International Journal of Pharmaceutics, 81 (1992) 225–233

IJP 02705

A comparison of the extrusion and spheronization behaviour of wet powder masses processed by a ram extruder and a cylinder extruder

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(Received 17 September 1991)
(Accepted 31 October 1991)

Key words: Extrusion/spheronization; Microcrystalline cellulose; Particle size effect; Lactose; Ram extruder; Cylinder extruder; Die diameter; Spherical granule

Summary

The preparation of spherical granules by spheronization of extrudate obtained by extrusion through either a cylinder or ram extruder of a mixture of microcrystalline cellulose, lactose (with median diameter of either 18 or 117 μm) and water has been undertaken. Spheroids of a uniform size and shape could be produced from both particle size ranges of lactose if the cylinder extruder was used but not if the ram extruder formed the extrudate. The differences appear to be associated with the different rates of shear and the shear stresses involved in the two extrusion processes.

Introduction

Wet powder masses intended for extrusion and spheronization must have specific rheological requirements in order to undergo successful processing (Conine and Hadley, 1970; Reynolds, 1970). Characterization of these rheological properties requires application of a theoretical treatment which depends on the ability to measure the extrusion force and rate. Most commercial extruders, however, do not allow for these types of measurement. The ram extruder designed by Benbow and Ovenston (1968) provides a suitable alternative and lends itself to application of theory derived from capillary rheometry. Harrison et al. (1987) have used this system to characterize the rheological behaviour of wet powder mixtures used in the extrusion-spheronization process. Its usefulness as a small-scale technique for evaluating the suitability of preparations for processing by this method has been established by several workers (Fielden et al., 1989, 1992; Anderson and Newton, 1990; Baines et al., 1991). The object of this study is to determine whether the ram extruder can be used to predict the extrusion and spheronization behaviour of wet powder masses processed on a larger scale with a different type

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of extruder, namely a cylinder extruder. A comparison has been made of the spheronization properties of extrudate obtained from these two systems.

Materials and Methods

The materials used were microcrystalline cellulose (Avicel PH101, FMC Corp., U.S.A.) and two grades of lactose (Dairy Crest, U.K.), one with a number median particle size of 18.0 ± 3.0 μm (equivalent spherical diameter by image analysis, Quantimet Q720) and another with a weight median diameter of 117.0 ± 1.5 μm (sieve analysis). Wet powder masses were prepared by mixing equal quantities of the microcrystalline cellulose and lactose and adding water to a moisture content of 37.5% with a planetary mixer (Hobart). The mixtures were allowed to equilibrate in sealed polythene bags at room temperature for at least 12 h prior to use.

Extrudates of 1.0 and 1.5 mm diameter were prepared using a ram extruder fitted with dies of length-to-radius ratio (L/R) of 8 and at a constant extrusion rate of 10 cm min^{-1} as described by Harrison et al. (1987). These conditions produced extrudates with smooth external surfaces. The same preparations were extruded on a laboratory-scale cylinder extruder (Alexanderwerk) fitted with cylinders of either 1.0 or 1.5 mm diameter dies with L/R of 8 rotating at 100 rpm. The extrudates were spheronized in 200 g batches for durations of 20 s, 1, 2, 5, and 10 min on a 22.5 cm radial hatched plate rotating at 1000 rpm (GB Caleva Ltd, U.K.). The granules were dried in a fluid bed drier (PRL Engineering Ltd, U.K.) at 60°C for 30 min to give a constant weight. Granules were characterized in terms of the weight and number median diameters obtained from size distributions by sieving and by image analysis (Quantimet Q720) respectively. The mean particle length and width, and the 'One Plane Critical Stability' (OPCS) shape factor after Chapman et al. (1988) of the largest size fractions were determined by microscopy. Visual confirmation of the shape changes occurring during spheronization was obtained by taking high-speed photographs of the process. The above procedures have been described by Fielden et al. (1992).

Results and Discussion

Spheronization of the two wet powder mass formulae, containing the fine and coarse grades of lactose, was evaluated by comparing the changes in granule dimensions as indicated by the granule sizes obtained within the limits of the interquartile range after 20 s and 10 min spheronization (Table 1). Granules containing the coarse and fine grades of lactose produced on the cylinder extruder, and granules containing the fine lactose derived from the ram extruder, all had a similar spread of sizes for each die diameter. Both the 1.0 and 1.5 mm diameter ram extrudate containing coarse lactose also had similar

TABLE 1

The influence of spheronization time, particle size of lactose, extruder type and die diameter on the particle size range of spherical granules produced from a mixture of microcrystalline cellulose, lactose and water

Die diameter	Extruder type	Interquartile range limits (mm) after spheronization for							
		20 s				10 min			
		Fine lactose		Coarse lactose		Fine lactose		Coarse lactose	
		Number	Weight	Number	Weight	Number	Weight	Number	Weight
1.5 mm	cylinder	1.7–2.0	1.3–1.6	1.5–1.9	1.4–1.6	1.4–1.7	1.5–1.7	1.3–1.6	1.5–1.8
	ram	1.6–2.0	1.5–1.6	1.5–1.9	1.5–1.7	1.7–1.8	1.6–1.9	2.2–3.0	2.7–4.5
1.0 mm	cylinder	0.9–1.2	0.9–1.0	0.9–1.2	0.9–1.0	0.8–1.0	1.0–1.1	0.9–1.0	1.0–1.2
	ram	1.0–1.4	1.0–1.1	1.2–1.7	1.1–1.6	0.9–1.1	1.1–1.3	2.3–3.0	2.5–4.3

size distributions at the initial stage of spheronization but the interquartile range increased from approx. 0.2 mm to 1.8 mm after 10 min spheronization as a result of uncontrolled agglomeration. Hence, the extrudates derived from the cylinder and ram extruders are not equivalent and have differing spheronization properties.

Further evidence of the quality of spheres obtained from the two extruders is shown by plotting the median particle diameters as a function of the spheronization time (Fig. 1). The cylinder extrudate containing the coarse and fine grades of lactose produces granules of similar size at each stage of the process following a pattern that establishes controlled spheronization, i.e., a gradual increase in the weight median diameter (as the granule width increases) and a concurrent reduction in the number median diameter (as the particle length is reduced). Both the 1.0 and 1.5 mm diameter extrudates containing the coarse and fine lactose grades of lactose form spheroids of constant median diameter within 3–5 min. Extrudate from the ram extruder containing fine lactose also demonstrates controlled spheronization. However, the coarse lactose extrudate from the ram extruder results in a grossly agglomerated product.

The granule length and width changes observed microscopically on the sieve fraction containing the largest proportion of material also follow the above trend (Fig. 2). It was noted that the length and width dimensions of the extrudates from the ram extruder were slightly greater than that of the cylinder extrudates. This was caused by variation in the die diameters of the two extruders and was not attributed to a difference in spheronization properties, i.e., the actual diameters of the ram extruder dies used were 1.04 and 1.54 mm, while the average diameters of

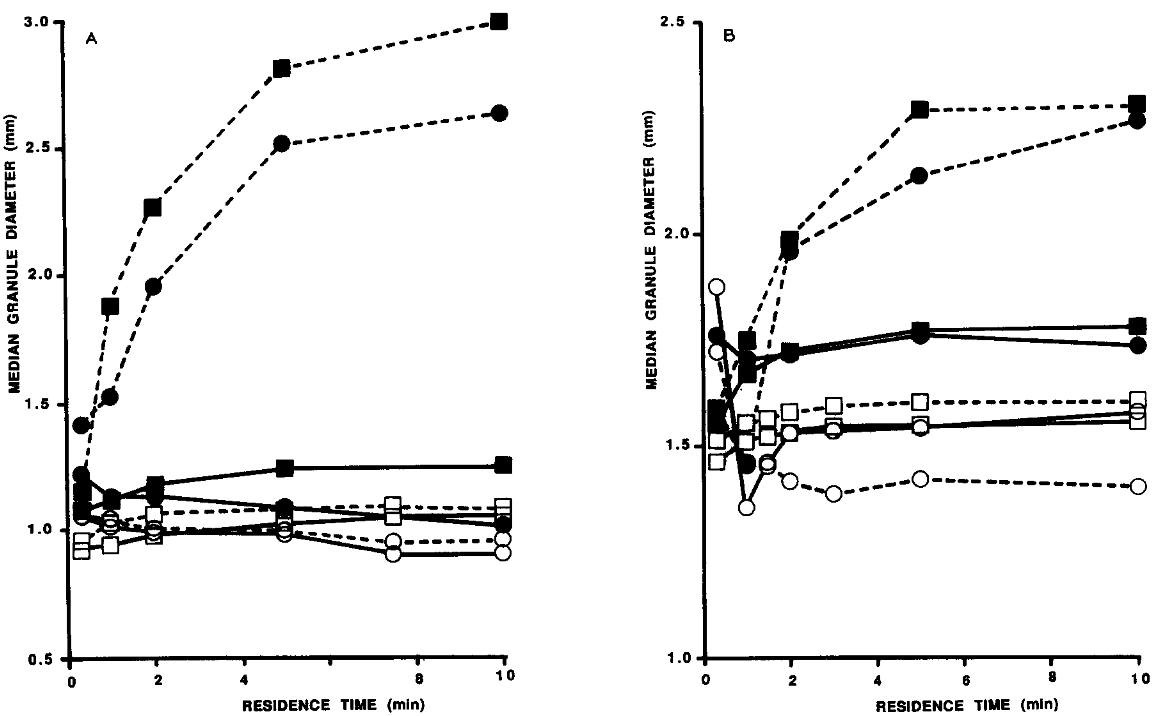

Fig. 1. Comparison of the change in number and weight median granule diameters with spheronization time for extrudates containing coarse and fine grades of lactose processed by ram and cylinder extruders. (A) 1.0 mm diameter die; (B) 1.5 mm diameter die. (———) Fine lactose; (- - - - - -) coarse lactose; (●, ○) number median diameter; (■, □) weight median diameter; (□, ○) cylinder extruder; (■, ●) ram extruder.

the cylinder dies were 0.96 and 1.48 mm. Therefore, extrudate, and subsequently granules, of slightly larger diameter are produced by the ram extruder.

High-speed photographs taken at 10 min spheronization emphasise the lack of agglomeration observed with the cylinder extrudate containing coarse lactose (Fig. 3). Due to similarity in the spheronization properties of the coarse and fine lactose cylinder extrudates, only photographs of the former are presented in order to demonstrate its controlled spheronization.

The changes in granule shape in terms of 'roundness' as in OPCS with time (Fig. 4) show that cylinder extrudates containing the coarse and fine lactose are spheronized via the same mechanism as previously reported for extrudate from the ram extruder (Fielden et al., 1992), and result in spheroids of approximately equivalent OPCS values (approx. 16).

The above results indicate the suitability of the cylinder-type commercial extruder (which must operate under optimal conditions) to produce good-quality consistent extrudate that is relatively insensitive to the particle size of lactose used in the wet powder mass. It has also been established that extrudate produced from the ram extruder is not equivalent to that of the cylinder extruder, since when coarse lactose is used, the product agglomerates if produced by the ram, but does not if produced by the cylinder extruder. The reason for this may be due to a fundamental difference in the method by which a wet powder mass is processed in the two extrusion systems.

An attempt is made to describe the processing conditions within the cylinder extruder as follows. The 1.0 mm diameter cylindrical system consists of 1960 holes and rotates at 100 rpm providing a total throughput rate of 3.83 g s^{-1}. According to Harrison (1982), adjustment can be made to ac-

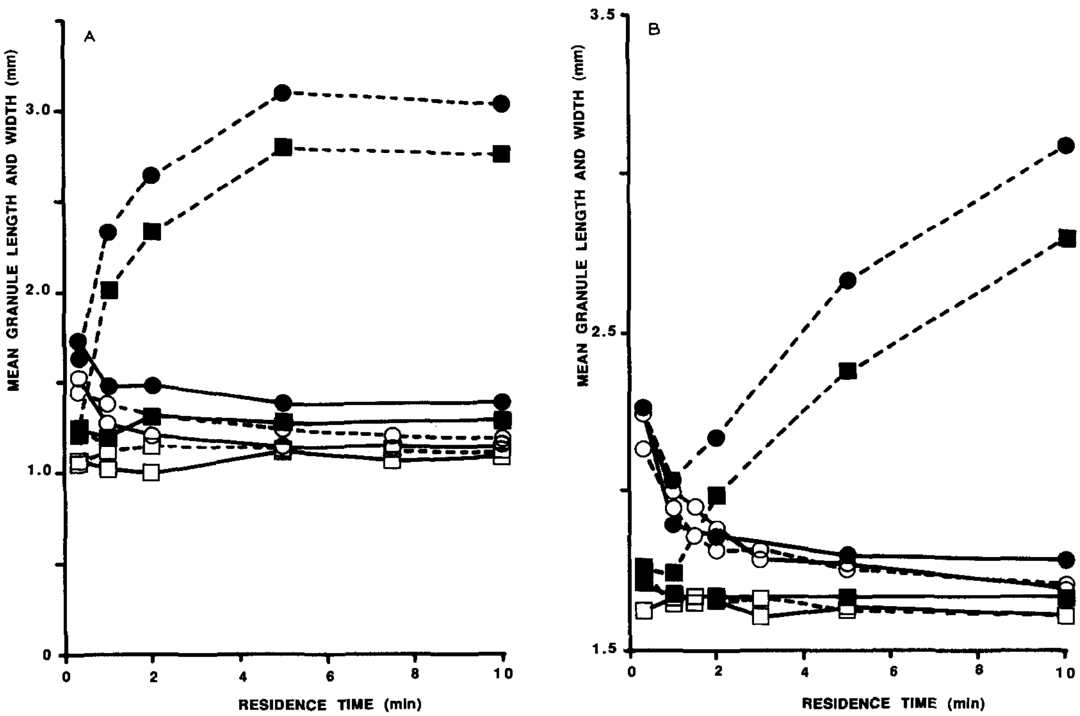

Fig. 2. Comparison of the change in mean length and width of granules from the most frequently occurring size fraction with spheronization time for extrudates containing coarse and fine grades of lactose processed by ram and cylinder extruders. (A) 1.0 mm diameter die; (B) 1.5 mm diameter die. (———) Fine lactose; (- - - - - -) coarse lactose; (●, ○) mean granule length; (■, □) mean granule width; (□, ○) cylinder extruder; (■, ●) ram extruder.

count for flow through a multiholed die by converting the total volumetric output to the output rate per hole. The intermittent nature of flow through the cylinder extruder must also be considered, i.e., flow only takes place over approx. 1/4 of each revolution, at the point of contact

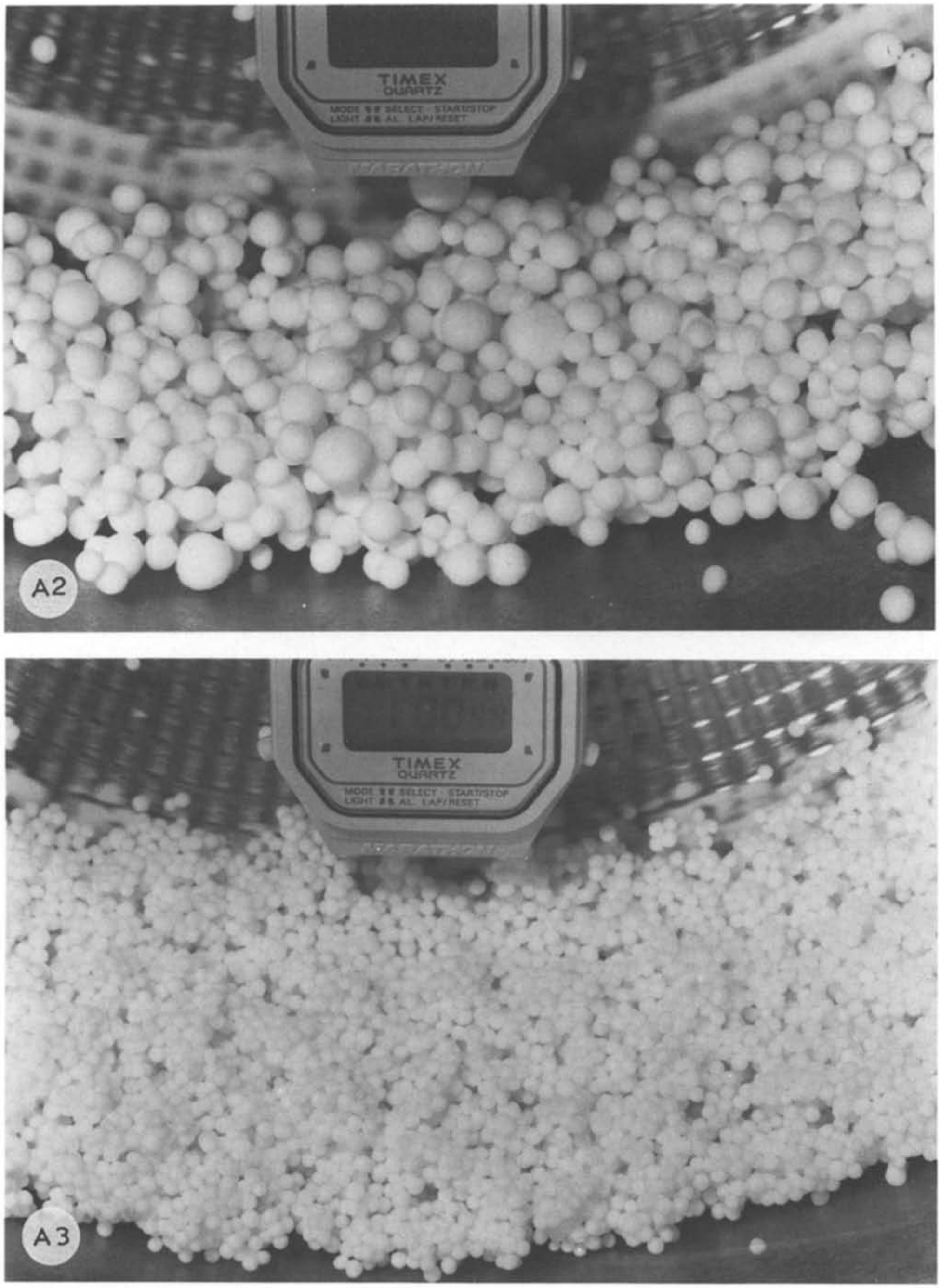

Fig. 3. Spheronization at 10 min residence time of extrudate containing coarse lactose processed by ram and cylinder extruders for dies of diameter (A) 1.0 mm and (B) 1.5 mm.

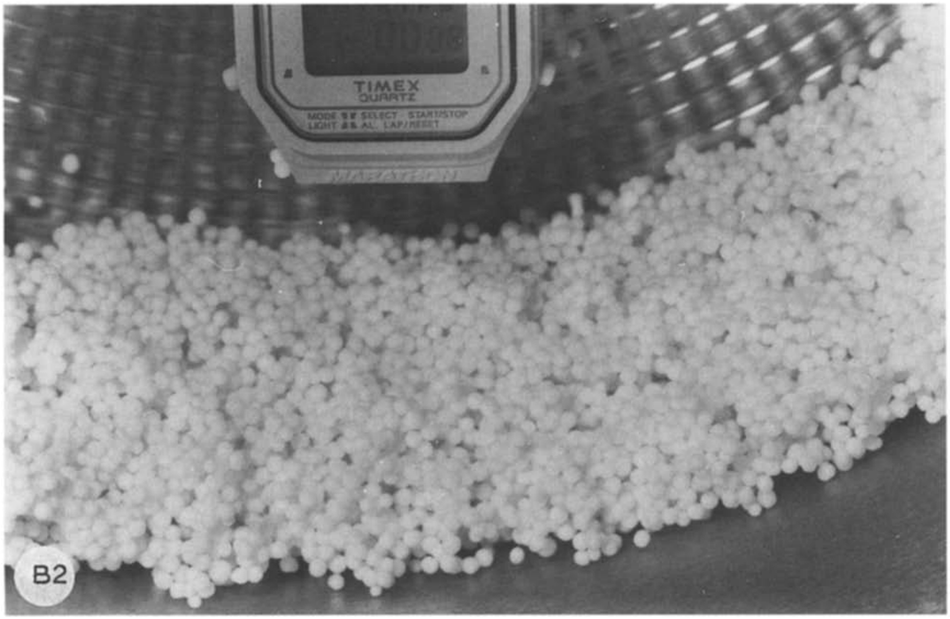

Fig. 3 (continued).

between the rollers. Thus, the flow rate is approx. 4.7×10^{-3} g s^{-1} $hole^{-1}$. The same volumetric output would be achieved on the ram extruder with the piston descending at 0.043 cm min^{-1} which is equivalent to a shear rate of 36 s^{-1} $hole^{-1}$ calculated from the equation:

$$(-dv/dr)_w = 4Q/\pi R^3$$

where $(-dv/dr)_w$ is the shear rate at the die wall (Wilkinson, 1960), Q denotes the volumetric flow rate and R is the die diameter.

If this is the case, the shear stress per die in the cylinder extruder, estimated from the shear stress-shear rate flow curves from the ram extrusion data according to Fielden et al. (1989), is approximately equal to the value obtained for the extrapolated yield stress of the wet powder mass (250 kN m^{-2}) as seen in Fig. 5. Similarly, the shear rate through the 1.5 mm diameter cylinder die is estimated at 22 s^{-1} $hole^{-1}$. The corresponding shear stress derived from extrusion through 1.5 mm diameter dies with a ram extruder is again close to the value of the yield stress of the material (130 kN m^{-2}) at that die diameter (Fielden, 1987). In other words, the cylinder extruder performs extrusion at low shear rates and at pressures close to the yield value of the wet powder mass.

The calculated shear rates for the cylinder dies are significantly lower than those provided by the ram extruder even when used with a low piston velocity of 10 cm min^{-1}, i.e., approx. 4000 s^{-1} for the 1.0 mm diameter die and 1200 s^{-1} for the 1.5 mm diameter die. An evaluation of the quality of the extrudate prepared from the wet powder masses containing coarse and fine lactose using a ram extruder was previously reported and it was shown that extrusion at these low shear rates would take place under conditions of forced flow (Fielden et al., 1989). This causes a moisture gradient between the extrudate and material in the reservoir and provides a poor quality extrudate of variable moisture content which is the cause of the agglomeration seen in Fig. 3. However, with the cylinder extrudate the converse appears to be true, i.e., the coarse and fine lactose extrudates produced are equivalent and both demonstrate controlled spheronization. Hence, the consistent quality of the extrudate achieved

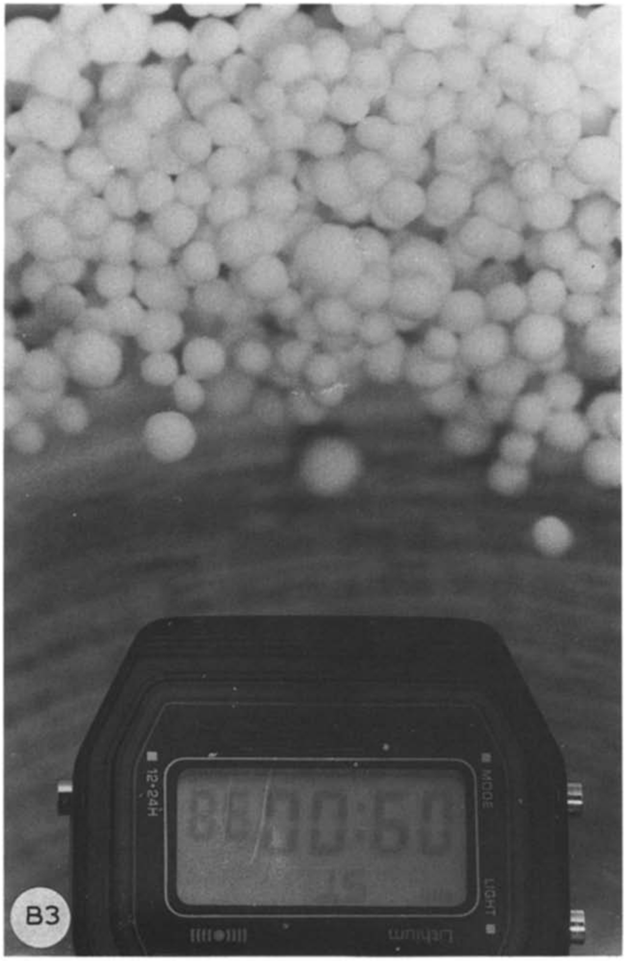

Fig. 3 (continued).

by both wet powder masses cannot be accounted for in terms of the rheological conditions (shear stresses and shear rates) encountered in the cylinder dies alone, and an additional explanation is necessary.

The cylinder extruder is an open system relying on mechanical force from the solid knurled roller to push the wet powder mass through the dies in the opposing cylinder. This arrangement provides a material reservoir in the form of a thin film of material adhering to the solid roller. Therefore, by comparison with the ram extruder, the consolidation stage of extrusion is either absent or coincides with the steady-state flow stage, since the material adhering to the roller is pushed directly through the die holes. The above mechanism achieves a higher total throughput rate than the ram extruder while generating considerably lower pressures (shear stresses) at the die wall. Consequently, the tendency to create a moisture gradient, or even a lubricating layer at the die wall, is greatly reduced. This process achieves a consistent extrudate regardless of the different particle size of lactose used. Hence the product will spheronize in a controlled manner.

In contrast, the ram extruder is a closed system, the reservoir consisting of a thick plug of material, and extrusion at the low rates of shear encountered in the cylinder extruder results in an extended consolidation stage. This stage in the extrusion cycle has previously been identified as the most critical period since migration of water from the wet powder mass in the reservoir is initiated at this point prior to extrusion (Fielden et al., 1989). Extrusion at shear rates below 16500 s^{-1} for 1.0 mm diameter dies and 5000 s^{-1} for 1.5 mm diameter dies resulted in a moisture gradient while at higher shear rates, above 35000 and 10000 s^{-1} for 1.0 and 1.5 mm diameter dies, respectively, a consistent extrudate was produced.

Conclusions

This study has demonstrated that extrudates produced on the ram and cylinder extruders are not always equivalent. Wet powder masses containing either the coarse or the fine particle sizes of lactose produced good-quality extrudates from the cylinder extruder whereas this was not so for extrudate produced by the ram extruder. Thus, agglomeration that occurred with the coarse lactose extrudate from the ram extruder did not take place when the material was processed by the cylinder extruder. This was attributed to a fundamental difference in the method by which the wet powder mass is processed in the two extrusion systems.

Interpretation of the shear stress-shear rate curves from the ram extruder (Fielden, 1987; Fielden et al., 1989) has been useful in predicting the extrusion conditions in the cylinder extruder and indicated that it operates at low shear rates

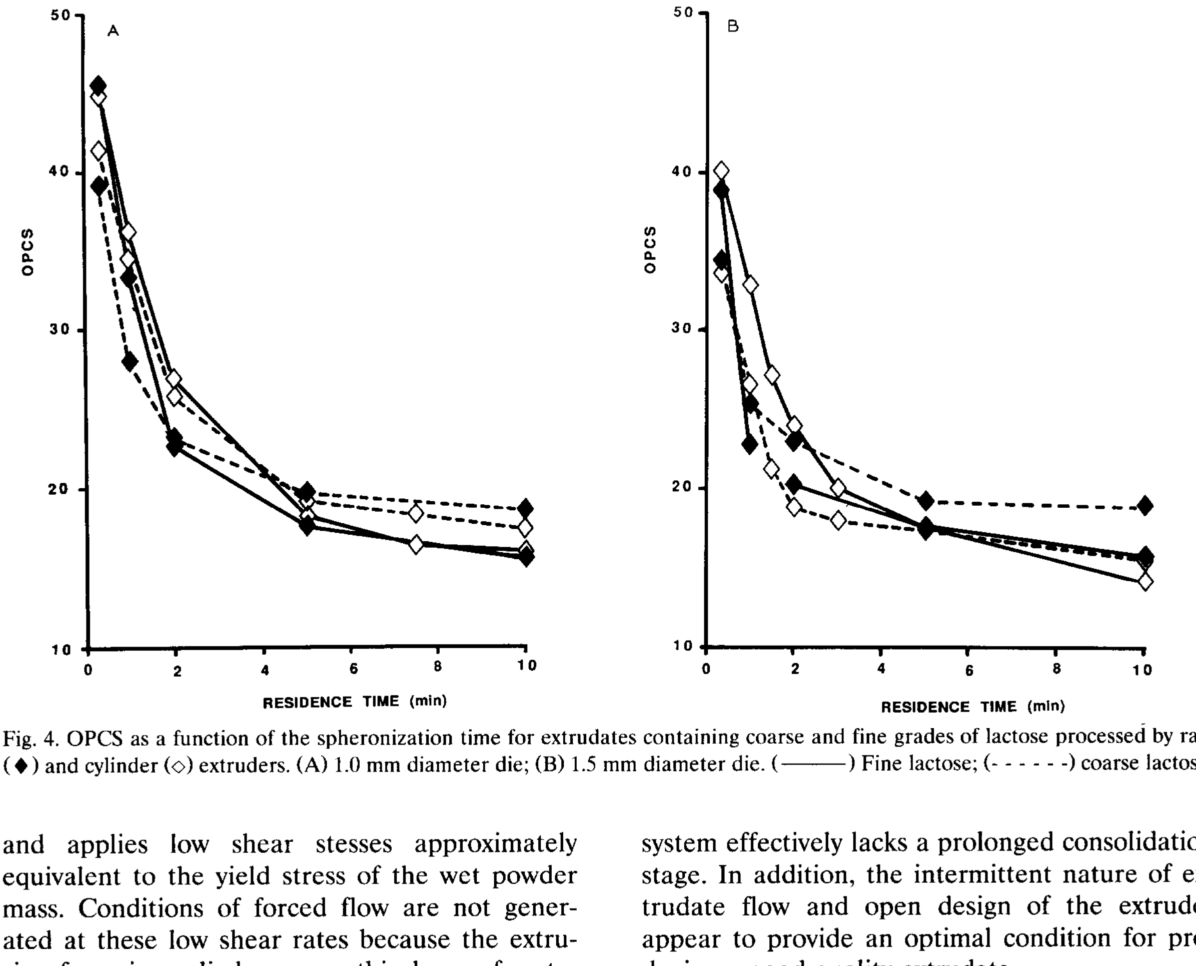

Fig. 4. OPCS as a function of the spheronization time for extrudates containing coarse and fine grades of lactose processed by ram (♦) and cylinder (◇) extruders. (A) 1.0 mm diameter die; (B) 1.5 mm diameter die. (———) Fine lactose; (- - - - - -) coarse lactose.

and applies low shear stesses approximately equivalent to the yield stress of the wet powder mass. Conditions of forced flow are not generated at these low shear rates because the extrusion force is applied across a thin layer of material immediately above the die, such that the system effectively lacks a prolonged consolidation stage. In addition, the intermittent nature of extrudate flow and open design of the extruder appear to provide an optimal condition for producing a good-quality extrudate.

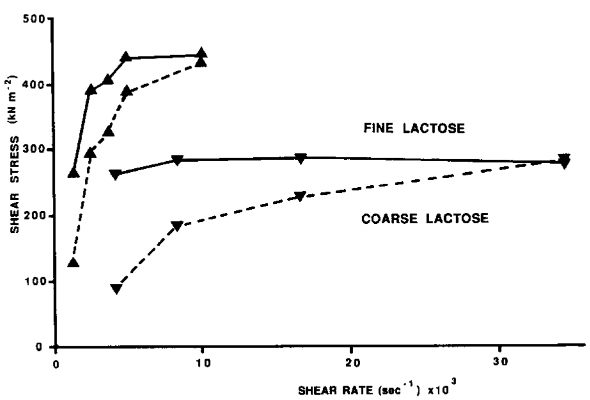

Fig. 5. Influence of lactose particle size on the shear stress vs shear rate for dies of diameter 1.0 mm (▼) and 1.5 mm (▲). (———) Fine lactose; (- - - - - -) coarse lactose.

Although the ram and cylinder extrudates are not equivalent, the ram extruder is nevertheless valuable as a small-scale technique for assessment of the flow and spheronization properties of particular mixtures. The reduced sensitivity of a proposed formulation to extrusion and spheronization variables indicates that processing on a larger scale is likely to succeed if it can be processed by ram extrusion. Formulations which require critical processing conditions on a small scale are more likely to fail at various stages on scale up.

References

Anderson, A.H. and Newton, J.M., The influence of moisture content and particle size of barium sulphate on the extrusion properties of mixtures with microcrystalline cellulose. *Rheology of Food, Pharmaceutical, and Biological Materials*, Elsevier, Amsterdam, 1990, pp. 258–267.

Baines, D., Boutell, S.L. and Newton, J.M., The influence of moisture content on the preparation of spherical granules of barium sulphate and microcrystalline cellulose. *Int. J. Pharm.*, 69 (1991) 233–237.

Benbow, J.J. and Ovenston, A., Effects of die geometry on extrusion. *Trans. Br. Cer. Soc.*, 67 (1968) 543–567.

Chapman, S.R., Rowe, R.C. and Newton, J.M., Characterization of the sphericity of particles by the one plane critical stability. *J. Pharm. Pharmacol.*, 40 (1988) 503–505.

Conine, J.W. and Hadley, H.R., The preparation of small solid pharmaceutical spheres. *Drug Cosm. Ind.*, 106 (1970) 38–41.

Fielden, K.E., PhD Thesis, Extrusion and spheronization of microcrystalline cellulose and lactose mixtures, University of London (1987).

Fielden, K.E., Newton, J.M. and Rowe, R.C., The effect of lactose particle size on the extrusion properties of microcrystalline cellulose-lactose mixtures. *J. Pharm. Pharmacol.*, 41 (1989) 217–221.

Fielden, K.E., Newton, J.M. and Rowe, R.C., The influence of lactose particle size on spheronization of extrudate processed by a ram extruder. *Int. J. Pharm.* 81 (1992) 205–224.

Harrison, P.J., Newton, J.M. and Rowe, R.C., The application of capillary rheometry to the extrusion of wet powder masses. *Int. J. Pharm.*, 35 (1987) 235–242.

Reynolds, A.D., A new technique for the production of spherical particles. *Manuf. Chem.*, 41 (1970) 40–44.

Wilkinson, W.L., *Non-Newtonian Fluids*, Pergamon, London, p. 33.