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The influence of moisture content on spheronization of extrudate processed by a ram extruder

K.E. Fielden [a], J.M. Newton [b] and R.C. Rowe [c]

[a] *The Wellcome Foundation Ltd, Temple Hill, Dartford DA1 5AH (UK),* [b] *The School of Pharmacy, University of London, Brunswick Square, London WC1N 1AX (UK) and* [c] *ICI Pharmaceuticals, Hurdsfield Industrial Estate, Macclesfield SK10 2NA (UK)*

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Summary

The presence of water is an essential feature of formulations containing mirocrystalline cellulose (MCC) for the preparation of spherical granules by the process of extrusion/spheronisation. The current work provides further proof of this observation. Formulations consisting of MCC and either a coarse (118.0 μm) or a fine grade (18.0 μm) of lactose mixed with two levels of water have been examined as they spheronise and after collection and drying. The shape changes on the plate, plus the size and shape changes, as a function of spheronisation time, show that the mixtures containing fine particle size will form good spheres at either 33 or 37% water content, but the mixtures containing the coarse particle size will only form controlled size spheres at 33% moisture content. The results were found to be equivalent for both 1.0 and 1.5 mm extrudates. The effect can be related to the mobility of the water in the different packing structures produced by the different particle sizes of lactose.

Introduction

Using the technique of ram extrusion, Fielden et al. (1989, 1992a) have demonstrated that the particle size of lactose (used as a water soluble drug model) in a mixture with microcrystalline cellulose and water influences the extrusion rheology of that mixture and the subsequent ability of the extrudate to satisfactorily spheronize. Steady state extrusion, necessary for production of a consistent uniform extrudate, was achieved with a fine particle size grade of lactose. This extrudate underwent controlled spheronization producing spheroids within a narrow size range. Increasing the lactose particle size resulted in predominantly forced flow and high extrusion pressures producing a poor quality extrudate of variable moisture content. The system behaved as though it was over wetted and formed large agglomerates when spheronized. Using a pressure membrane technique, Fielden et al. (1992b) have attributed this phenomenon to the increased pore diameter of the mixture containing coarse lactose in which the movement of liquid through the wet powder mass is facilitated. The objective of this study is to determine whether the mobility of this

Correspondence to: J.M. Newton, The School of Pharmacy, University of London, Brunswick Square, London WC1N 1AX, U.K.

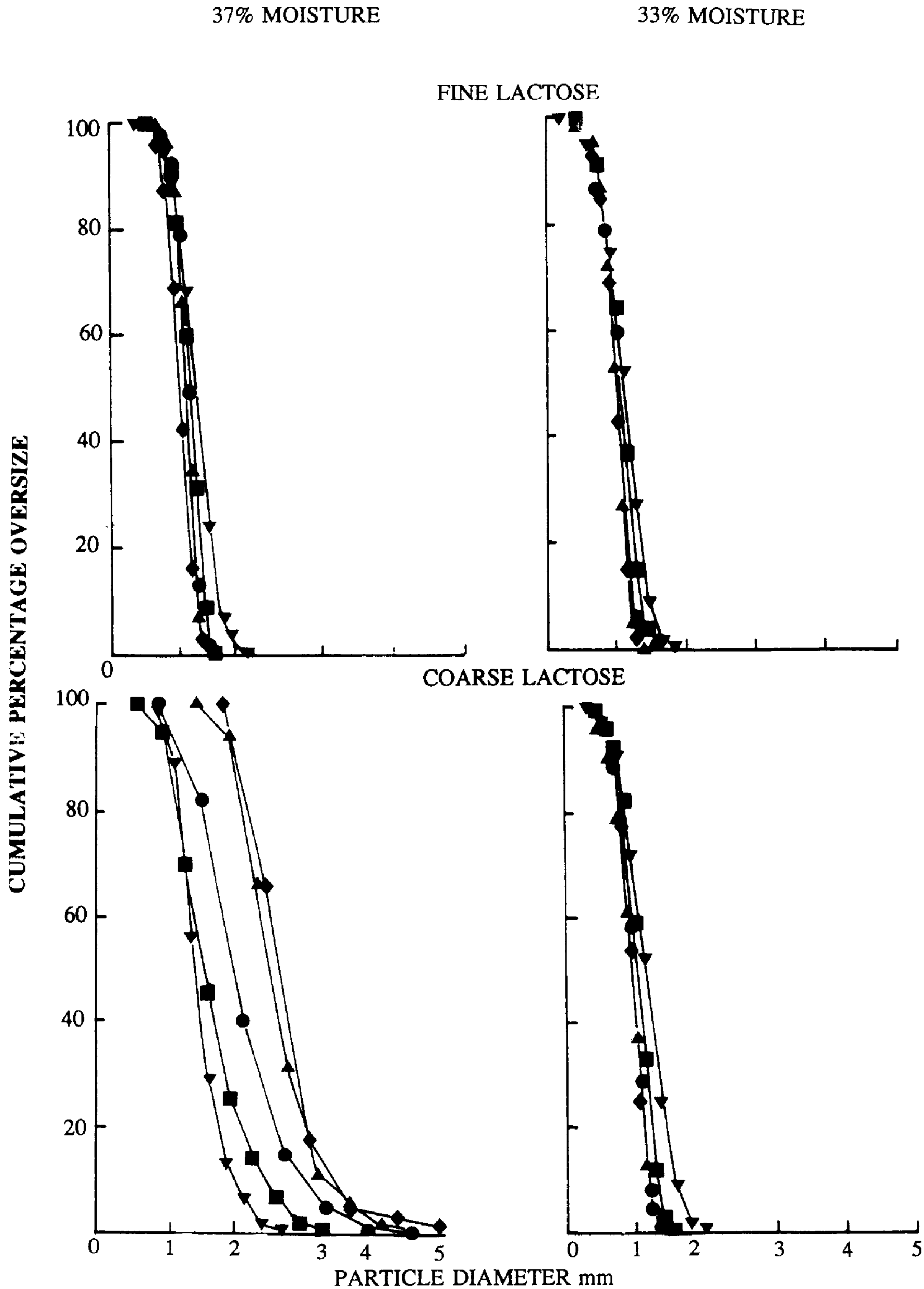

37% MOISTURE
33% MOISTURE
FINE LACTOSE
COARSE LACTOSE
CUMULATIVE PERCENTAGE OVERSIZE
100
80
60
40
20
0
0
1
2
3
4
5
PARTICLE DIAMETER mm

TABLE 1

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

Die diameter	Lactose grade	20 s spheronization				10 min spheronization			
		37.5% moisture		33.3% moisture		37.5% moisture		33.3% moisture	
		Number	Weight	Number	Weight	Number	Weight	Number	Weight
1.0 mm	fine	1.0–1.4	1.0–1.1	1.0–1.3	1.0–1.1	0.9–1.1	1.1–1.3	0.9–1.1	1.1–1.3
	coarse	1.2–1.7	1.1–1.6	1.0–1.4	1.0–1.2	2.3–3.0	2.5–4.3	0.9–1.1	1.2–1.4
1.5 mm	fine	1.6–2.0	1.5–1.6	1.3–1.8	1.5–1.6	1.7–1.8	1.6–1.9	1.1–1.5	1.6–1.9
	coarse	1.5–1.9	1.5–1.7	1.3–1.8	1.5–1.7	2.2–3.0	2.7–4.5	1.1–1.5	1.5–2.0

TABLE 2

The effect of moisture content and lactose particle size on the percentage of granules within the largest sieve fraction as a function of the spheronization time: (A) 1.0 mm and (B) 1.5 mm diameter extrudate

	Time (min)		Fine lactose		Coarse lactose	
		Moisture content:	33.3%	37.5%	33.3%	37.5%
		Sieve diameter:	1.18 mm	1.18 mm	1.18 mm	2.80 mm
(A) 1.0 mm	0.3		33.5%	6.1%	13.7%	0.0%
diameter	1.0		14.1%	29.4%	35.8%	5.8%
extrudate	2.0		24.3%	48.7%	49.0%	21.0%
	5.0		48.0%	65.9%	61.6%	39.9%
	10.0		63.8%	68.6%	70.3%	38.9%
(B) 1.5 mm		Moisture content:	33.3%	37.5%	33.3%	37.5%
diameter		Sieve diameter:	1.70 mm	1.70 mm	1.70 mm	2.36 mm
extrudate						
	0.3		1.8%	12.4%	15.4%	1.2%
	1.0		11.2%	33.8%	22.0%	6.9%
	2.0		21.3%	41.4%	27.9%	21.5%
	5.0		30.1%	42.2%	43.2%	17.5%
	10.0		53.5%	45.9%	51.5%	32.8%

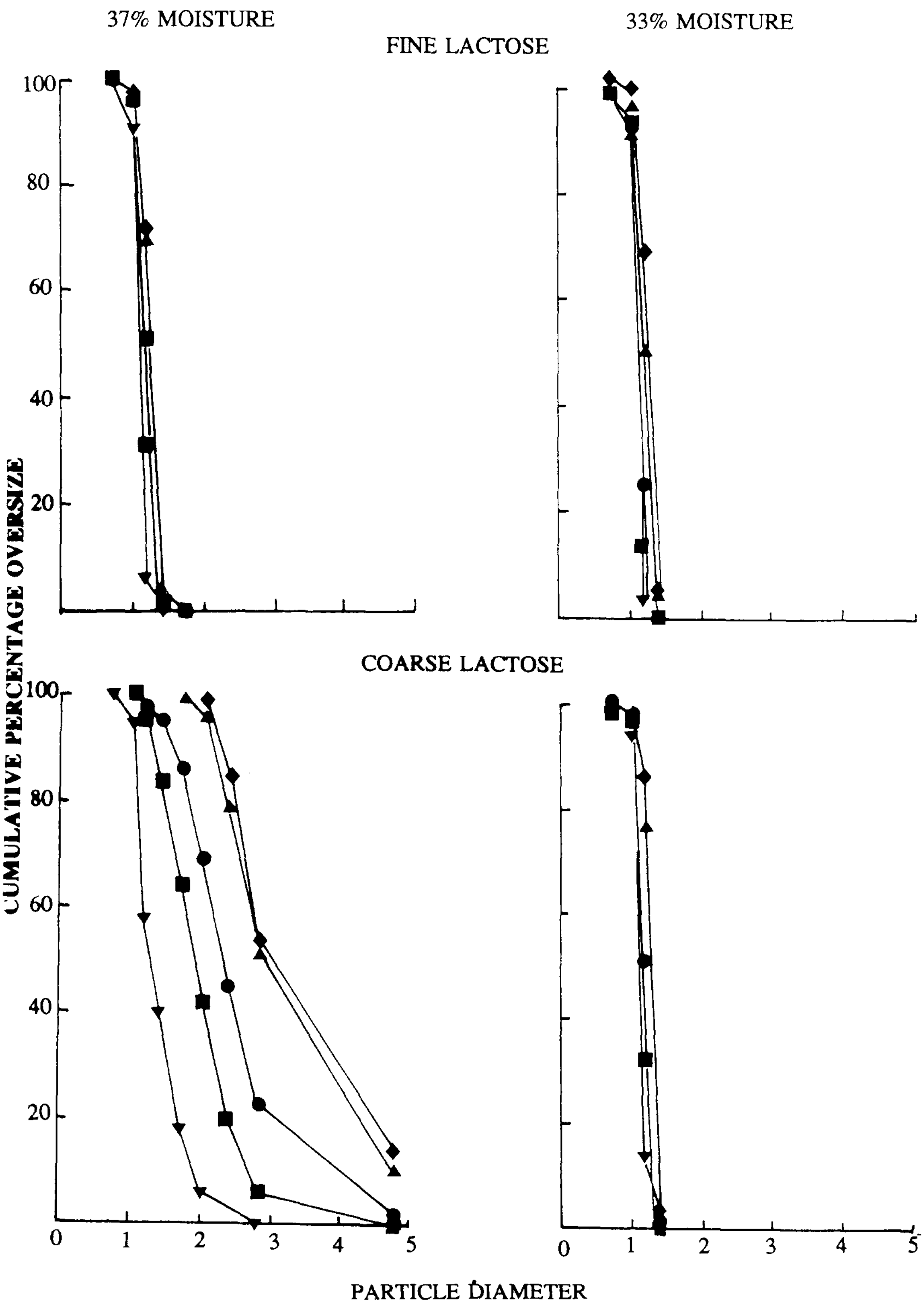
water and hence, the resultant tendancy of the extrudate to agglomerate, can be restricted by reducing the moisture content of the wet powder mass from 37.5 to 33.3% of the total weight.

Materials and Methods

The wet powder mass consisted of microcrystalline cellulose, lactose and 33.3% w/w water.

Fig. 1. The effect of moisture content and lactose particle size on the size distribution of granules as a function of the spheronization time for 1.0 mm diameter extrudate. Spheronization time (min): 0.3 (▼), 1.0 (■), 2.0 (●), 5.0 (▲), 10.0 (♦). (A) Number analysis. (B) Weight analysis.

Fig. 1 (continued).


37% MOISTURE
33% MOISTURE
FINE LACTOSE
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CUMULATIVE PERCENTAGE OVERSIZE
PARTICLE DIAMETER
0
20
40
60
80
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1
2
3
4
5

The materials and extrusion-spheronization procedures utilized have been described previously for the same mixture containing 37.5% w/w water (Fielden et al., 1992a). The microcrystalline cellulose used was Avicel PH101 (FMC Corp., U.S.A.) and the lactose (Dairy Crest, U.K.) was either a fine grade with median particle size 18.0 ± 3.0 μm (equivalent spherical diameter by image analysis, Quantimet Q720) or a coarse grade with median diameter 117.0 ± 1.5 μm (sieve analysis). The wet powder mass was made by mixing the microcrystalline cellulose and lactose in equal quantities with a planetary mixer (Hobart Model A200) and adding water to a moisture content of 33.3% w/w. All mixtures were equilibrated in sealed polythene bags for at least 12 h prior to extrusion. Smooth extrudate of 1.0 and 1.5 mm diameter was prepared using the ram extruder described by Harrison et al. (1987) with dies of length to radius ratio of 8 and cross-head velocities of 10 cm min^{-1}. The extrudate was spheronized in 200 g batches for durations of 20 s, 1, 2, 5 and 10 min using a 22.5 cm radial hatched plate spheronizer (GB Caleva Ltd, U.K.) rotating at 1000 rpm. The granules were dried to constant weight in a fluid bed dried (PRL Engineering Ltd, U.K.) at 60°C for 30 min. The granules were characterized in terms of their size and shape as follows. The batch weight and number size distributions were obtained by sieving and by image analysis (Quantimet Q720), respectively, and from these the number and weight median diameters were determined. The mean particle length and width and 'one plane critical stability' (OPCS) of the most frequently occurring size fraction (separated by sieving) were determined microscopically using the technique developed by Chapman et al. (1988). A visual record of the change in granule shape was also obtained by taking high speed photographs of the spheronization (Fielden, 1987).

Results and Discussion

1.0 mm diameter extrudate

The agglomeration that had previously been observed for the extrudate containing coarse lactose at a moisture content of 37.5% w/w was not apparent at the reduced moisture content of 33.3% w/w, hence, the pattern of curves produced by the number and weight size distributions are significantly different (Fig. 1). The interquartile range values are initially similar at both moisture contents. However, at 37.5% moisture the number and weight distribution curves subsequently shift to the right, indicating a large increase in granule size and distribution of sizes as spheronization progresses. The corresponding curves at 33.3% w/w moisture follow a pattern that demonstrates controlled spheronization, i.e., the number distribution gradually shifts to the

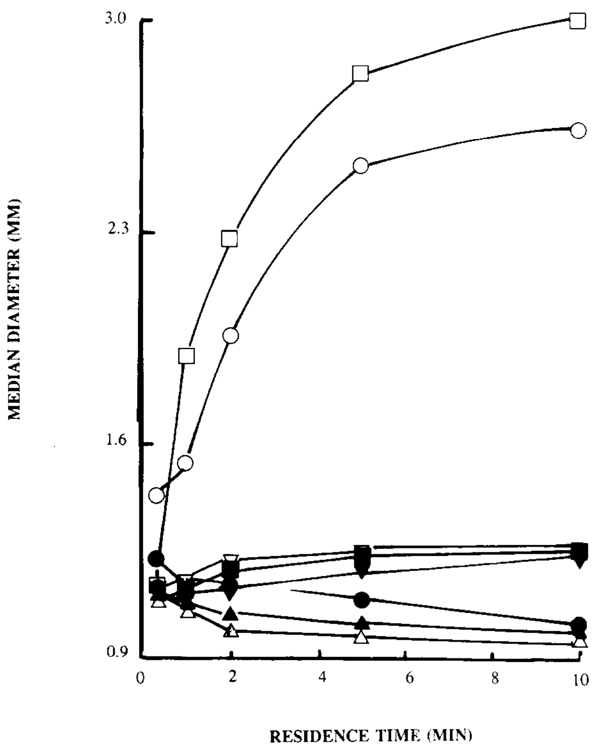

Fig. 2. The effect of moisture content on the number and weight median diameter of granules produced from 1.0 mm diameter extrudates containing fine and coarse lactose as a function of spheronisation time. Symbols:

Moisture content (%)	Number		Weight	
	Coarse	Fine	Coarse	Fine
37	○	●	□	■
33	△	▲	▽	▼

left as the particle length is reduced while the weight distribution is displaced to the right as the granule width is increased. The final spheroid size is significantly lower than that obtained at 37% w/w moisture as indicated by the limits of the interquartile range (1.2–1.4 and 2.5–4.3 mm, respectively), and demonstrates that the agglomeration has been controlled by reducing the moisture content of the wet powder mass. The number size distributions also indicate the presence of approx. 3% fines and smaller particles < 0.5 mm diameter at the end of spheronization which are absent from the spheroids produced at a moisture content of 37.5% w/w. Fines are generated as the extrudate breaks up during the initial stages of spheronization and the persistence of

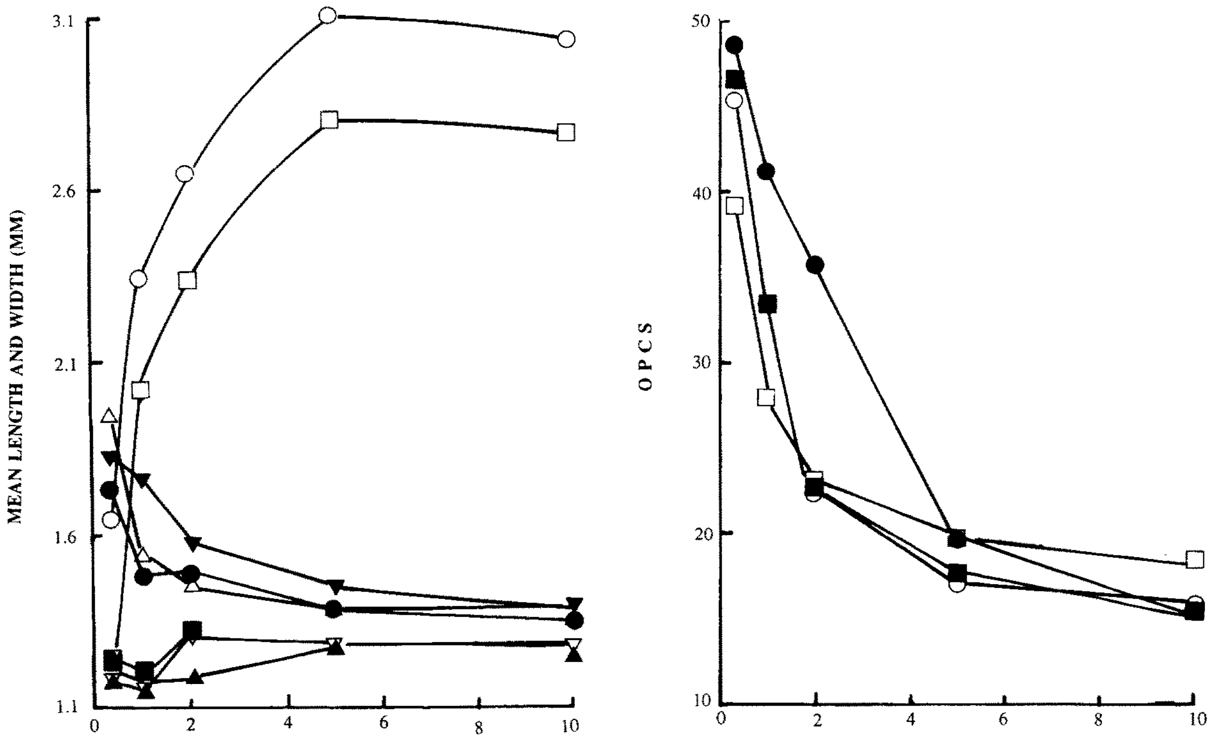

Fig. 3. The effect of moisture content on (A) the mean granule length and width, and (B) the 'one plane critical stability of the most frequently occurring size fraction of spheroids produced from 1.0 mm diameter extrudates containing fine and coarse lactose. Symbols:

	Moisture content (%)	Coarse		Fine	
		Length	Width	Length	Width
A	37	○	□	●	■
	33	△	▽	▲	▼
B		OPCS			
		Coarse	Fine		
	37	□	■		
	33	○	●		

these particles, rather than their removal by surface coalescence, implies a reduction in the surface moisture of the extrudate.

The number and weight size distribution curves and interquartile range values for the granules containing fine lactose at 33.3% w/w moisture were not significantly different to the results obtained using coarse lactose (Fig. 1 and Table 1). The same quantity of undersized spheroids, 3%, was also present after 10 min. Hence, the two extrudates are spheronized in a similar manner. Close similarity in the size distribution curves and interquartile range values obtained for the fine lactose extrudate at moisture contents of 33.3 and 37.5% w/w indicates that the general characteristics of the spheroids produced are not influenced by the reduction in the water content of the wet powder mass. The data in Table 2 confirm that a similar quantity of spheroids (64 and 69%, respectively) is retained within the largest sieve fraction, 1.18 mm, at 10 min spheronization. At 33.3% w/w moisture, however, the spheronization process is carried out at a slower rate as shown by the lower yield of 1.18 mm diameter granules between 20 s and 5 min. It was noted that at the same moisture content, the extrudate containing coarse lactose appears to be more plastic than the fine lactose extrudate since it produces a greater percentage of granules within that size fraction at all time points. In fact, spheronization of this extrudate closely resembles that of the fine lactose extrudate at a moisture content of 37.5% w/w. This is illustrated by the change in median diameters (Fig. 2) and mean granule length and width of the most frequently occurring size fraction with the spheronization time (Fig. 3A). The reduction in granule length (indicated by the number median diameter and

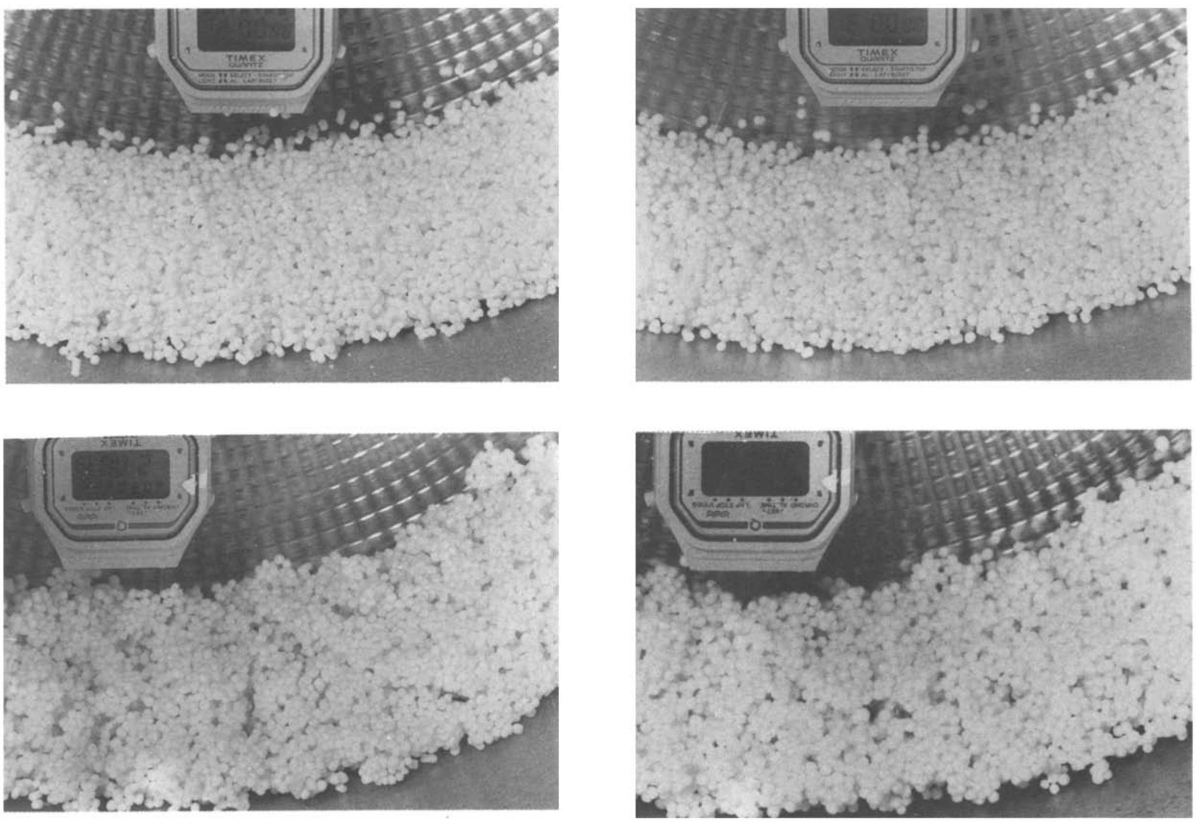

Fig. 4. Effect of moisture content on spheronization of the 1.0 mm diameter extrudate containing fine lactose. (A) 1 min and (B) 5 min at 33.3% w/w moisture. (C) 1 min and (D) 5 min at 37.5% w/w moisture.

mean length) concurrent with an increase in granule width (weight median diameter and mean width) that was observed for extrudates containing coarse and fine lactose at 33.3% w/w moisture are distinctive curves typical of controlled spheronization (Rowe, 1985; Chapman et al., 1986). Changes in granule length and width were more pronounced with the extrudate containing coarse lactose confirming a faster rate of spheronization. At 37.5% w/w moisture, the extrudate containing fine lactose spheronized more rapidly whereas the coarse lactose extrudate agglomerated.

The pattern of shape changes in the OPCS curves (Fig. 3B) and the high speed photographs (Figs 4 and 5) support these findings. A reduction in the moisture content of the coarse lactose extrudate from 37.5 to 33.3% w/w results in controlled spheronization and causes the shape of the OPCS curve to be very similar to that given by the extrudate containing fine lactose at 37.5% w/w moisture. This implies that the same changes in shape take place at the same time intervals. The spheronization rate of the fine lactose extrudate is significantly slower at the reduced moisture content of 33.3% w/w as indicated by the correspondingly greater OPCS values. At 1 min the granules were still in the form of long cylinders with rounded ends or dumb-bells (OPCS = 41.3 ± 12.4) while at 37.5% w/w moisture ovoids had formed at this stage (OPCS = 33.4 ± 10.0). At a moisture content of 33.3% w/w the major change in granule shape occurred between 2 and 5 min when the OPCS value declined from 35.8 ± 10.2 to 19.8 ± 4.4 as spheroids were formed, while at 37.5% w/w moisture a similar stage was reached between 1 and 2 min, the OPCS value being reduced to 22.7 ± 4.6. The final shapes of

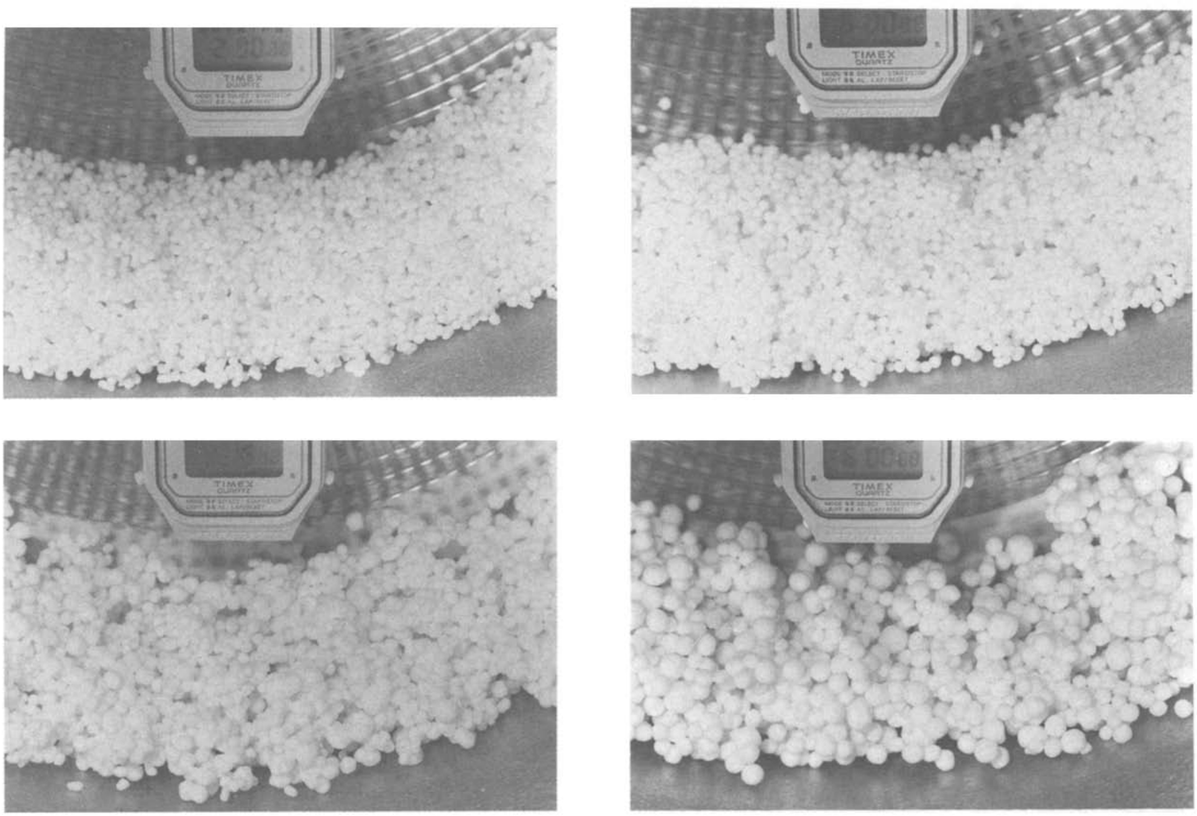

Fig. 5. Effect of moisture content on spheronization of the 1.0 mm diameter extrudate containing coarse lactose. (A) 1 min and (B) 5 min at 33.3% w/w moisture. (C) 1 min and (D) 5 min at 37.5% w/w moisture.

the spheroids were, however, identical hence similar OPCS values were obtained after 10 min spheronization, 15.5 ± 3.2 (33.3% w/w moisture) and 15.6 ± 2.8 (37.5% w/w moisture).

1.5 mm diameter extrudate

The general pattern of the size distribution curves produced follow a similar trend to that described previously for the 1.0 mm diameter extrudate (Fig. 1). Control of granule agglomeration with the 1.5 mm diameter extrudate containing coarse lactose was similarly achieved at the reduced moisture content of 33.3% w/w. This is demonstrated by the reduction in the limits of the interquartile range from 2.7–4.5 mm (37.5% w/w moisture) to 1.5–2.0 mm (33.3% w/w moisture) at 10 min spheronization (Table 1). The results are very similar to that obtained for the formulation containing fine lactose indicating that successful controlled spheronization had occurred. As found previously, the size distribution of spheroids containing the fine lactose was not significantly affected by a reduction in the moisture content. At the reduced moisture content, 33.3% w/w, the spheroids containing the fine and coarse lactose also contained a quantity of fines and smaller particles, approx. 15% < 1.0 mm diameter due to lack of surface moisture. A greater amount of fines were produced than with the corresponding 1.0 mm diameter extrudates indicating that the extrudates are more friable. A lower rate of granules yielded on the largest sieve fraction, 1.7 mm, also shows that the extrudate is less plastic at 33.3% w/w moisture content (Table 2). The above results are summarized by the changes observed in the median granule diameters (Fig. 6). Extrudate containing coarse lactose at 37.5% w/w moisture showed an increase in the weight and number median diameters caused by agglomeration whereas at 33.3% w/w moisture there was a gradual decrease in the number median diameter concurrent with an increase in the weight median diameter which is indicative of controlled spheronization. These findings are supported by the direct length and width measurements of the sample from the most frequently occurring size fraction (Fig. 7A). Extrudate containing fine lactose also demonstrated controlled spheronization but the change in median granule diameter was more gradual at 33.3% w/w moisture. The OPCS curves reflect the above observations and closely follow the results previously described for the 1.0 mm diameter extrudates (Fig. 7B). Photographs of the granules containing fine lactose at 33.3% w/w moisture show mostly dumb-bells at 1 min (OPCS = 36.1 ± 9.5) whereas at 37.5% w/w moisture spheronization

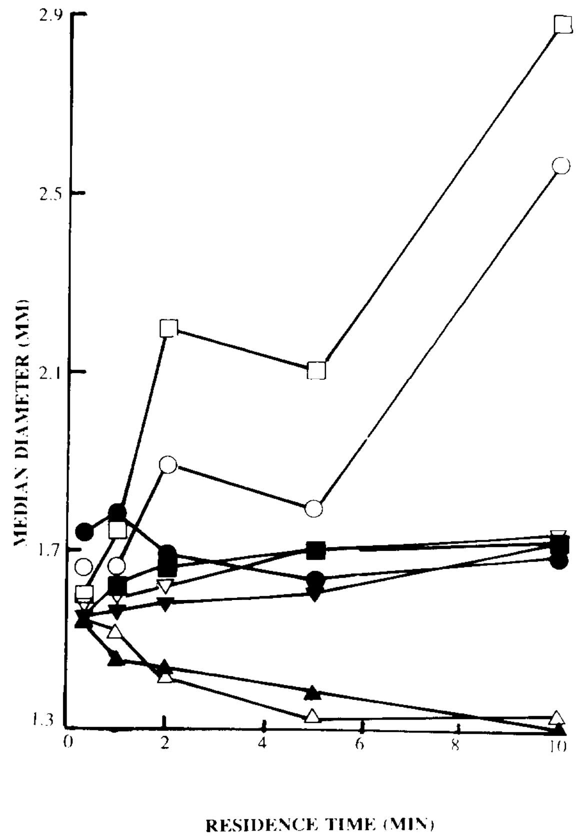

Fig. 6. The effect of moisture content on the number and weight median diameter of granules produced from 1.5 mm diameter extrudates containing fine and coarse lactose as a function of spheronisation time. Symbols:

Moisture content (%)	Number		Weight	
	Coarse	Fine	Coarse	Fine
37	○	●	□	■
33	△	▲	▽	▼

has progressed further to mainly ovoids and spheres (OPCS = 22.8 ± 5.0) (Fig. 8). Extrudate containing coarse lactose at 33.3% w/w moisture also demonstrated controlled spheronization in which the intermediate dumb-bell shape was formed at 1 min (OPCS = 33.9 ± 11.9). At 37.5% w/w moisture, the extrudate had agglomerated at this stage and continued forming large aggregates throughout spheronization (Fig. 9).

Discussion

The moisture content of the wet powder mass containing coarse lactose was shown to be critical

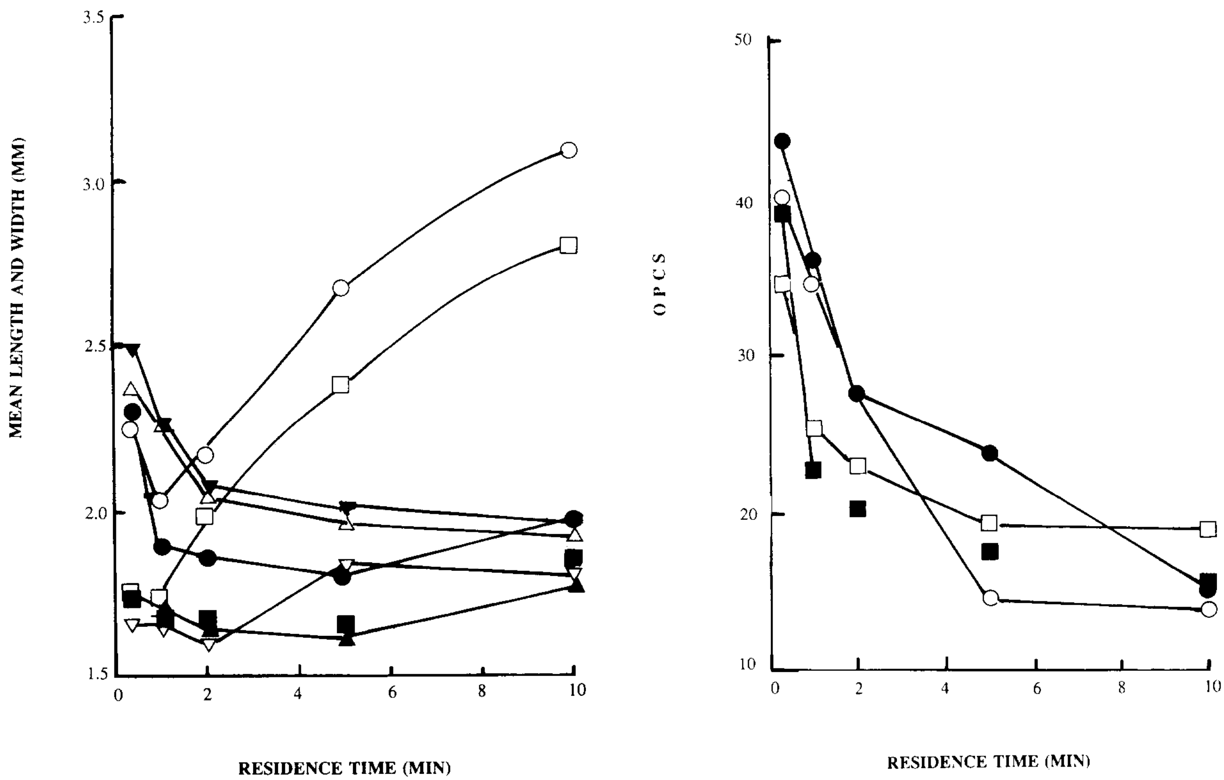

Fig. 7. The effect of moisture content on (A) the mean granule length and width and (B) the 'One plane critical stability' of the most frequently occurring size fraction of spheroids produced from 1.5 mm diameter extrudates containing fine and coarse lactose. Symbols:

	Moisture content (%)	Coarse		Fine	
		Length	Width	Length	Width
A	37	○	□	●	■
	33	△	▽	▲	▼
B		OPCS			
		Coarse	Fine		
	37	□	■		
	33	○	●		

since the granule agglomeration that was observed at 37.5% w/w moisture could be controlled by reducing the moisture content to 33.3% w/w. In contrast, satisfactory spheroids could be produced at both moisture contents by using the fine lactose in the wet powder mass. However, a moisture of 37.5% w/w was shown to be optimal for this mixture since it enabled the spheroids to form more rapidly. The above implies the existence of a 'specific moisture content range' unique to a wet powder mixture above and below which spherical granules cannot be prepared. This phenomenon may be explained as follows by applying the powder saturation model of Newitt and Conway-Jones (1958) to represent a magnified view of the surface of an extrudate or granule formed on spheronization (Fig. 10). The degree of surface saturation is critical in determining whether spheronization will be satisfactory or whether, under certain conditions, a particular formulation might agglomerate. Below the 'specific moisture content range' the particles in the wet powder mass are held together by discrete bridges at each point of contact in the pendular or funicular state (Fig. 10A). Satisfactory extrusion of such dry systems is unlikely since excessive pressure is required to consolidate the material in order to remove the air voids. Extrudate which is in this low state of saturation is brittle, will shatter generating a large quantity of fines when broken up on spheronization and will have insufficient plasticity to form spheres.

Addition of more water to the system allows the formation of bonds which increases the tensile strength of the granule, as the mechanism of bonding changes to the capillary state depicted in Fig. 10B. This degree of saturation achieves maximum density since the voids are completely filled

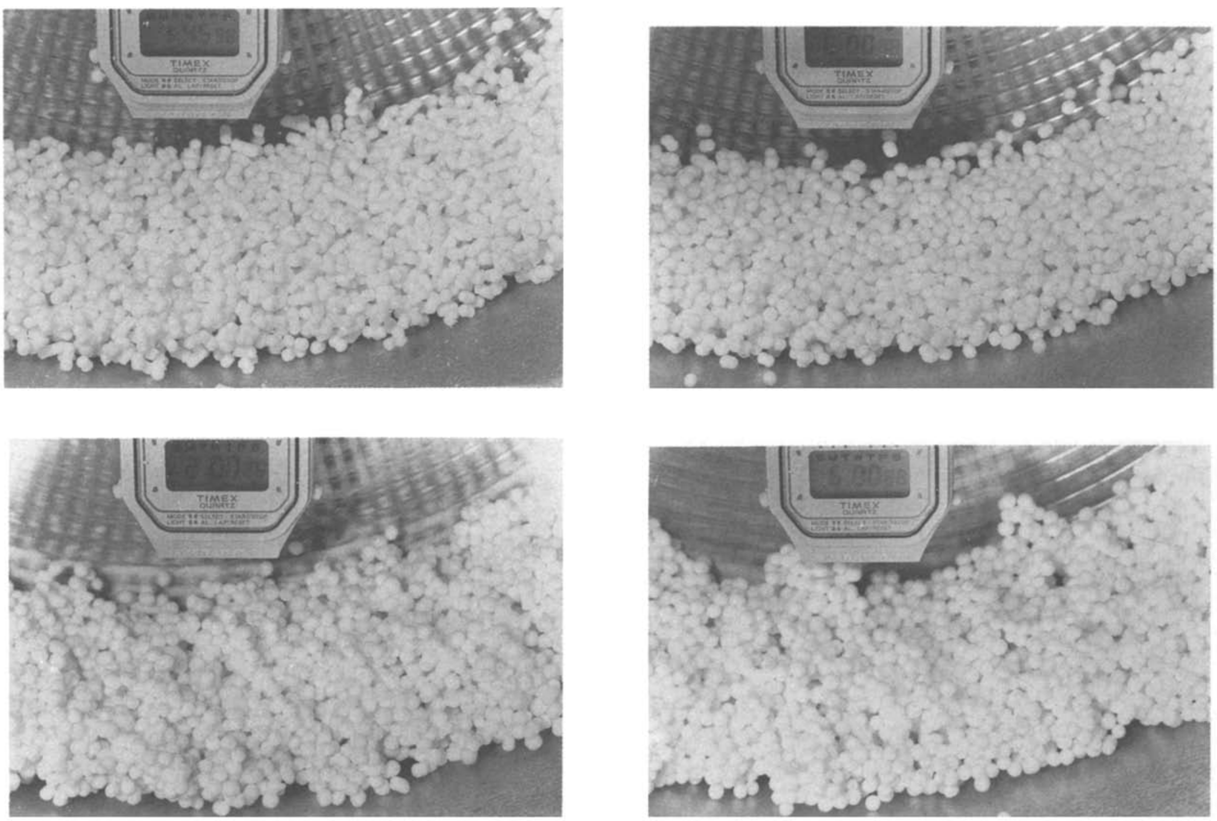

Fig. 8. Effect of moisture content on spheronization of the 1.5 mm diameter extrudate containing fine lactose. (A) 1 min and (B) 5 min at 33.3% w/w moisture. (C) 1 min and (D) 5 min at 37.5% w/w moisture.

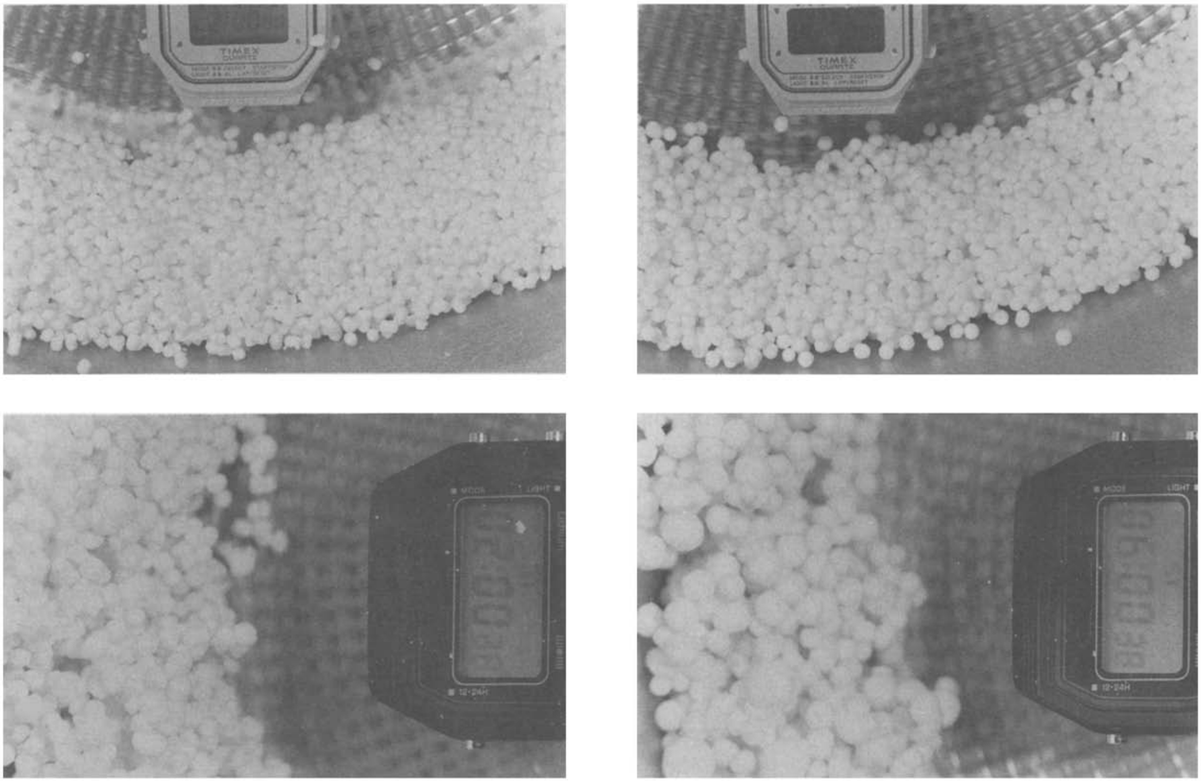

Fig. 9. Effect of moisture content on spheronization of the 1.5 mm diameter extrudate containing coarse lactose. (A) 1 min and (B) 5 min at 33.3% w/w moisture. (C) 1 min and (D) 5 min at 37.5% w/w moisture.

with liquid and the wet powder mass is in an ideal form for extruding. The increased plasticity of the extrudate enables more of the impact energy on spheronization to be absorbed in deformation with less energy available for breakage, hence, the product will form satisfactory

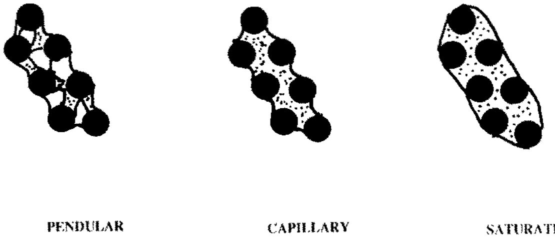

Fig. 10. Depiction of the granule surface showing (A) pore in lowest state of saturation (B) saturated pores but relatively dry surface (C) saturated pores and overwetted surface.

spheroids. The above conditions are applicable to the wet powder mass made with fine lactose to a moisture content of 37.5% w/w in which the resultant extrudate and granules showed little tendency to aggregate when spheronized.

Liquid distribution within a granule is known to be non-uniform (Sherrington, 1968); pores between particles in the interior of the granule are saturated with the liquid phase, while the surface is relatively dry, and the liquid is withdrawn to a depth *d*, into the interstices between the outermost particles by capillary suction (Fig. 10B). For satisfactory spheronization, it is desirable that the surface moisture of an extrudate should be withdrawn as far as possible since in these circumstances, the granules will not agglomerate. The study of liquid movement through powder beds showed that microcrystalline cellulose increased

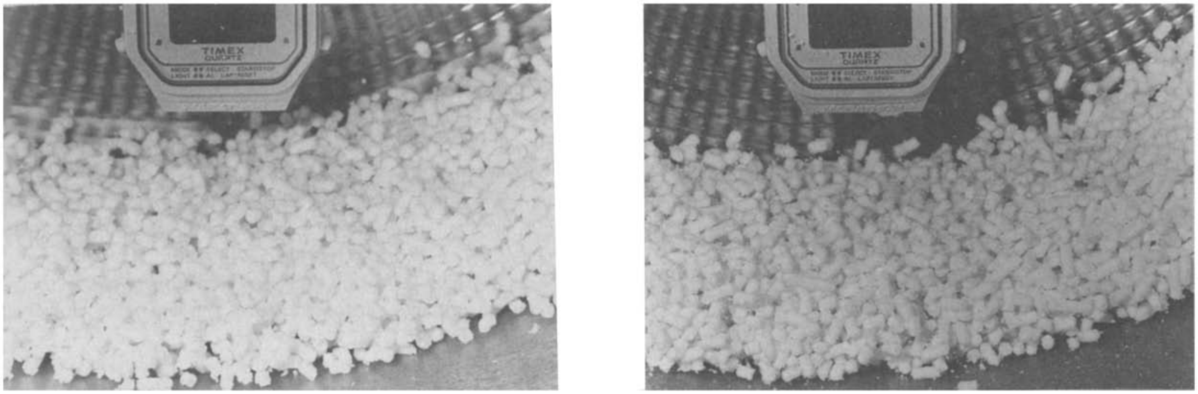

Fig. 11. Spheronization at 10 s of the 1.5 mm diameter extrudate containing fine lactose. (A) 37.7% w/w moisture (B) 33.3% w/w moisture.

the capillary suction of a powder mixture and the use of finely divided lactose was shown to enhance this effect (Fielden et al., 1992b). The resultant granules made from the fine lactose mixture showed little tendancy to aggregate when spheronized. It might be concluded that the quantity of fines which are produced at the initial stages of spheronization are beneficial if the surface moisture of the granules is in slight excess. This was demonstrated by the extrudate containing fine grade lactose at a moisture content of 37.5% w/w. Photographic evidence (Fig. 11A) shows that as the granules roll over each other the fines make contact and are subsequently lost due to adhesion onto the surface of the cylindrical granules. Fines have a lower moisture content than the large granules and therefore a higher suction potential. This effectively absorbs surface moisture which might otherwise encourage adjacent granules to agglomerate. This is the principle behind the practice of adding a finely divided powder eg. microcrystalline cellulose, talc, starch, as suggested by Reynolds (1970), onto the surface of spheronizing granules in an attempt to prevent a poorly formulated product from agglomerating. Conversely, extrudate lacking in surface moisture can be detected by the tendency to generate an excessive amount of fines and small particles which are not lost by adhesion but persist throughout spheronization. This was demonstrated by the extrudate containing fine lactose at a moisture content of 33.3% w/w (Fig. 11B).

Fielden et al. (1989) have shown that, in contrast to the extrudate containing fine lactose at 37.5% w/w moisture, the moisture content of the coarse lactose extrudate is variable, hence its surface must be saturated in varying degrees ranging from the acceptable capillary state to the saturated (or droplet) state shown in Fig. 10C. Here, the liquid is withdrawn to the interior of the granules to a lesser extent due to the lower capillary suction pressure of the coarse particle size lactose. Photographic evidence showed that after the extrudate had been reduced to short lengths in the spheronizer at 1 min the granules associated loosely into clusters (Figs 5 and 9). The impact energy subsequently acting on the granules resulted in coalescence of one or more particles, which was symptomatic of the overwetted surface. Kristensen et al. (1985b) have shown that any means which tends to increase the deformability of moist agglomerates, e.g., by reducing their tensile strength, and/or improving their plastic deformation, favours their agglomeration by coalescence. Deformability depends on the strength of the agglomerate to withstand the strain induced by agitation and the ability to be strained without degredation. The effect of excessive surface moisture on the granules containing the coarse lactose on the agglomeration process may be interpreted on this basis. The strength of a granule is reduced as the particle size is increased and the moisture content is increased (Kristensen et al., 1985a,b). Rumpf (1958a,b) showed that when the void space in a granule is completely filled with liquid, i.e., in the capillary state of saturation, the tensile strength of the granule as a whole is approximately equal to the average capillary suction pressure (P) given by the equation:

$$P = T/m(\cos \delta)$$

where T is the surface tension of the liquid, m denotes the mean hydraulic radius of the pores and δ is the solid-liquid contact angle.

Fielden et al. (1992b) have applied a similar expression, used in soil science, to describe the relationship between the pore size distribution and saturation of a wet powder bed consisting of lactose and microcrystalline cellulose alone and as binary mixtures. Here, the equation:

$$(h_t = T/\rho g m)$$

was used to relate the equivalent hydraulic head, h_t (the height of water standing in a capillary tube corresponding to a given pressure) to the mean hydraulic pore radius, where g is the acceleration of gravity and ρ represents the density of the liquid. It was shown that apart from producing an extrudate of variable moisture content the use of coarse lactose results in relatively larger diameter pores which decreases capillary suction in the granules. The surface moisture of the granules produced is increased and tensile strength is reduced, hence, both effects contribute to promoting coalescence during spheronization. By reducing the moisture content of the coarse lactose formulation to 33.3% w/w the powder bed is less saturated and the above effects are not apparent. The persistence of fines throughout spheronization of this extrudate proved that the surface moisture had been reduced.

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