of convergence, demonstrating that a more uniform extrudate is produced at high volumetric throughput rates.

Measurement of the convergent angle provides a qualitative indication of the ease of flow of wet powder masses through capillaries. Any reduction in the angle results in the onset of forced flow. Conversely, this implies that mixtures showing the largest angle of convergence will extrude with

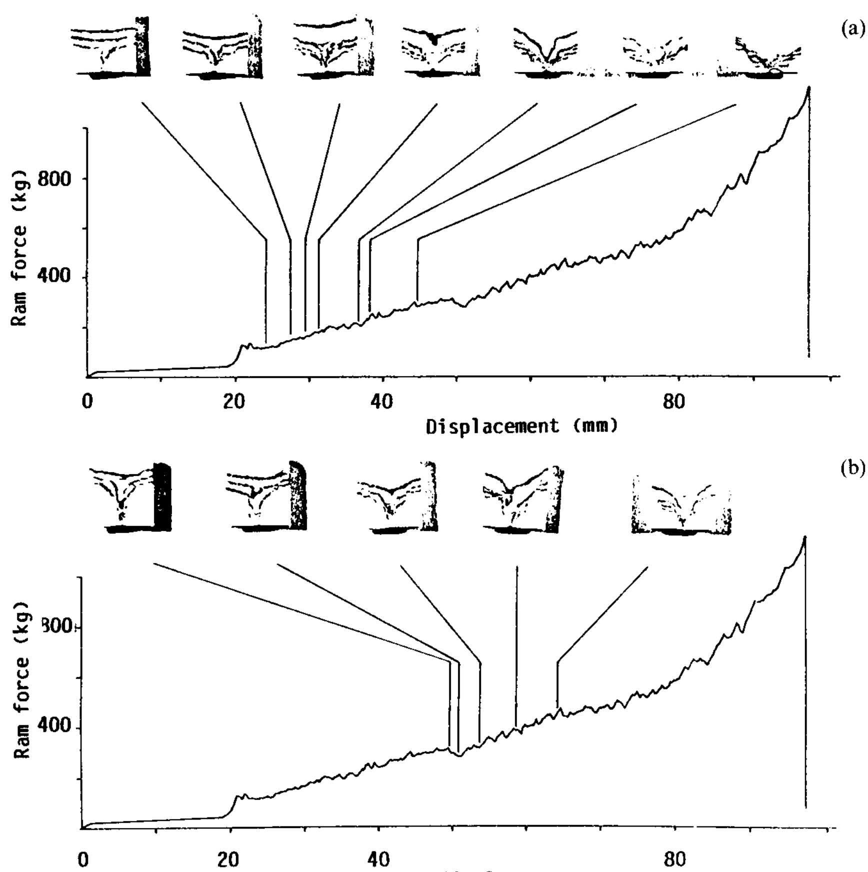

FIG. 4. A flow visualization study showing the development of convergent flow patterns into the die. Microcrystalline cellulose: lactose: water (5:5:6): coarse lactose. Die diameter 1·0 mm, length 4 mm. (a) Steady state flow at 5 cm min^{-1}. (b) Forced flow at 5 cm min^{-1}.

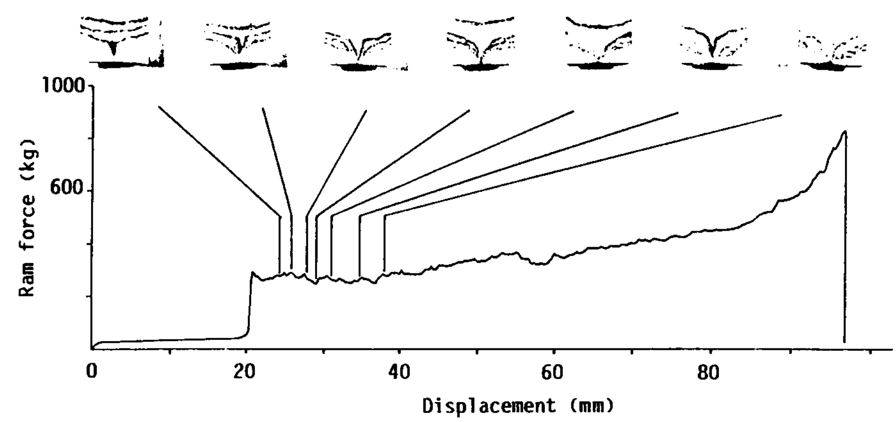

FIG. 5. A flow visualization study showing the development of convergent flow patterns into the die. Microcrystalline cellulose: lactose: water (5:5:6): coarse lactose. Die diameter 1·0 mm, length 4 mm. Steady state flow at 20 cm min^{-1}.

relative ease. This assumption is reasonable since, with an extreme example, the flow of non-Newtonian fluids such as glycerol has been demonstrated at a angle of 180° (Metzner et al 1969). Forced flow extrusion is characterized by a systematic reduction in the angle of convergence and increase in the stagnant area. Such large die entry vortices have been correlated with large entrance pressure losses. This indicates that the vortices act to increase the effective capillary die length (White 1973), which may be thought of as extending from the die entrance into the vortex (Bagley 1957). This causes the increased pressure during the forced flow stage of extrusion, since the pressure across the ends of a capillary is proportional to its length. The continual pressure build-up then results in removal of water from the material in the barrel, as described in Table 2, the resultant extrudate having a variable moisture content.

Shear stress-shear rate relationship

The rheological characteristics of the wet powder masses can also be described by a shear stress-shear rate flow curve (see Fig. 6). The materials exhibit non-Newtonian flow properties and possess a yield stress and shear thinning properties. The apparent flow curves may be used to distinguish between the formulations containing different particle size lactose. At low shear rates (or extrusion rates) the stress at the die wall is reduced in the formulation containing coarse lactose. The extrapolated yield stress is zero, while that for the fine lactose formulation is approximately 250 KN m^{-2}. A low yield stress in the former might be expected since at the start of extrusion

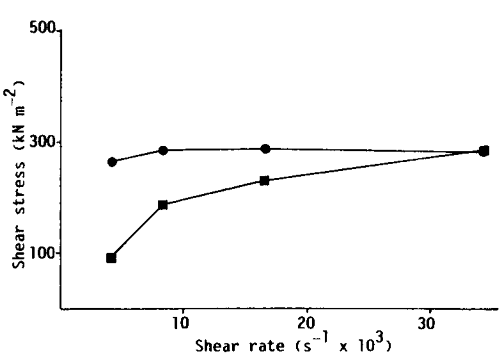

FIG. 6. Influence of lactose particle size on the die wall shear stress as a function of the shear rate for microcrystalline cellulose: lactose: water. Die diameter: 1·0 mm; moisture content 37·5% w/w. Fine lactose ●. Coarse lactose ■.

a slurry (50% w/w water) is ejected at low shear rates, as opposed to 'solid matter' with the fine lactose formulation. At higher shear rates the flow curves of the two formulations merge. This indicates that the mixture containing coarse lactose is more shear rate-dependent and that at high rates of shear the rheological properties are equivalent to that of the mix containing fine lactose when in steady state flow. Similar trends are exhibited at various die diameters and moisture content of material mix (Fielden 1987). The variation in the flow curves with lactose particle size implies that the rheological properties of the extrudates of both formulations, produced under identical conditions, will differ. Hence the spheronized products are expected to differ with the most diverse result occurring from extrudates produced at low shear rates, where the maximum deviation in the flow curves was observed.

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