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The influence of lactose particle size on spheronization of extrudate processed by a ram extruder

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Summary

The spheronization of extrudate produced by a ram extruder fitted with either 1.0 or 1.5 mm diameter dies from mixtures of microcrystalline cellulose, lactose (with median diameter of either 18.0 or 117.0 μm) and water has been observed. The spherical granules produced have been characterized in terms of their median length (number diameter by microscope) and width (weight diameter by sieving) and the roundness ('One Plane Critical Stability'), width and length (microscope observation) of the most frequently occurring size fraction. Extrudate produced through both 1.0 and 1.5 mm diameter dies with the fine particle size lactose formed granules within 5 min which were well rounded and of a narrow size distribution. Extrudate produced through both the 1.0 and 1.5 mm diameter dies with the coarse grade of lactose, produced spheres, but these were considerably larger in size and had a larger range of size, due to agglomeration of the granules. The changes in shape and size could be observed within the spheronizer by using a photographic technique. The median diameter of spheroids produced by the controlled spheronization of the fine grade lactose mixture was about 1.2 times the diameter of the die producing the extrudate. The median diameter of the spheroids produced by the uncontrolled spheronization of the coarse grade lactose mixture was not related to the die diameter. In fact, extrudate produced from the 1.0 and 1.5 mm dies both produced spheroids of approx. 3.0 mm diameter. The reasons for the difference in processing of the two particle size fractions of lactose appear to be associated with the movement of water in the formulation.

Introduction

The preparation of spherical pellets (spheroids) with a high drug content (up to 90%) is most economically achieved by the technique of extrusion-spheronization as described by Conine and Hadley (1970) and Reynolds (1970). Harrison et al. (1987) have described the rheological properties required of a wet powder mass to produce satisfactory extrudate. These properties must also be compatible with the rheological characteristics required of the extrudate if it is to undergo successful spheronization. During spheronization, the cylindrical extrudate undergoes a series of subtle shape changes in which the long strands

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are initially broken into short rods and subsequently form spherical pellets of regular size, shape, density, and surface characteristics. Successful processing is dependent upon achieving an extrudate which exhibits the following characteristics:

(i) It must possess sufficient mechanical strength to retain its structure when wet, yet it must be brittle enough to break down into short uniform cylindrical lengths in the spheronizer.
(ii) It must have the required plasticity to enable the cylindrical rods to be rolled into spheres by the action of the friction plate.
(iii) It must be non-adhesive to itself and the plate in order that the spherical granules remain discrete throughout the process.

Several studies have shown that it is essential to include in the formulation a quantity of material which acts as an extrusion aid and provides extrudate satisfying the above requirements. For pharmaceuticals, microcrystalline cellulose is most commonly used as observed by Conine and Hadley (1970), Miyake et al. (1973), and Harrison et al. (1984). Microcrystalline cellulose is thought to provide a dual function: in the presence of water it modifies the rheological properties of the other ingredients in the mixture so that a degree of plasticity is attained which facilitates extrusion and the shape changes occurring during spheronization. It also controls the movement of the water through the plastic mass and prevents phase separation when it is forced through apertures during extrusion or subjected to centrifugal forces during spheronization. This interaction with water stems from the ability of microcrystalline cellulose to retain within its structure a large quantity of moisture by either adsorption and/or hydraulic isolation. The adsorption capacity of microcrystalline cellulose determined by a differential thermal analysis technique has been found to be 15.4 ml of water per 100 g solid (Fielden et al., 1988), while the quantity of water that can be physically entrapped while applying pressure to a moistened powder bed of the material has been shown to be approx. 62.2 ml per 100 g solid (Fielden et al., 1992).

The above parameters assume a greater significance when preparing spheres with a high drug content (Bodmeier et al., 1986; Bataille et al., 1990; Baines et al., 1991). For example, Baines et al. (1991), using barium sulphate as a water-insoluble drug model, demonstrated that the quantity of water required in the wet powder mass to produce a consistent product by extrusion-spheronization was related to the proportion of microcrystalline cellulose in the mixture; a critical level of moisture content was reported for all mixtures above and below which spherical granules could not be prepared. This level became more restrictive for systems containing 80% barium sulphate and 20% microcrystalline cellulose.

The physico-chemical characteristics of the drug (particularly water solubility and particle size) will also determine whether the outcome of extrusion-spheronization is successful. Anderson and Newton (1990) found, with mixtures of microcrystalline cellulose and barium sulphate (used as a water-insoluble drug model), that the particle size and water content influenced the rheology of the wet powder mass and subsequent ability of the extrudate to satisfactorily spheronize. Utilizing ram extrusion, Fielden et al. (1988) demonstrated significant differences in the flow characteristics and quality of extrudate formed from mixtures containing equal parts of microcrystalline cellulose and lactose (a water soluble drug model), where two different particle sizes of lactose were used. As a continuation of this work, the studies described herein assess the effects of lactose particle size on the spheronization of extrudates prepared from these wet powder masses at a constant level of water content of 37.5% w/w.

Materials and Methods

Preparation of the spherical granules

Wet powder masses containing microcrystalline cellulose (Avicel PH101, FMC Corp., U.S.A.) with either fine lactose or coarse lactose (Grades B170 and B50, respectively, Dairy Crest, U.K.) were prepared to a moisture content of 37.5% w/w using a Hobart planetary mixer. The

median particle sizes of the two grades of lactose used were, fine, 18.0 ± 30 μm (equivalent spherical diameter by Quantimet image analysis) and, coarse, 117.0 ± 15 μm (obtained by sieve analysis). Mixtures were equilibrated for at least 12 h at room temperature then extruded with a ram extruder as described by Harrison et al. (1985) using a 1.5 and a 1.0 mm diameter die with length to radius ratios of 8, at a constant extrusion rate of 10 cm min^{-1}. These conditions produced smooth extrudates from both wet powder mixtures. There was steady-state flow with the fine particle size lactose but forced flow with the coarse grade. Details of these flow curves have been presented previously (Fielden et al., 1989). Spheronization was performed using a 22.5 cm diameter spheronizer (GB Caleva Ltd, U.K.) fitted with a radial designed plate rotating at 1000 rpm. Extrudate was loaded into the spheronizer in 200 g quantities and a stop-watch positioned close to the path of the moving granules was started. Extrudates prepared from the fine and coarse grades of lactose under particular conditions of die diameter and moisture content were spheronized for durations of 20 s, 1, 2, 5, and 10 min. Granules were then collected and dried in a fluid bed drier (PRL Engineering Ltd, U.K., Model FBD/L70) to a constant moisture level at 60°C for 30 min.

Characterization of the spherical granules

Size distribution Each batch of granules was characterized by both number and weight size distributions to avoid bias towards either the largest or smallest size fractions. For the number size distributions, a representative sample of approx. 500 granules was removed from the bulk by a spinning riffler (Microscal Model TM1, U.K.), and was analysed using a Quantimet image analyser (Model Q720) according to Fielden (1987) as follows. Samples were photographed against a contrasting background and the calibrated film was scanned by means of an epidiascope attachment which provided a video input to a Quantimet processor. The equivalent spherical diameter of the particles was calculated and the number size distribution obtained by sorting the measurements into 10 (arithmetically spaced) size ranges extending between the largest and smallest value of equivalent spherical diameter.

The weight size distribution was obtained by sieving each batch of granules on a $\sqrt{2}$ progression of sieves of appropriate size using a mechanical agitator on a sieve shaker (Endecott Ltd, U.K.).

Shape analysis Characterization of the particle sizes observed during spheronization was achieved when measuring the 'One Plane Critical Stability' (OPCS) as described by Chapman et al. (1988) using a miscroscope and computer-linked digitising tablet. The shape analysis, and also measurement of mean granule length and width, was performed on a sample of 50 granules from the most frequently occurring size fraction randomly obtained with the spinning riffler.

Chapman et al. (1988) have divided the process of spheronization into distinct stages in terms of the changes in shape of the extrudate. Cylinders occur in the early stages which form dumbbells as the cylinders are compressed along the axis. These are rounded into ovoid particles, then finally spheroids. The mean OPCS values corresponding to these shapes are as follows: cylinders 41.9 ± 10.0, dumb-bells 33.0 ± 7.9, spheroids 17.1 ± 3.4. Hence, the lower the OPCS value, the more spherical the product.

Photography of the spheronization process

A visual record of the change in granule size and shape was obtained by photographing the spheronization process with a camera (Nikon FM using a 135 mm lens, 1/125 s shutter speed, flash and motor drive) mounted above the spheronizer. A stop-watch, suspended inside the drum, close to the path of the moving granules, was included in the photographs as an accurate record of spheronization time. Spheronization was initiated as the stop-watch displayed 1 min, and photographs were taken at suitable time intervals.

Results and Discussion

Spheronization of 1.5 mm diameter extrudate

The granule size distributions for 1.5 mm diameter extrudates obtained as number and weight

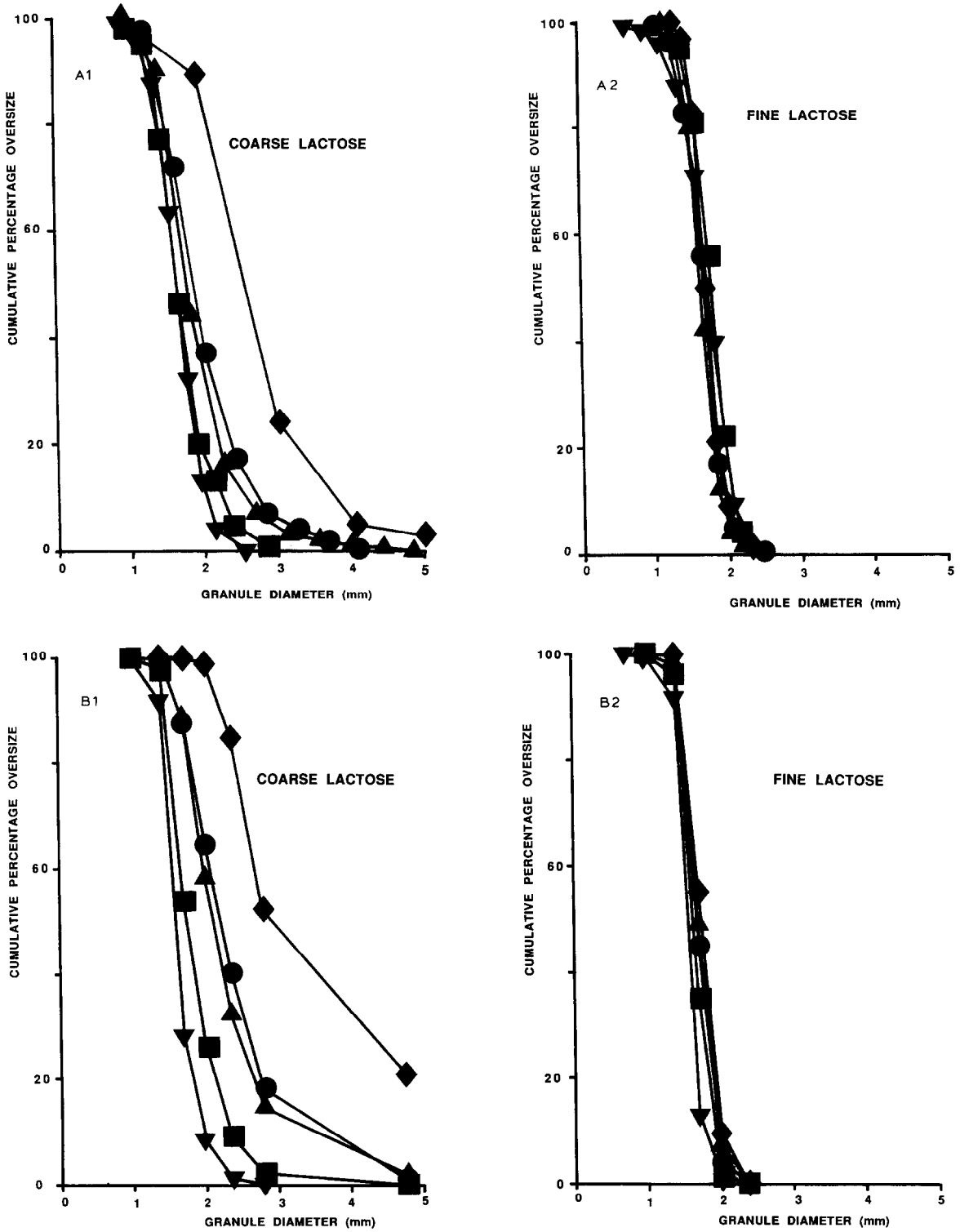

Fig. 1. The effect of lactose particle size on the size distribution of granules as a function of the spheronization time for 1.5 mm diameter extrudate. Residence time (min): 0.33 (▼), 1 (■), 2 (●), 5 (▲), 10 (◆). (A) Number analysis. (B) Weight analysis.

cumulative percentage oversize curves as a function of spheronization time are shown in Fig. 1. The curves referring to extrudate made with fine grade lactose typify the changes in size which take place during spheronization. Here, the number size distributions, which are related to granule length, become narrower and shift to the left as this dimension progressively decreases during spheronization. At 20 s residence time, approx. 30% of the particles are greater than 2 mm in length, the proportion reducing to 8% after 10 min spheronization. The changes in granule length are further illustrated by noting the reduction in the interquartile size range from 0.4 mm (limits 1.6–2.0 mm) to 0.1 mm (limits 1.7–1.8 mm) at 10 min. The number distributions also indicate the presence of small particles and fines, approx. 2% less than for 1.0 mm diameter, at the initial stages of spheronization which are subsequently lost, presumably by incorporation onto the larger granules.

A general pattern is similarly observed in the corresponding size distribution curves obtained from the weight analysis, which quantifies the change in granule width during spheronization. In contrast to the number analysis, the interquartile size range increases with the residence time, from 0.1 mm at 20 s (limits 1.5–1.6 mm) to 0.3 mm diameter (limits 1.6–1.9 mm) after 10 min, indicating that spheronization is associated with an increase in granule width. Further evidence for this is provided by the increase in the quantity of granules within the largest sieve fraction of 1.7 mm diameter, from 13% at 20 s to 55% at 10 min residence time.

There are marked differences between the corresponding number and weight size distributions obtained from the extrudate containing coarse grade lactose (Fig. 1B). The initial spread of granule sizes, as indicated by the interquartile range limits at 20 s (1.5–1.7 mm diameter by weight analysis), is similar to that of the extrudate containing fine lactose. However, noticeably fewer fines and smaller particles less than 1.0 mm diameter are produced. Both the number and weight analysis curves subsequently shift to the right such that at 10 min the interquartile limits are 2.7–4.5 mm diameter. This demonstrates a large

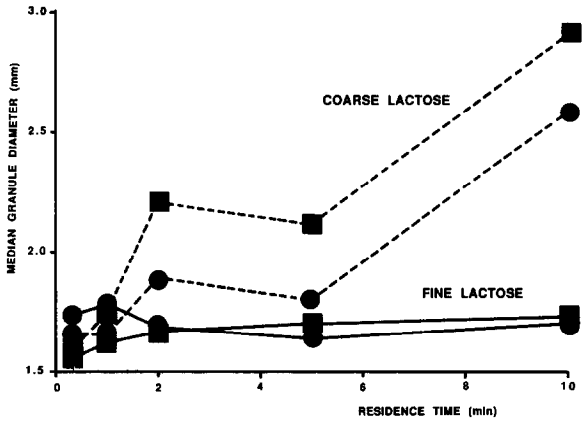

Fig. 2. The effect of lactose particle size on the number (●) and weight (■) median diameter of granules produced from 1.5 mm diameter extrudate as a function of the spheronization time.

increase in granule size with a wide distribution of particle sizes at the end of spheronization.

The general trends observed on spheronizing both extrudate formulations are summarized by plotting the median diameters from the number and weight cumulative percentage oversize curves as a function of the residence time (Fig. 2). Extrudate containing fine lactose shows a reduction in the number median diameter of the granules between 20 s and 2 min which is concurrent with an increase in the weight median diameter. This feature has been associated with a densification process that takes place as the extrudate is being compressed along its length by the forces exerted during spheronization (Chapman et al., 1986). Subsequent changes in granule shape appear to be completed by 5 min, since thereafter the number and weight median diameters are constant, at approx. 1.7 mm.

The above trend indicates the stability of the formulation to spheronization, where the granules remain discrete throughout the process. Extrudate containing the coarse grade lactose demonstrates a substantially different pattern when spheronized. The initial median number diameter (representing granule length) is slightly lower than that obtained with the fine grade lactose extrudate, and is caused by more facile break up of the extrudate. The granule size sub-

sequently increases in two stages. The median diameter first increases to 2.2 mm within 2 min, momentarily remaining constant between 2 and 5 min, then increasing finally to 2.9 mm at 10 min residence time. This indicates that agglomeration is taking place and that spheronization is out of control.

The shape changes implied from the above particle size analysis are verified and detailed by the OPCS values and corresponding granule length and width measurements obtained at various spheronization times (Fig. 3A, B). Extrudate containing fine lactose shows a reduction in OPCS with the residence time, resulting in a distinctive curve that is typical of controlled spheronization as shown by Rowe (1985) and Chapman et al. (1986). The shapes described by the OPCS curves are also consistent with the general shape characteristics of the batch illustrated by the sequence of high-speed photographs (Fig. 4). Breakage of the extrudate to short cylindrical lengths is completed within 5 s, demonstrating the brittleness or friability required of an extrudate. This initial process generates a large quantity of fines as previously described by the number size distribution curve. The fines are clearly seen adhering to the moist surface of the granules and their subsequent removal is caused by coalescence as they undergo spheronization. Within 20 s the granules have been compressed along the axis, reducing the length and rounding at the ends to form the characteristic dumb-bell shape. The shape curve indicates an OPCS value of 38.9 ± 10.0 consistent with this shape, while the large standard deviation implies the presence of a range of granule shapes, i.e., cylinders, dumb-bells, and ovoids as confirmed by the photograph.

A large reduction in OPCS values occurs between 20 s and 1 min, coinciding with the major changes in granule length and width described previously at the same time points. The OPCS value of 22.8 ± 5.0 at 1 min residence time is

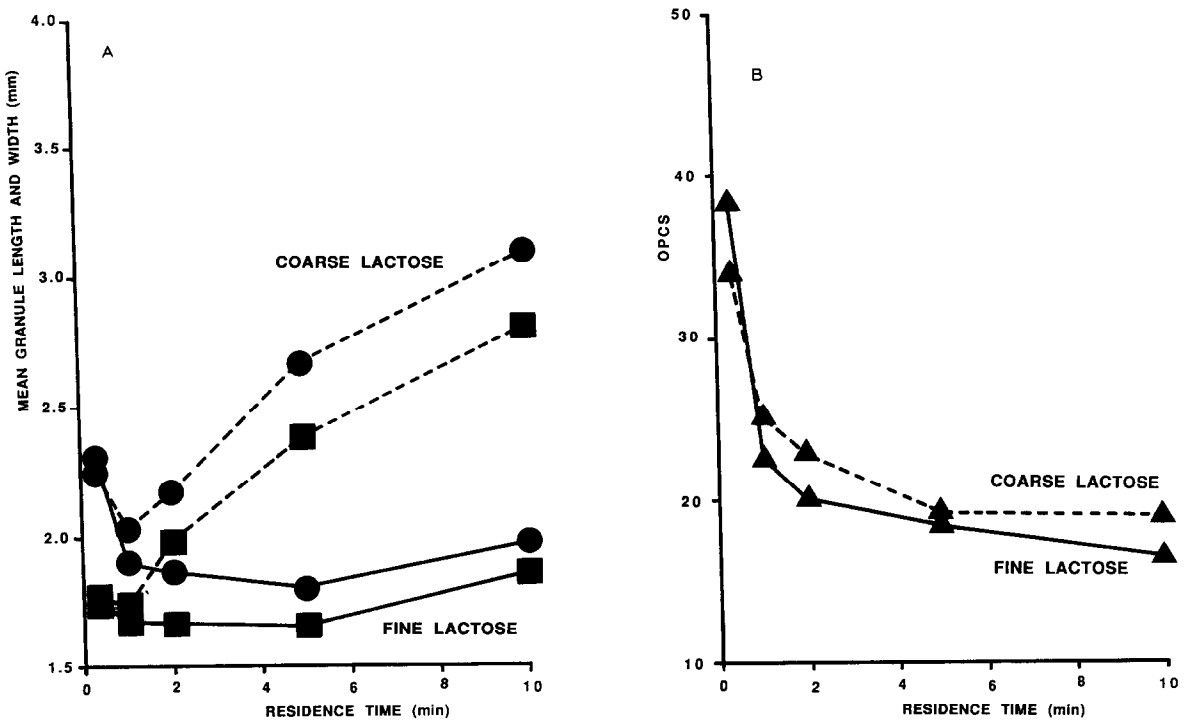

Fig. 3. The effect of lactose particle size on (A) the mean granule length (●) and width (■) and (B) the 'One Plane Critical Stability' of the most frequently occurring size fraction of spheroids produced from 1.5 mm diameter extrudate.

consistent with the largely ovoid appearance of the particles shown in the photograph. Between 1 and 2 min the value of OPCS declines more gradually to 20.3 ± 5.4 due to the more subtle changes in particle shape occurring as the proportion of ellipsoids reduces and the proportion

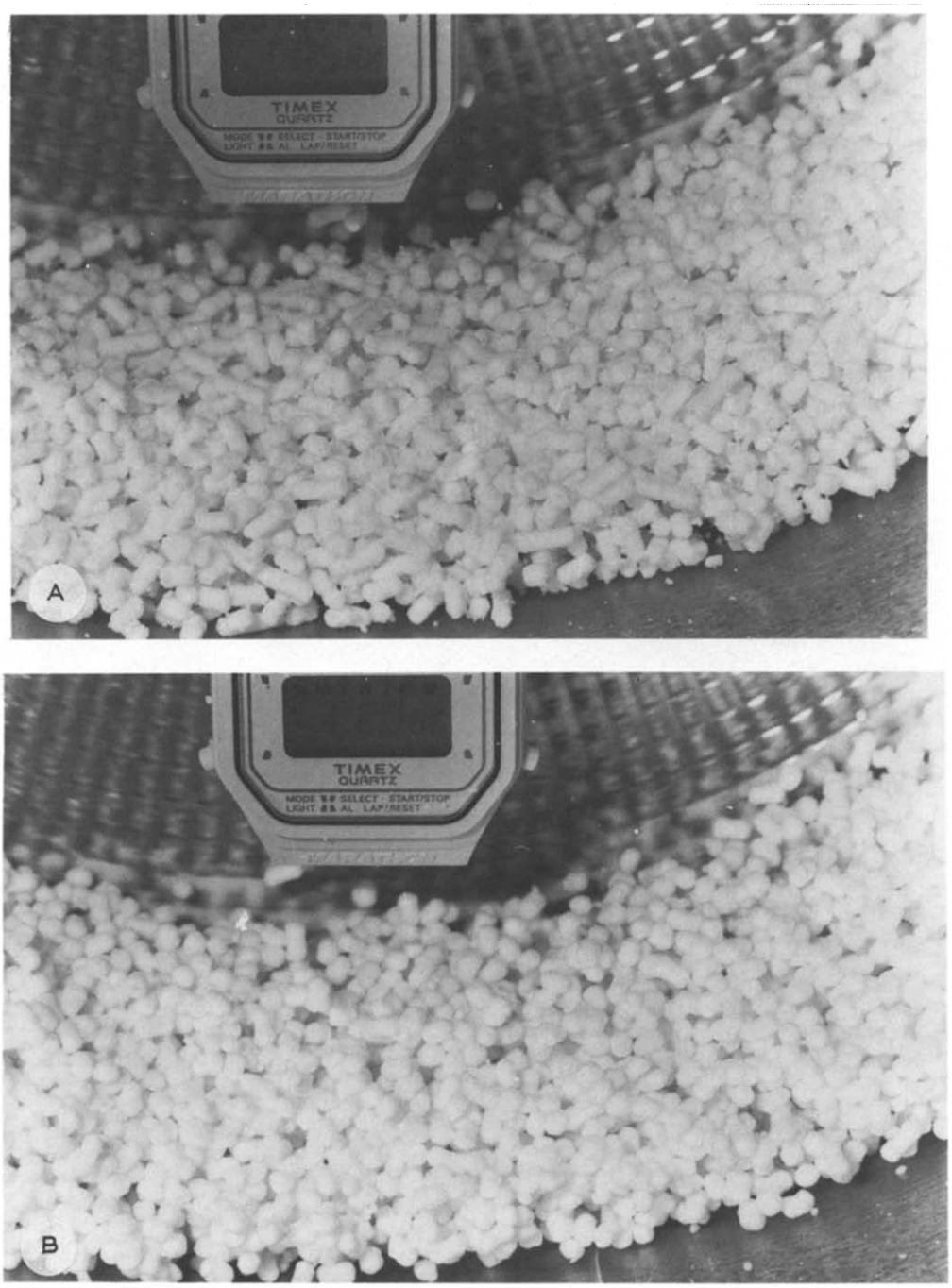

Fig. 4. Spheronization of the 1.5 mm diameter extrudate containing fine lactose. (A) 5 s, (B) 20 s, (C) 1 min, (D) 5 min.

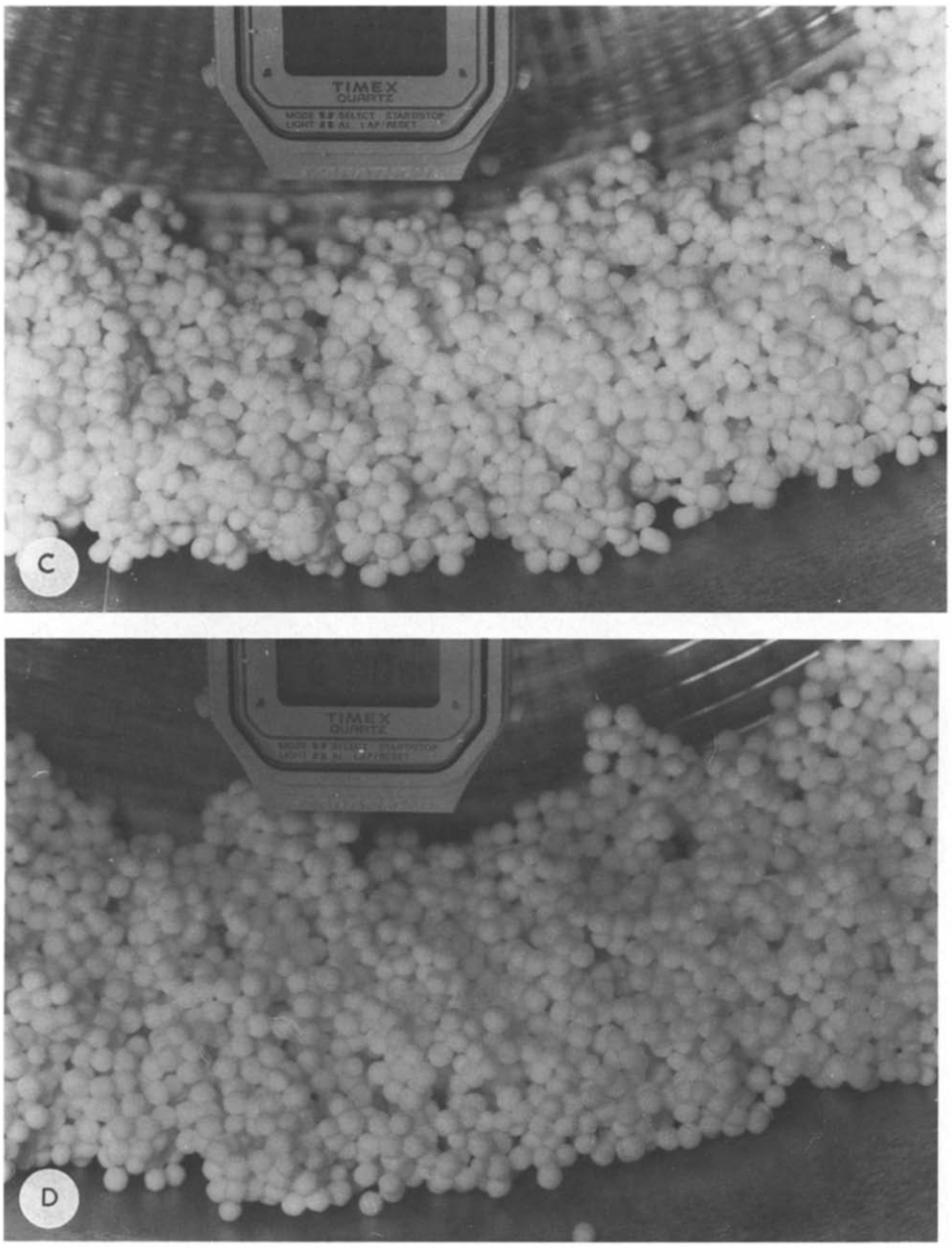

Fig. 4. (C, D)

of spheroids increases. The OPCS value continues to decline to 18.5 ± 3.9 at 5 min residence time as the granules continue becoming more spherical. Only a slight reduction in OPCS value to 16.5 ± 3.4 takes place between 5 and 10 min, indicating that the spheronization process is largely completed within the initial 5 min. This is confirmed by the photograph and by the median

granule diameter curves shown in Fig. 2 in which the granule dimensions remain constant after 5 min spheronization.

The above results demonstrate the shape changes which normally take place during spheronization of suitable extrudate. Marked differences occur when the process is not successful, as with the extrudate made with coarse grade lactose. Here, changes in OPCS in the initial stages up to 1 min residence time are smaller than that depicting normal spheronization with extrudate made with fine lactose. This implies that although agglomeration is occurring, the rounding-off process still takes place, since the final product has an OPCS equivalent to spheres but the spheronization proceeds by way of a different mechanism. However, no information can be derived from the shape analysis curve as to the extent of the agglomeration. The photograph at 5 s spheronization shows that in the initial stages the extrudate is reduced to short cylindrical lengths in a similar way to the extrudate containing fine lactose (Fig. 5). Similarly, the granules are present as discrete particles at this stage, although a noticeably similar quantity of fines are produced, which agrees with the number size distribution discussed previously. However, by 20 s, a significant proportion of the cylinders have rounded off directly into the ellipsoid stage, by-passing the intermediate dumb-bell

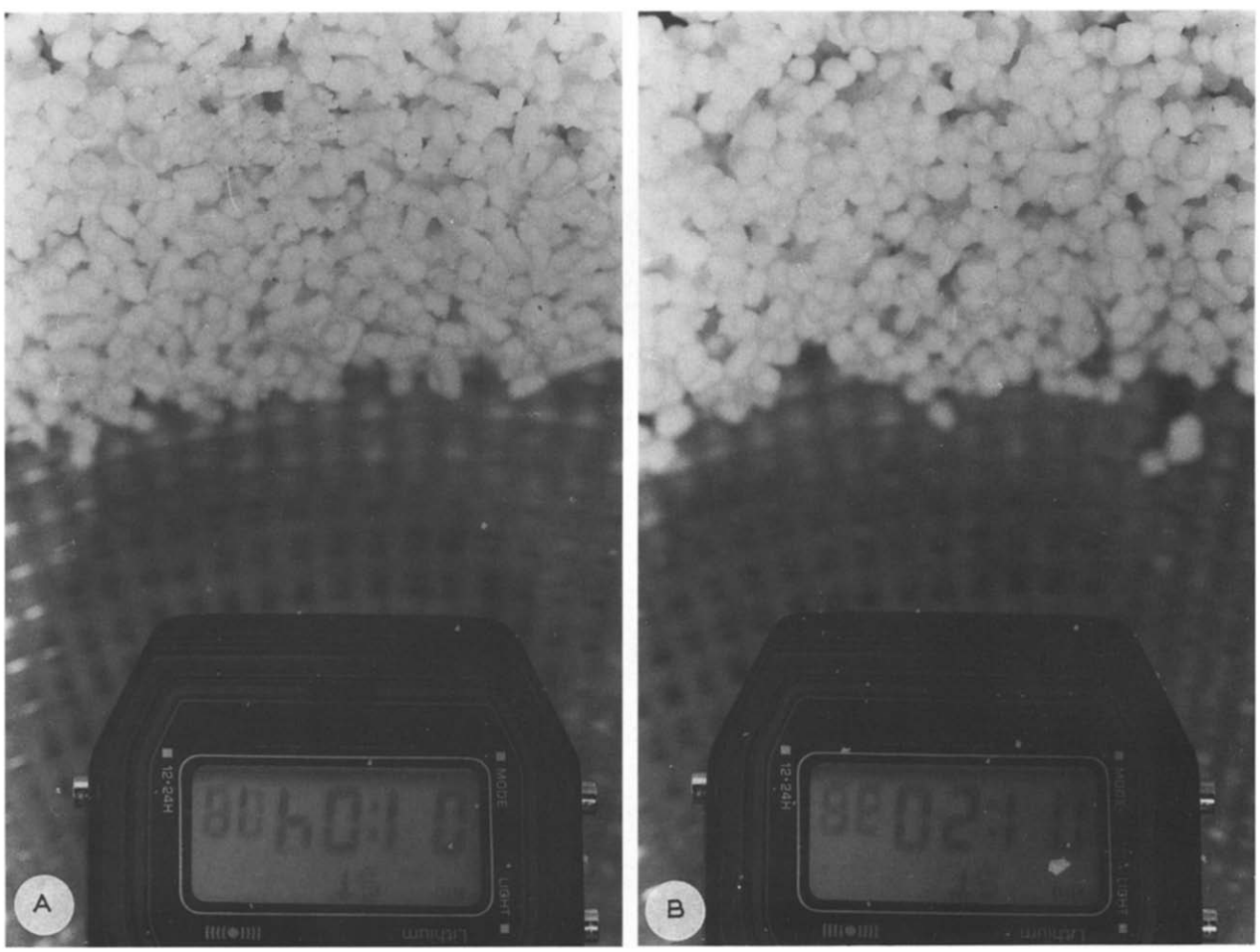

Fig. 5. Spheronization of the 1.5 mm diameter extrudate containing coarse lactose. (A) 5 s, (B) 20 s, (C) 1 min, (D) 5 min.

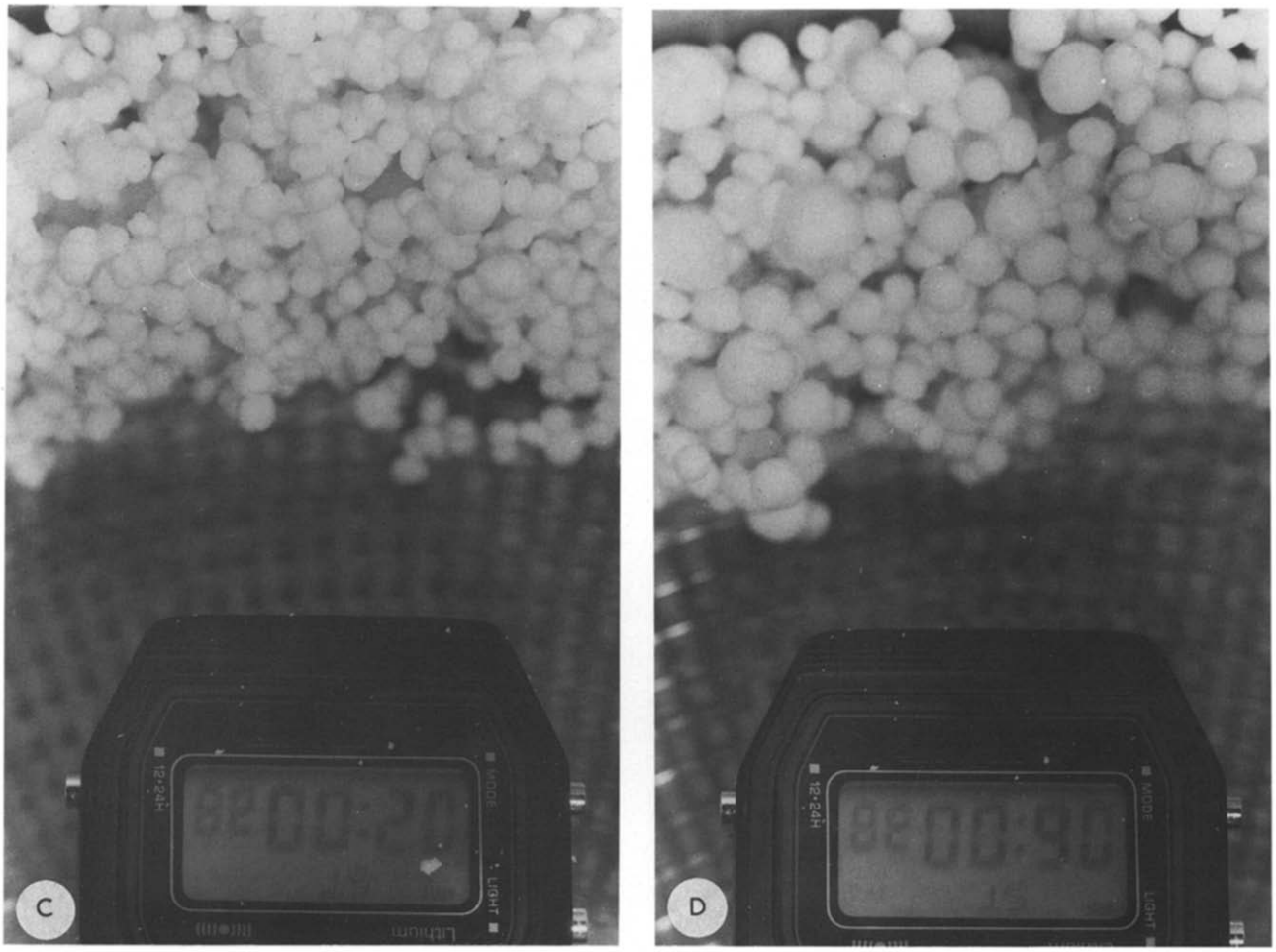

Fig. 5. (C, D)

shape. Some aggregates are also noticeable at this stage. As a result of the accelerated spheronization the initial OPCS value is significantly lower at 34.5 ± 10.0 than the value obtained for the fine lactose extrudate, and broadly represents dumb-bells or ellipsoids, as shown in the photograph. Conversely, the OPCS values after 1 min residence time for the extrudate made with coarse lactose are consistently higher than the corresponding values obtained for the fine grade lactose extrudate. The cause of this is apparent from the photographs. Between 20 s and 1 min contact between the granules has resulted in initiation of agglomeration such that the irregular shapes of the aggregated granules give rise to higher OPCS values than that obtained for ovoid particles formed at this stage during controlled spheronization. Further agglomeration is seen between 1 and 5 min (Fig. 5), but at the same time aggregates are rounded off, causing the OPCS to reduce to 19.3 ± 4.7 consistent with spherical particles. The photograph at 5 min shows the product as a mass of large round pellets clearly indicating that spheronization is out of control.

Spheronization of the 1.0 mm diameter extrudate

The general patterns of the curves produced by the number and weight analysis are similar to that demonstrated previously with the 1.5 mm diameter extrudate (Fig. 1). As before, the extru-

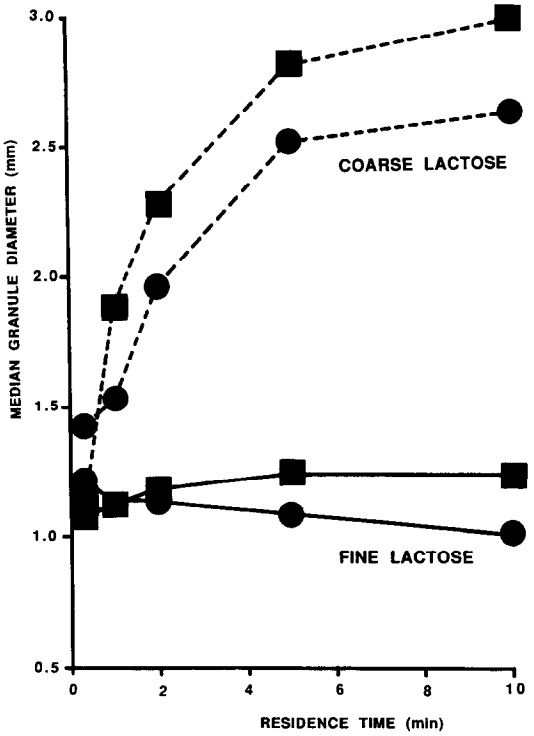

Fig. 6. The effect of lactose particle size on the number (●) and weight (■) median diameter of granules produced from 1.0 mm diameter extrudate as a function of the spheronization time.

date containing coarse lactose demonstrates its unsuitability by agglomerating during spheronization, whereas the formulation containing the fine grade lactose produces an acceptable product with narrow particle size distribution. This is shown by comparing the limits of the interquartile range derived from the number analysis, for the two formulations. Using fine lactose, this decreases from 1.0–1.4 mm at 20 s, to 0.9–1.1 mm after 10 min spheronization. The decrease in the number diameter with residence time again reflects a decrease in granule length as the cylindrical extrudate is formed into a spheroid. This is supported by an observed reduction in the numbers of granules greater than 1.25 mm diameter, from about 50% at 20 s to 10% at 10 min residence time. In contrast, the limits of the interquartile range for the extrudate containing coarse lactose are similar at 20 s, 1.21–1.68 mm, but a considerable increase occurs to 2.26–3.00 mm diameter after 10 min, caused by the formation of aggregates.

The 1.0 mm diameter extrudate containing fine lactose generates a lower percentage of fines and small diameter granules, compared to the 1.5 mm diameter extrudate, when spheronised (approx. 2% granules less than 0.5 mm diameter are present at 20 s). These fines are noticeably absent in the extrudate containing coarse lactose, indicating its lower friability.

The corresponding weight analysis for both formulations reflects a similar general pattern of change to that of the 1.5 mm diameter extrudate. Granules containing fine grade lactose show a corresponding increase in diameter, the limits of the interquartile range increasing from 1.03–1.15 mm at 20 s, to 1.18–1.35 mm at 10 min residence time. Thus, the process achieves a narrow size distribution with 73% of the spheroids retained on the 1.18 mm sieve, the largest size fraction.

As anticipated, the extrudate containing coarse lactose demonstrates an increase in weight diameter, and wide range of particle sizes, with the residence time, e.g. the interquartile range limits increase from 1.09–1.62 mm at 20 s to 2.53–4.29 mm at 10 min. The above results are summarized by the changes observed in the median granule diameters (Fig. 6). The curves for extrudate made using fine lactose demonstrate the same features that were apparent with the 1.5 mm diameter extrudate, and indicate controlled spheronization, i.e., the decrease in number diameter concurrent with an increase in the weight diameter within the first 5 min (caused by cutting of the extrudate and densification), followed by little further change.

Extrudate made with coarse lactose shows an increase in median granule diameter with the residence time as a consequence of agglomeration which is more extensive than for the corresponding 1.5 mm diameter extrudate. The mean length and width measurements on the shaped granules of the largest size fraction (Fig. 7) indicate that the aggregation proceeds immediately on spheronization and continues throughout the process. The sequence of timed photographs (Fig. 9) supports this, while the OPCS curves indicate

the shape changes throughout the process. At 5 s residence time, the extrudate containing fine lactose is reduced to short lengths in a similar manner to the 1.5 mm diameter extrudate (Fig. 8) and within 20 s the granules have begun to form dumb-bells and ovoids (OPCS = 45.5 ± 10.3). The granule shape is more uniform by 1 min as the OPCS value reduces to 33.4 ± 10.0, representing ellipsoids and the formation of spheroids as shown in the photograph. There is further reduction in the value of OPCS to 22.7 ± 4.6 at 2 min as more granules are rounded, and the process is virtually completed within 5 min, as indicated by an OPCS value of 17.6 ± 3.0. The presence of some aggregates at 5 min (Fig. 8) indicates that the 1.0 mm diameter extrudate may be less stable to spheronization than the 1.5 mm diameter extrudate which previously showed no evidence of agglomeration. However, the size distribution shows that the problem is not extensive as only 2% of the spheroids obtained were greater than 1.5 mm diameter.

The curve relating the value of OPCS and residence time for the coarse lactose extrudate indicates that despite agglomeration, the granules proceeded to spheronize. The extent of agglomeration is observed in the photographs of Fig. 9. Breaking of the extrudate takes place at a much earlier stage, within 5 s, however, thereafter granules are seen to move in loose clusters or groups. Further agglomeration occurs at 20 s, although the majority of the granules present are of small diameter which is in agreement with the size analysis. The OPCS value of 39.2 ± 14.2 at this stage is lower than that for fine lactose extrudate, since the granules have formed mainly ovoids. Most of the small diameter granules have aggregated and rounded off by 1 min to an approximately spherical shape, hence the OPCS value, 28.0 ± 7.6, is lower than with standard extrudate.

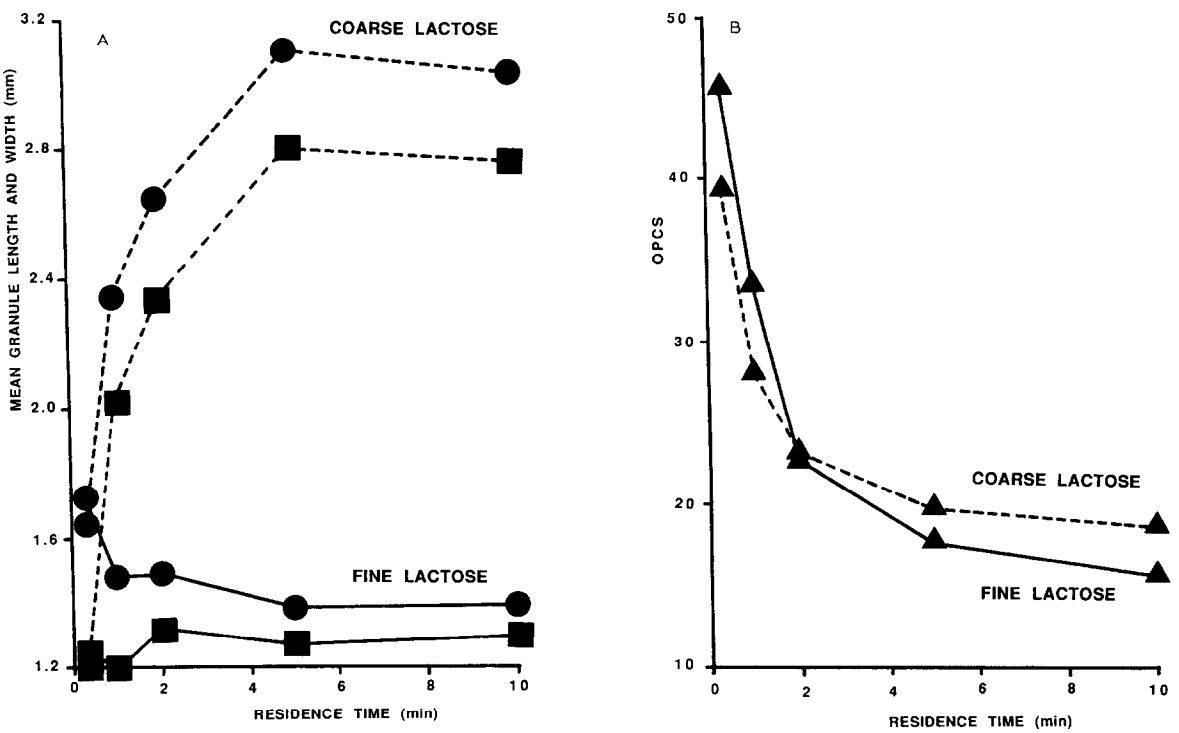

Fig. 7. The effect of lactose particle size on (A) the mean granule length (●) and width (■) and (B) the 'One Plane Critical Stability' of the most frequently occurring size fraction of spheroids produced from 1.0 mm diameter extrudate.

The process continues to go out of control and by 2 min no small diameter granules are present (OPCS = 23.2 ± 6.2). Little subsequent change in the OPCS value is seen as the ball growth continues, until at the end of the process the batch resembles a mass of spherical aggregates.

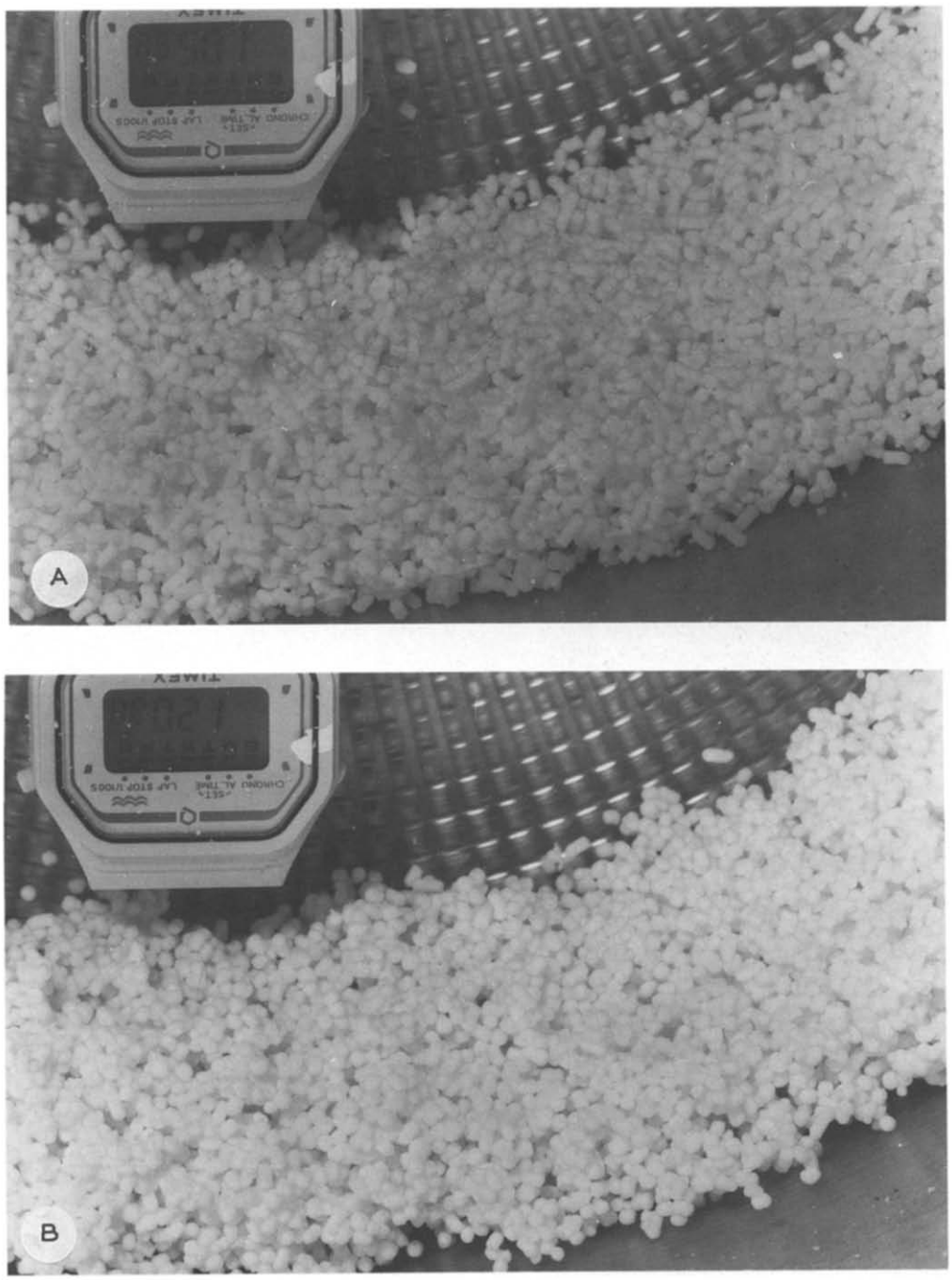

Fig. 8. Spheronization of the 1.0 mm diameter extrudate containing fine lactose. (A) 5 s, (B) 20 s, (C) 1 min, (D) 5 min.

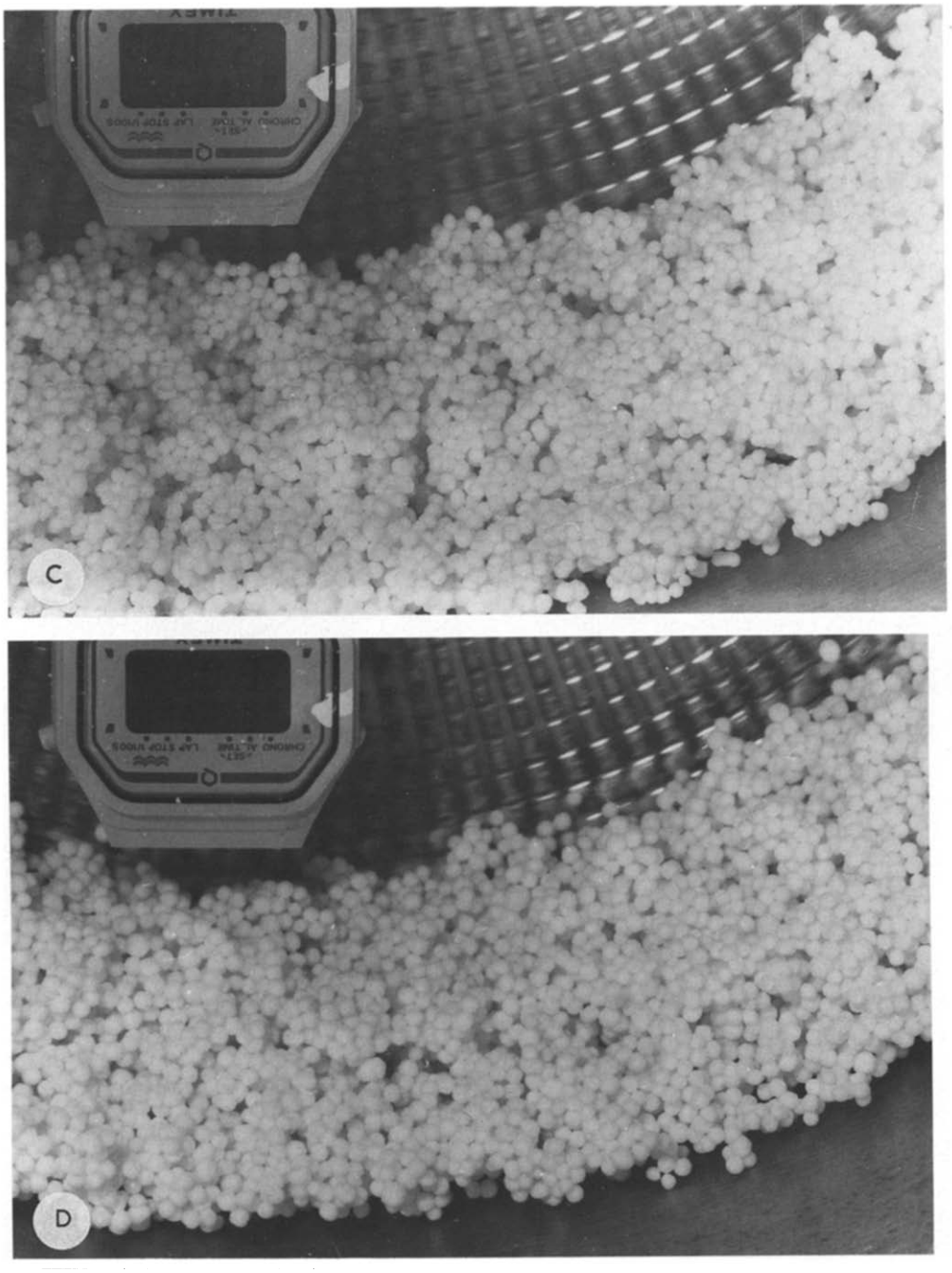

Fig. 8. (C, D)

Mechanism of granule agglomeration

An analogy may be made between the type of agglomeration encountered in spheronization and the condition of ball growth that is encountered during the wet granulation of powders in pans and drums and results in oversized granules. Sev-

eral mechanisms for this type of granule growth have been proposed. Newitt and Conway-Jones (1958) stated that growth occurs by way of larger granules breaking into two or three pieces, which then recombine with smaller granules and with themselves to form larger ones. No evidence of

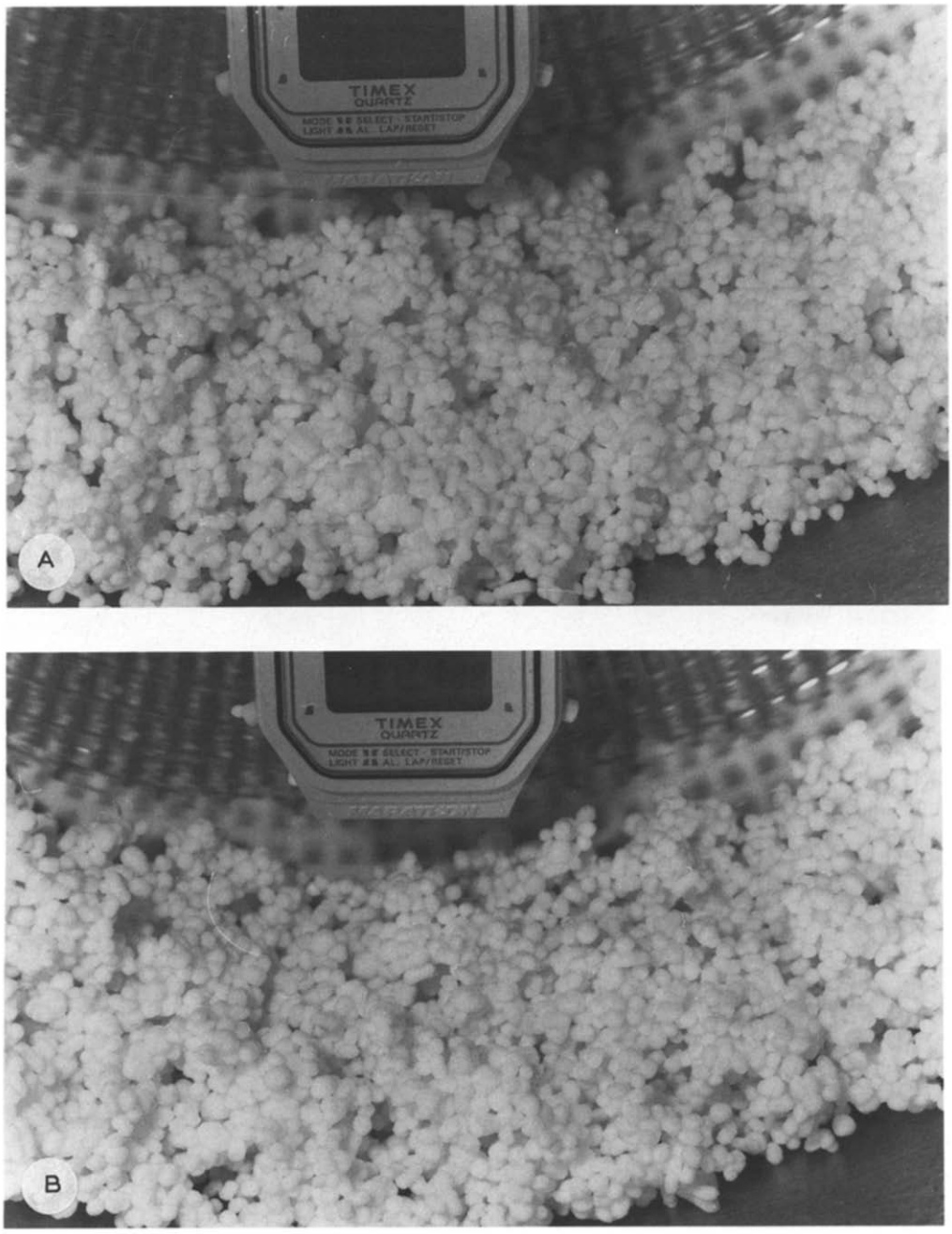

Fig. 9. Spheronization of the 1.0 mm diameter extrudate containing coarse lactose. (A) 7 s, (B) 20 s, (C) 1 min 15 s, (D) 2 min, (E) 5 min.

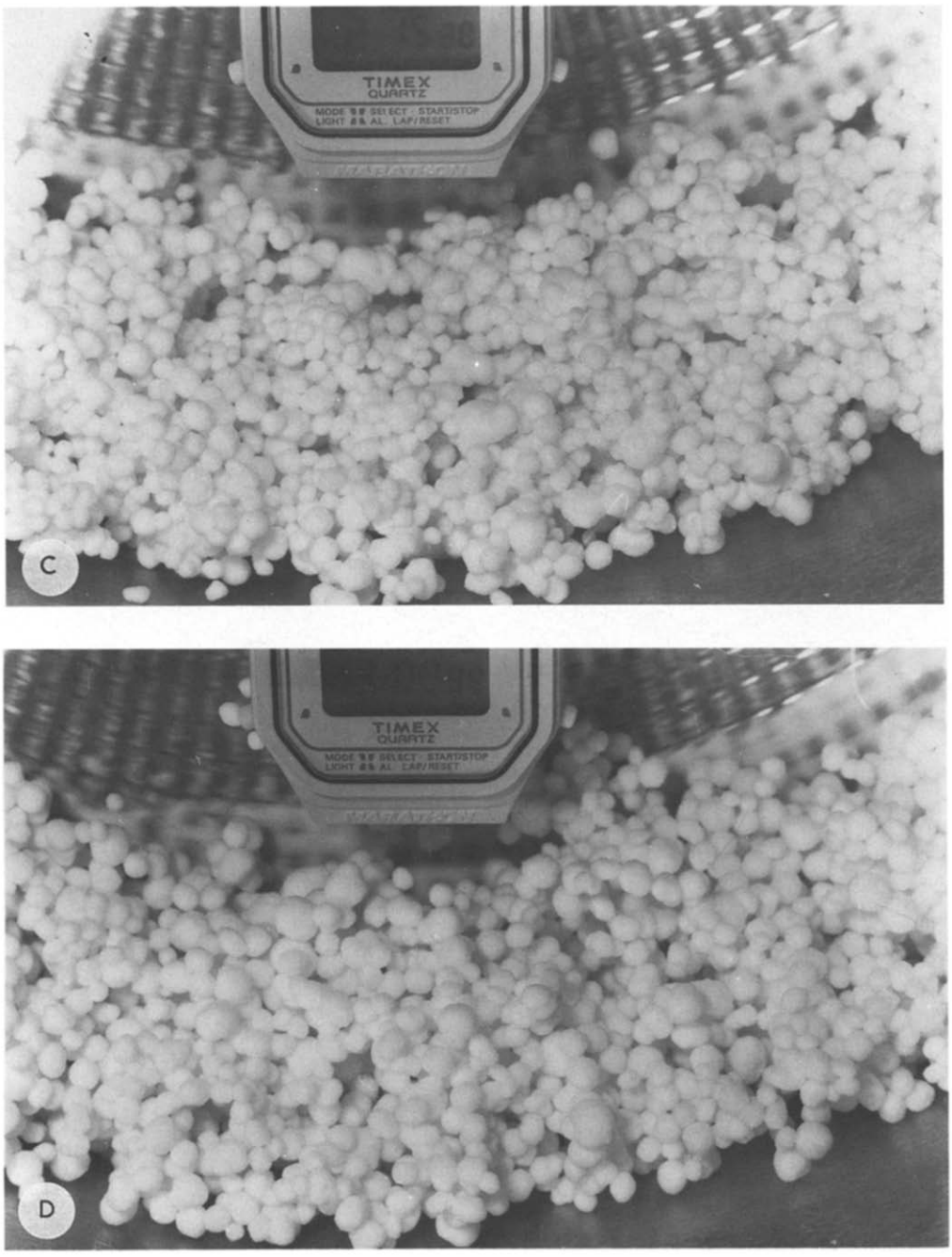

Fig. 9. (C, D)

this was seen in the high-speed photographs, which show that the large agglomerates (greater than 5 mm diameter) remain discrete throughout spheronization. An alternative explanation proposed by Capes and Danckwerts (1965) suggests that agglomeration occurs by way of selective

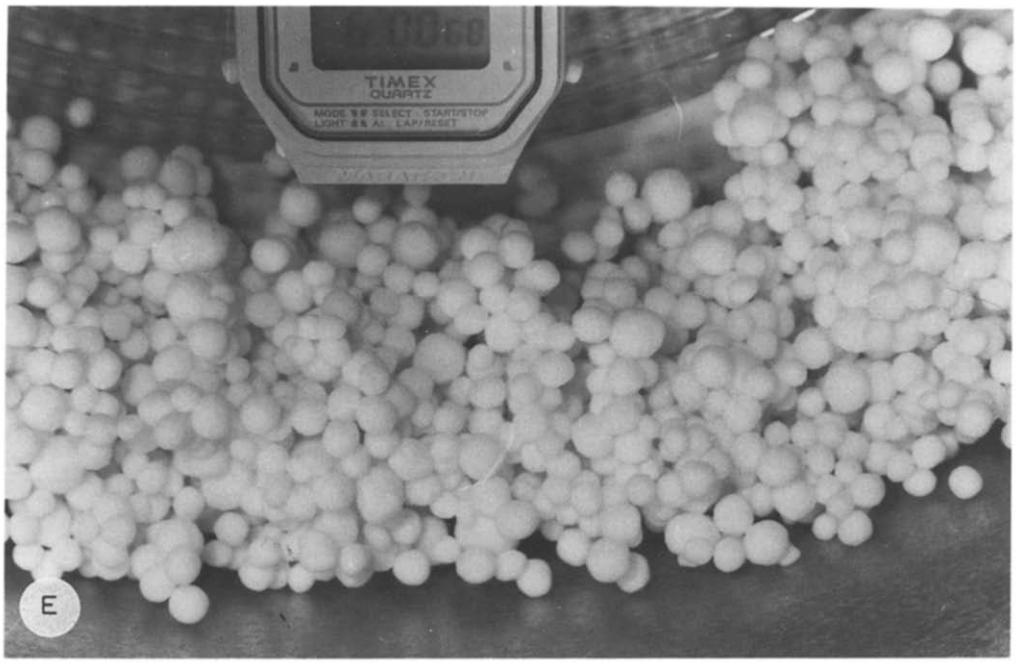

Fig. 9. (E)

comminution of the smaller granules with the material being distributed over the surface of the larger granules. This is unlikely to be the cause of particle growth in the spheronizer since the extrudate, consisting of a densified wet powder mass, possesses an inherent strength making it unlikely to fragment. A third possibility, put forward by Kapur and Fuerstenau (1966) is more likely. The authors suggest that large granules are formed by the coalescence of two or more granules regardless of their relative size. The timed sequence of photographs clearly shows that aggregates are formed from individual granules, after the extrudate has been reduced to short lengths. This takes place at about 30 s, when two or more granules coalesce into an aggregate, and the process of ball growth continues throughout the process.

Prior to this, it was thought that agglomeration might have occurred by way of entanglement between the long lengths of extrudate when the spheronizer is first started. Although photographic evidence showed that this was not the major mechanism, evidence of it occurring was occasionally encountered, particularly when a batch showed extreme agglomeration. For example, Fig. 10 shows a large aggregate (approx. 10 mm diameter) with a highly irregular (contoured) external surface, that was produced by spheronizing the 1.0 mm diameter coarse lactose extrudate. On dissecting the moist granule, strands of extrudate could be seen, in addition to the outlines of smaller granules, situated within the mass. This type of open structure is possible because the aggregate has built up a relatively dense outer shell and the forces in the spheronizer are insufficient to compact the large granule further. This enables large voids filled with air to be sustained within its interior.

Spheronization is a complex process involving concurrent changes in the granule shape size and density. In this study, the process has been characterised by monitoring changes in shape within the largest sieve fractions by the shape factor OPCS and by direct measurement of granule length and width while changes occurring within

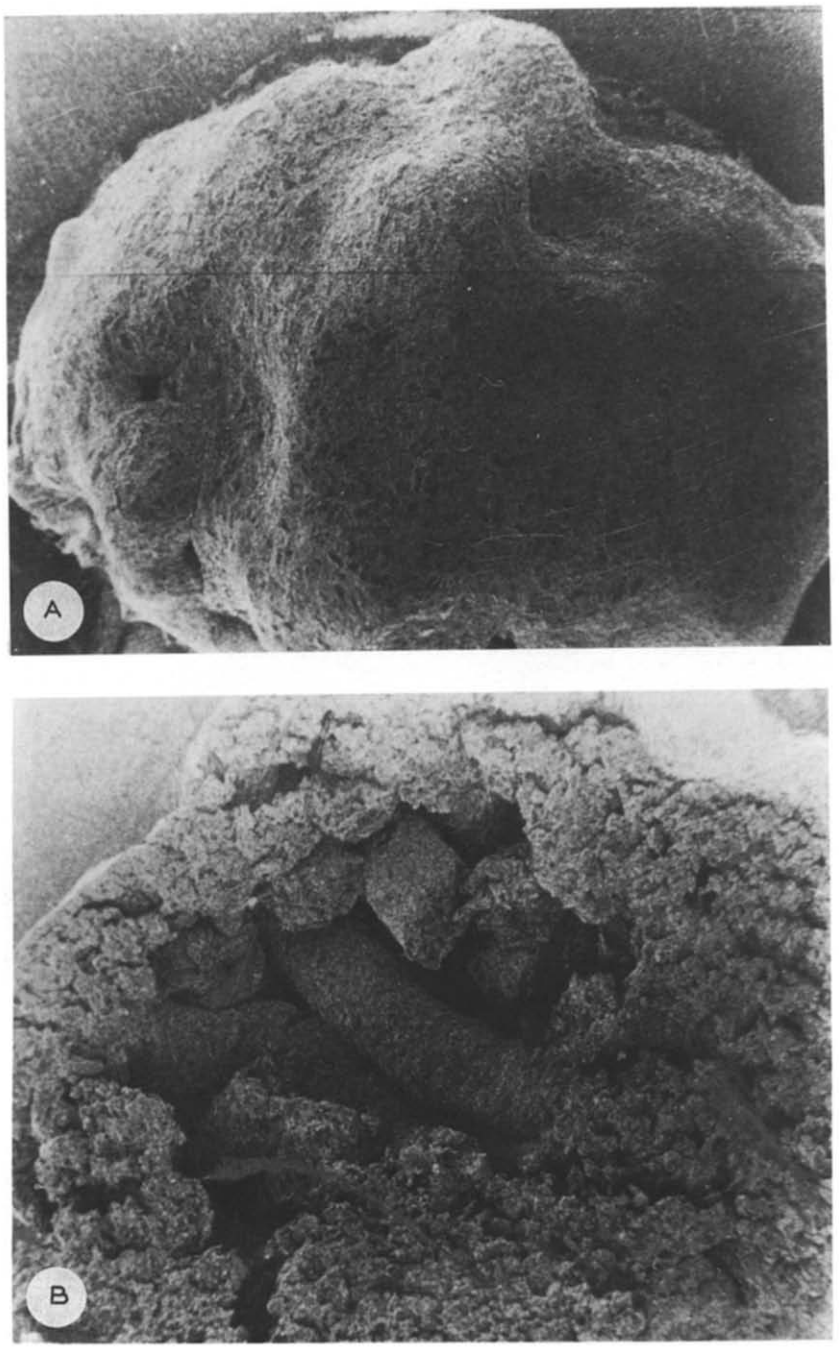

Fig. 10. Scanning electron micrographs of (A) the surface and (B) internal structure of an agglomerated granule produced on spheronizing the 1.0 mm diameter extrudate containing coarse lactose. Magnification ×13.

the bulk were described by the particle size distribution using sieve analysis and direct measurement by Quantimet analysis. A standard pattern has emerged that signifies controlled spheronisation, i.e., a large initial decrease in OPCS within 2 min, followed by a smaller decrease over 10 min

concurrent with an increase in granule width and reduction in granule length. Changing the particle size of one of the components of the extrusion mixture, the lactose used as a water-soluble drug model, from a fine to a coarse grade produced an extrudate which no longer satisfied the criteria required for satisfactory spheronization and resulted in uncontrolled agglomeration. Photographic evidence showed that after the extrudate had been reduced to short cylindrical lengths the granules associated loosely into clusters. Forces subsequently acting on the granules resulted in coalescence of one or more particles, which is symptomatic of an over-wetted surface. Lactose particle size was previously shown to be an important factor in the preparation of a uniform, consistent extrudate (Fielden et al., 1988). In this respect, extrusion should ideally take place at a constant force as observed for the wet powder mass containing fine lactose. Increasing the lactose particle size significantly affected the force-displacement profile and caused extrusion to occur at high pressures under conditions of forced flow. This resulted in expression of water from the plug in the extruder barrel to the extrudate such that the moisture content of the latter varied and was, on average, approx. 4% greater than that of the wet powder mass. A study by Fielden et al. (1992), using a pressure membrane technique, indicated that this phenomenon is attributable to an increase in the mean pore diameter of the mixture containing coarse lactose which facilitates movement of the liquid phase through the wet powder mass. The highly mobile liquid phase within the over-wetted portion of the extrudate thus produced was therefore responsible for the observed agglomeration during spheronization.

That the extrudates containing the coarse and fine particle sizes of lactose showed different spheronization properties could be predicted from the differing shear stress-shear rate curves for the wet powder masses, the former showing more marked shear rate dependency, (Fielden et al., 1989). This implied that the rheological properties of the extrudates, as distinct from that of the wet masses, produced under identical conditions, would also differ. Hence, in contrast to the extrudate containing the fine grade lactose, the spheronized extrudate containing the coarse lactose agglomerated.

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