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# The influence of process variables on the preparation and properties of spherical granules by the process of extrusion and spheronisation

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**Abstract**

The influence of spheronisation process variables of time, load, speed of rotation and plate texture on the properties of size, shape and density of granules has been assessed with a standard extrudate produced by a cylinder extruder. It was found that optimum conditions of load and speed of rotation existed in that too low a speed produced no significant shape changes in the extrudate, while too high a speed resulted in a size reduction of the particles. A low load appeared to give poor particle/particle interaction while a high load produced poor plate/particle interaction. Increase in the length of the die in the cylinder extruder resulted in the inability to spheronise the extrudate under what had been previously optimum conditions of speed and load. No such loss of spheronisation performance occurred with processing of extrudate from two lengths of die of a ram extruder on a spheroniser with different plate textures. The granules produced, however, were significantly larger than those obtained for the same wet mass processed by the cylinder extruder.

*Keywords:* Cylinder extruder; Granule density; Median particle diameter; Mean particle length; Mean particle width; One plane critical stability (roundness); Plate texture; Ram extruder

## 1. Introduction

There are several studies which investigate the influence of process variables on the product performance associated with the process of extrusion (Woodruff and Nuessle, 1972; Malinowski and Smith, 1975; O'Connor and Schwartz, 1989; Bianchini et al., 1991; Eerikäinen, 1991). The findings could be specific not only to a formulation but also to a particular extruder. Our experience is that the production of a standard extrudate involving compression in the extrusion process removes many of the sensitivities to process variables reported in the literature. Nevertheless, even for a standard extrudate, the process variables can influence the final product. To identify which these are, a standard formulation, which has been shown to give a good uniform product


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when processed under optimum conditions (Fielden et al, 1992; Newton et al., 1992), has been evaluated using pilot scale equipment.

## 2. Materials and methods

### 2.1. Materials

The basic formulation consisted of microcrystalline cellulose, Avicel PH 101 (FMC Corp., Philadelphia, USA), lactose (extra fine grade, Unigate, UK) and distilled water.

### 2.2. Preparation of extrudate

The formulation consisted of equal parts of microcrystalline cellulose and lactose with a quantity of water equivalent to 1.2-times that of the microcrystalline cellulose. The powders were dry blended in a planetary mixer (Model AE 200 Hobart, London, UK) for 5 min. The water was gradually added over a period of 1 min and mixing was continued for 10 min.

Extrudate was produced by two methods. The first involved passing the wet powder mass between the rolls of a rotary cylinder extruder (Model GA 65 Alexanderwerk, Germany). The diameter of the dies was 1 mm and two different cylinder wall thicknesses were used, 3.05 and 5.46 mm. The second extruder was the ram extruder described by Harrison et al. (1985) fitted with a 1 mm diameter die with a length of 4 mm, or 10 mm. The ram extruder was placed below the cross-head of a servo-hydraulic press (Model M1000/RE, Dartec Ltd, Stourbridge, UK) via a calibrated load cell. The cross-head was operated at a constant rate of 3 mm $s^{-1}$.

### 2.3. Preparation of spherical granules – spheronisation

Spheronisation was undertaken with a 21.2 cm plate spheroniser (C.B. Caleva, Sturminster Newton, Dorset, UK), fitted with a plate cut with either a radial or a cross-hatched surface. The plate was allowed to operate at a known speed for a fixed time after addition of a known mass of extrudate. The product was dried at 60°C in an oven for 12 h.

### 2.4. Evaluation of spherical granules

The particle size of the granules was determined in two ways. A sieve analysis with a nest of woven wire test sieves to give a $\sqrt{2}$ progression of sizes from 500 to 2000 μm on a mechanical sieve shaker (Endecott Ltd, London, UK). Such analysis gives a particle size distribution by weight. A median value was taken from the graph of cumulative % oversize which in this instant reflects the width of the particle.

A second method was to provide a number analysis based on a projected area, which corresponds to the maximum length of the granules. This was undertaken with a Hiac particle counter (Hiac Criterion Model PC 320; Hiac House, London, UK). Prior to analysis, a sample of approx. 1000 granules was removed from the batch by a spinning riffler (Microscal Ltd, London, UK). These were fed by a Hiac dry sample feed into the sensing zone. The instrument was operated to give six channels providing a $\sqrt{2}$ progression of sizes between 500 and 1400 μm.

A count of 1000 particles was undertaken and the numbers in each channel obtained. These were transformed into a cumulative frequency distribution and the median value determined.

The particle density of the granules was determined with a glass pycnometer as modified for use with granules by Strickland and Nuessle (1956).

The roundness was assessed by the one plane critical stability (OPCS) method described by Chapman et al. (1988) using 46 granules from the most frequently occurring size fraction.

## 3. Results and discussion

The influence of a range of variables was assessed as a function of the residence time of the extrudate on the plate.

### 3.1. Influence of plate speed

For a fixed load of 300 g of the standard extrudate, the influence of the plate speed on the median number and weight diameters, particle density and OPCS is given in Fig. 1. At speeds as low as 400 rpm it is apparent that the extrudate does not shorten and only increases in width marginally (Fig. 1a). There is no rounding (Fig. 1c) and only a slight increase in granule density (Fig. 1b). Thus, at this speed there is very little spheronisation even after 20 min on the plate.

Doubling the speed to 800 rpm reduces the length of the granules, even by 1 min (Fig. 1a) and after 2 min there is considerable densification (Fig. 1b). Rounding takes a little longer but

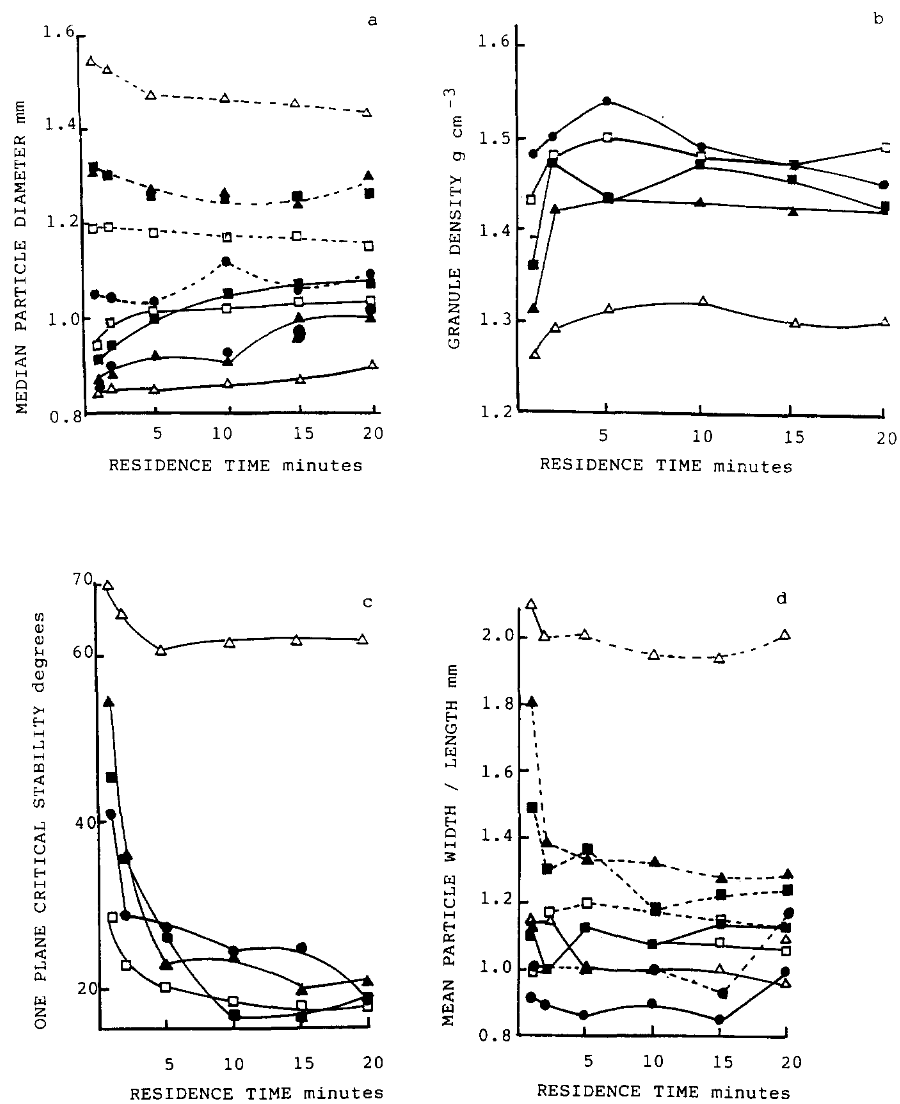


Fig. 1. Influence of residence time and plate speed on (a) the median weight (continuous line) and number (broken line) diameter, (b) mean particle density, (c) one plane critical stability of the granules within the modal sieve fraction and (d) the mean length (broken line) and width (continuous line) of particles within the modal sieve fraction. Spheronisation at (△) 400, (▲) 800, (■) 1000, (□) 1500, and (●) 2500 rpm of 300 g of extrudate produced on a cylinder extruder with a 1 mm diameter die and 3.05 mm length on a radial plate texture.

by 5 min the particles are well rounded and only slight further rounding takes place between this time and 20 min. This seems to be a critical machine feature for spheronisation. Operating the spheroniser at 1000 rpm produces a similar product to that at 800 rpm although there does

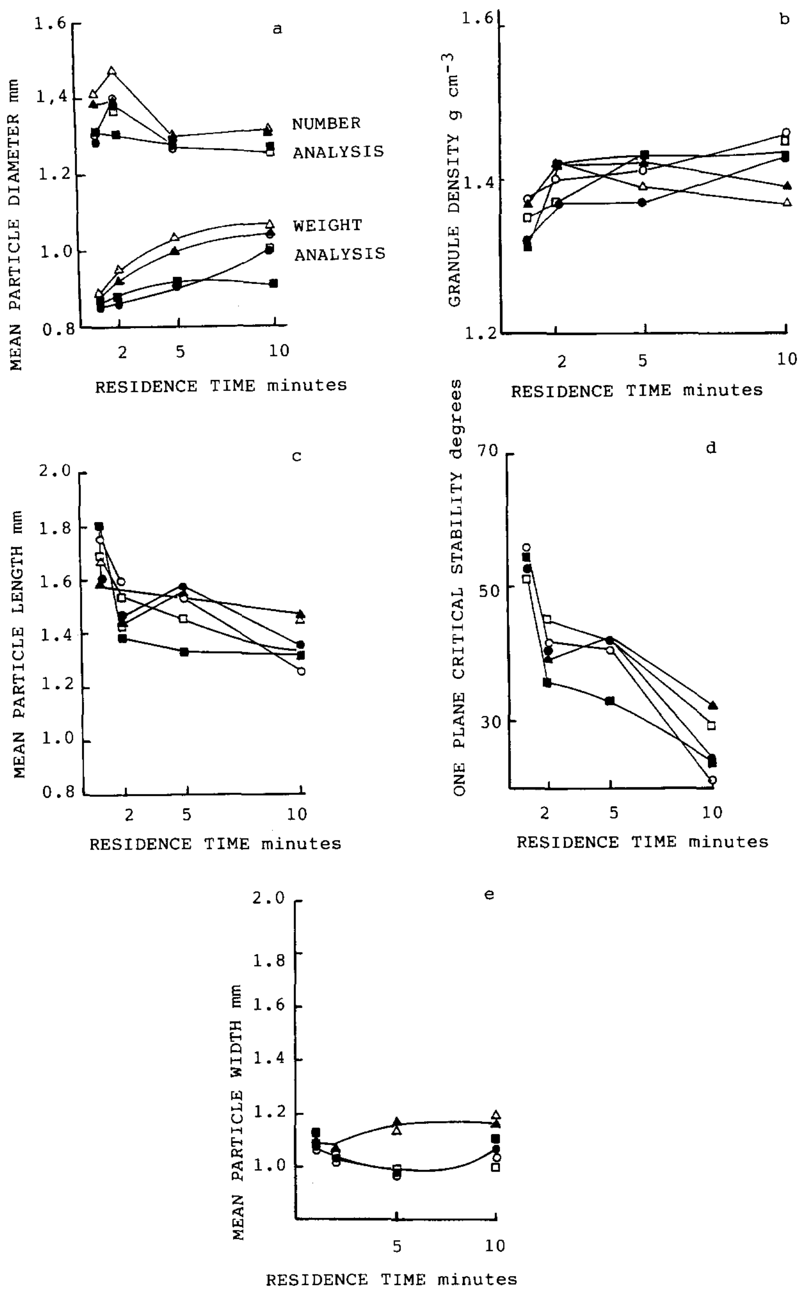


Fig. 2. Influence of residence time and load of extrudate on (a) the median weight and number diameter, (b) mean particle density, (d) one plane critical stability of the granules within the modal sieve fraction and (d) the mean length and (e) width of particles within the modal sieve fraction. Spheronisation at (△) 50, (▲) 100, (■) 300, (□) 500, (●) 750 rpm of 1000 g of extrudate produced on a cylinder extruder with a 1 mm diameter die and 3.05 mm length on a radial plate texture rotating at 800 rpm..

appear to be a larger value for width (Fig. 1a) and an improved roundness after 10 min (Fig. 1c), while densification is similar. With the high speeds of 1500–2500 rpm, there is a further reduction in particle length (Fig. 1a), increase in width (Fig. 1a) and the rounding occurs more rapidly. Granules prepared at 2500 rpm are less round, and generally smaller. The granule is, however, quite dense.

Thus, the spheroniser will produce a reasonably standard product within 10 min which is stable over a range of rotational speeds from 800 to 1500 rpm, which should reflect an adequate flexibility of operating conditions.

Further confirmation of the effect of processing variables on individual granules can be observed by examining the mean particle length and width of those granules within the modal sieve fraction (Fig. 1d). Such measurements are made when the determination of the OPCS values is made. This clearly shows that at 400 rpm the extrudates remain relatively unchanged by the

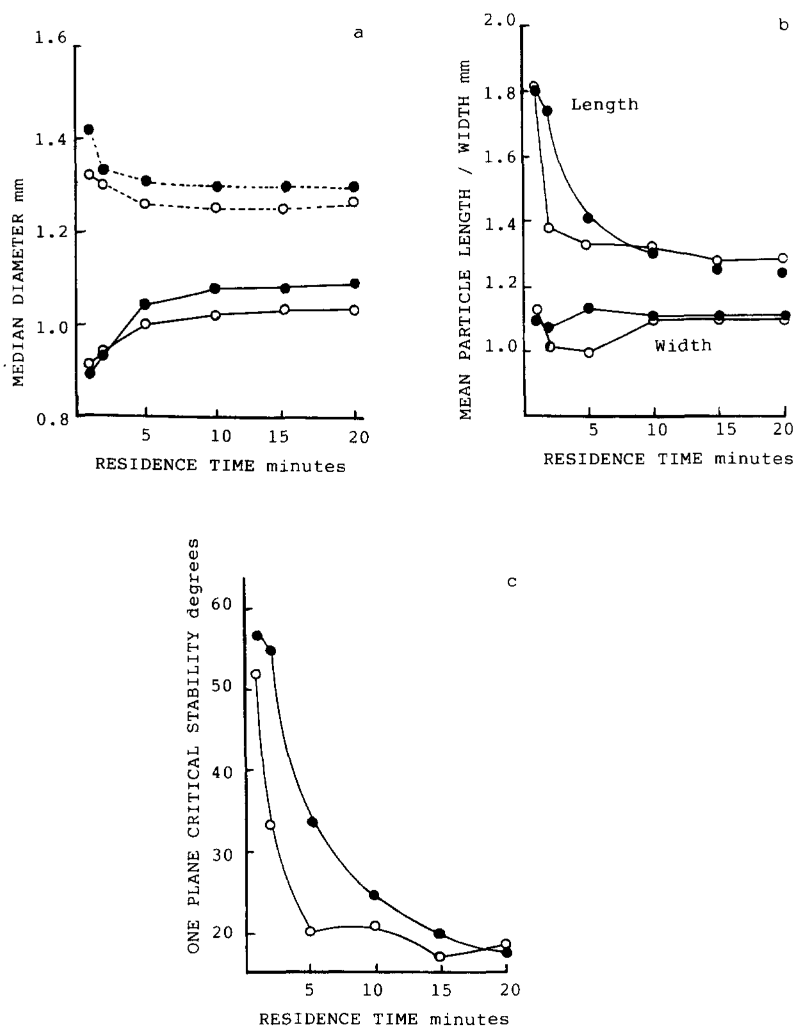


Fig. 3. Influence of spheronisation plate texture on (a) median weight (continuous line) and number (broken line) diameter, (b) mean length and width of granules within the modal sieve fraction, (c) one plane critical stability of the granules within the modal sieve fraction. 300 g of extrudate from a cylinder extruder (1 mm diameter die, 3.05 mm length) spheronised for 10 min at 800 rpm on a (○) cross-hatched plate, and a (●) radial plate.

process. The most rapid approach to equilibrium dimensions occurs at 800 and 1000 rpm, smaller granules with correspondingly higher density being formed at the higher speeds.

### 3.2. Influence of load

The standard extrudate was added to the spheroniser in weights ranging from 50 to 1000 g for periods between 1 and 10 min at a speed of 800 rpm. The small loads of 50 and 100 g produce granules of the greatest length and diameter (Fig. 2a) and which eventually have the lowest density (Fig. 2b) and least spherical form (Fig. 2d), The higher loads of 750 and 1000 g eventually produce round granules (Fig. 2d) but the process takes longer than for the loads of 300 and 500 g. These results are confirmed by consideration of

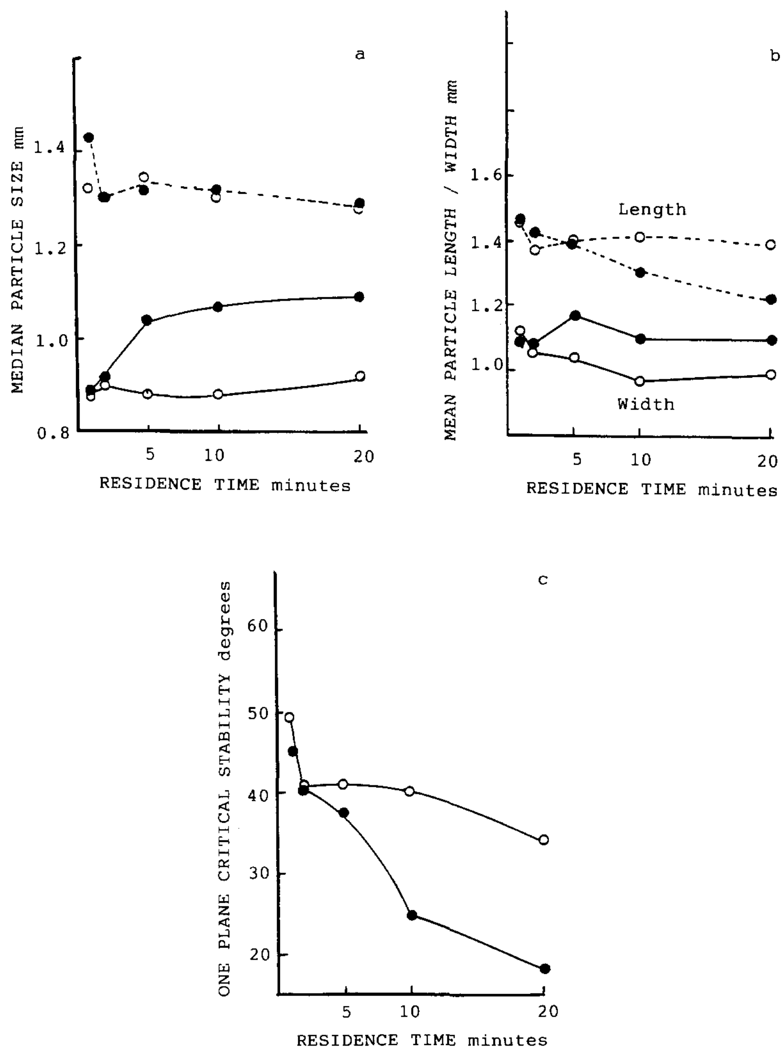


Fig. 4. (a) Median weight (continuous line) and number (broken line) diameter, (b) mean length (continuous line) and width (broken line) of granules within the modal sieve fraction, and (c) one plane critical stability of the granules within the modal sieve fraction of 300 g of extrudate produced with a 1 mm diameter die and a 5.46 mm length by a cylinder extruder, spheronised on a (○) cross-hatched, and a (●) radial plate spheroniser at 800 rpm.

the dimensions of the particles withdin the modal sieve fraction (Fig. 2c and e). In fact, 300 g appears to be optimum load size at this speed as the granules approach the spherical form more rapidly. It would appear that at too low a load there are insufficient granules to interact with each other and granule plate interaction dominates, while at the higher loads, there are too many granules to interact with the plate and granule/granule interaction dominates.

### *3.3. Influence of plate texture, die length and extruder type*

The spheronisation process depends on the friction between particles and the plate to ensure the continued motion of the particles. The design of the plate could therefore be of fundamental importance. For the standard extrudate, there appears to be little difference in the products produced with the optimum load of 300 g operat-

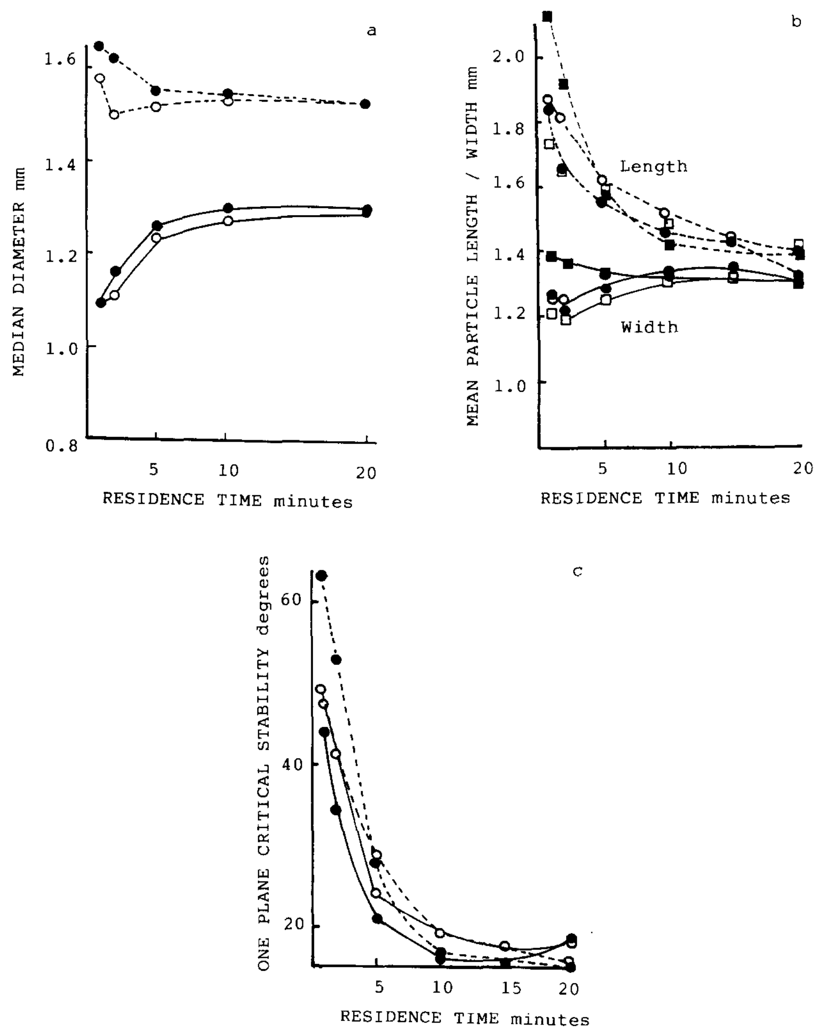


Fig. 5. (a) Median weight (continuous line) and number (broken line) diameter, (b) mean length (broken line) and width (continuous line) of particles within the modal sieve fraction, (c) one plane critical stability of the modal sieve fraction of granules produced from extrudate from a ram extruder with a die length of 4 mm (continuous line) and 10 mm (broken line) length. Spheronisation of 300 g of extrudate at 800 rpm with a (○) cross-hatched or radial (●) plate.

ing at the optimum rotational speed of 800 rpm. Thus, the changes in median width and length (Fig. 3a), mean width and length (Fig. 3b) and OPCS (Fig. 3c) of the granules within the modal sieve fraction are all comparable.

If the length of the die of the cylinder is increased to produce an extrudate through a 5.46 mm as opposed to a 3.05 mm length die, then the two plates do not perform in the same way (Fig. 4). Here the cross-hatched plate produces granules where median length and width are further apart than in those produced with the radial plate (Fig. 4a and b) and OPCS data (Fig. 4c) show clearly that these granules are not round even after 20 min of processing.

To check if the influence of plate texture was further dependent on the extrudate quality, extrudate was produced by a ram extruder through dies of 1 mm diameter with dies of 4 and 10 mm lengths. These results clearly show that the two types of plates produce granules which are equivalent in terms of median width and length (Fig. 5a), mean width and length of particles within the modal sieve fraction (5b) and equivalent sphericity of granules within the modal sieve fraction (Fig. 5c). Hence, there does not appear to be an influence of die length for extrudate produced by the ram extruder. Comparisons of the median weight and number analysis (Fig. 1a and 5a) and the mean length and width in the largest sieve fraction (Fig. 1d and Fig. 5b) show that the granules prepared by the ram extruder are generally larger than those produced by the cylinder extruder, whether the die length of the cylinder was 3.05 or 5.46 mm. This implies that the extrudate produced by the two types of extruders was not equivalent as reported previously (Fielden et al., 1992). In terms of ability to form round granules, there is little to choose between the two types of extrudate; both form well-rounded granules which do not change shape significantly once they have rounded. This indicates that the water is contained within the granules as they are being processed, and does not migrate to the surface to allow agglomeration (Fielden et al., 1992). The inability to round, of the extrudate from the longer die length cylinder extrudate, appears to be associated with the resistance of the extrudate to decrease its length and increase its width during processes, presumably due to the extrudate being more rigid in structure.

## 4. Conclusion

The most important feature to ensure a satisfactory transformation of an extrudate produced from a cylinder type of extruder into spherical granules is to operate the spheroniser at a critical speed and with sufficient load to provide appropriate interaction between particle/spheroniser plate and particle/particle. Overloading the plate will require a longer time course of the process while underloading reduces the efficiency. Low speeds fail to provide the necessary interactions to provide rounding of the particles. However, over a wide range of conditions a satisfactory product can be produced, unlike reports from other studies which have indicated high sensitivity to the conditions of spheronisation. This appears to be associated with the poor quality of the extrudate produced by screen extruders used extensively in these studies. The design of the plate appears to have only marginal influence on the ability to spheronise, but it may have a potential to influence less robust formulations.

## References

Bianchini, R., Bruni, G., Gazzaniga, A. and Vecchio G., Influence of extrusion spheronisation processing on the physical properties of d-indobrufen pellets containing pH control. *10th Pharmaceutical Technology Conference*, Bologna, Italy, 1991, pp. 577–592.

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

Eerikäinen, S., Effect of spheronisation on some properties of uncoated and coated granules containing different kinds of fillers. *Int. J. Pharm.*, 77 (1991) 89–106.

Fielden, K.E., Newton, J.M. and Rowe, R.C., A comparison of the extrusion and spheronisation behaviour of wet powder masses processed by a ram and a cylinder extruder. *Int. J. Pharm.*, 81 (1992) 225–232.

Harrison, P.J., Newton, J.M. and Rowe, R.C., The characterisation of wet powder masses suitable for extrusion/spheronisation. *J. Pharm. Pharmacol.*, 37 (1985) 686–691.

Malinowski, H.J. and Smith, W.E., Use of factorial design to evaluate granulations prepared by spheroniser. *J. Pharm. Sci.*, 64 (1975) 1088–1092.

Newton, J.M., Chow, A.K. and Jeewa, K.B., The effect of excipient source on spherical granules made by extrusion/spheronisation. *Pharm. Tech. Int.*, 4(8) (1992) 52–59.

O'Connor, R.E. and Schwartz, J.B., Extrusion and spheronisation technology. In Ghebre Selassie (Ed.), *Pharmaceutical Pelletisation Technology*, Dekker, New York, 1989, Ch. 7.

Strickland, C.W. and Nuessle, N.O., The physics of tablet compression: XI determination of porosity of tablet granulations. *J. Am. Pharm. Assoc. Sci. Ed.*, 45 (1956) 482–486.

Woodruff, C.W. and Nuessle, N.O., Effect of processing variables on particles obtained by extrusion-spheronisation processing. *J. Pharm. Sci.*, 61 (1972) 778–790.