Crystallization of Lactose from Carbopol Gels

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Purpose. To crystallize lactose under static conditions with a view to preparing crystals of well-defined morphology.

Methods. α-Lactose monohydrate was crystallized from neutralized Carbopol 934 gels. When the majority of crystals had grown to maturity, the gels were acidified using diluted hydrochloric acid and the crystals were harvested by filtration or centrifugation and washed with ethanol-water mixtures.

Results. Crystals prepared from the gel had a consistently narrower size distribution than control crystals, prepared from solution under constant stirring. If crystallization was effected in the gel without sedimentation of the crystals, then the resultant crystals had smooth surfaces without visually detectable surface roughness or asperities viewed by optical microscopy. The crystals from Carbopol gels also exhibited the uniform shape of an elongated tomahawk regardless of the crystallization conditions, in contrast to crystallization under constant stirring, where the crystal shape of lactose changed with crystallization conditions especially as a function of the initial concentration of lactose. All batches of lactose crystals prepared from Carbopol gels existed as α-lactose monohydrate, which showed better flowability than the controls of a similar particle size.

Conclusions. Crystallization from Carbopol gel produces lactose crystals of uniform size, regular shape, smooth surface, and improved flowability.

KEY WORDS: lactose; crystallization; Carbopol gels; morphology; crystal form; crystal habit.

INTRODUCTION

Constant stirring is essential for the crystallisation of a substance from solution so as to avoid caking and the formation of other non-dispersible aggregates. However, mechanical stirring introduces random energy fluctuations in the solution and causes heterogeneous distribution of local concentrations, leading to heterogeneous growth of crystals. It almost always results in the production of crystals with a wide particle size distribution (1). The crystals are often of irregular shape with rough surface. The size and morphology of a drug or excipient are known to affect many important pharmaceutical properties and some drug delivery systems such as inhalation aerosols require the drug or excipient to be of narrow particle size distribution with regular particle shape. One of the methods which can be employed to prepare such crystals, is to suspend the crystals in a gel (2). This which provides a protective barrier for the growing crystals and permits a steady diffusion of crystallising molecules. Without introducing any external turbulence to the solution, the gel can be expected to provide a homogeneous environment in which the crystals can grow and, thus, overcome some of the major problems associated with the use of mechanical stirring. Since the crystals are in a stagnant suspension, individual crystals can be grown to maturity without any fractures. Further, secondary nucleation will occur to much lesser extent in a gel than in the case of the solution under agitation (3). The inhibition of such nucleation may result in a narrower size distribution of the final particles.

A gel that could be employed to prepare pharmaceutical crystals must be non-toxic, and ideally should be capable of being efficiently removed from the surface of the final crystals so as not to affect any physico-chemical properties of the crystals. Carbopols, a group of polyacrylic acid polymers cross-linked with either allylsucrose or allyl ethers of pentaerythritol, might provide an ideal gel for the preparation of pharmaceutical crystals. Carbopols, widely used as pharmaceutical excipients (4–5), disperse in water to form acidic colloidal solutions of low viscosity which when neutralised, produce highly viscous gels. The viscosity reaches a maximum at pH 6–11 but is considerably reduced if the pH is less than 3 or greater than 12 (4). Hence, it is possible that the crystallisation could be carried out in a neutralised Carbopol gel, after which the gel could be converted to a fluid by acidification such that the crystals may be readily harvested. Carbopol is soluble in both water and ethanol (4) whereas many pharmaceutical materials dissolve in either solvent. Therefore, any adsorbed Carbopol residue on the crystals might be removed by washing the crystals with either ethanol or water without substantially changing the morphology of the crystals. It was the purpose of the present study therefore to attempt to crystallise a model pharmaceutical excipient, lactose, from Carbopol gels with a view to preparing crystals which possessed a regular shape, smooth surface and narrow size distribution. One application of such crystals might be as a carrier for dry powder aerosols, engineered to provide efficient and reproducible delivery of drugs to the lower airways.

MATERIALS AND METHODS

Crystallization of Lactose from Carbopol Gels

A predetermined amount of distilled water was agitated at about 500 rpm with a 4-bladed stirrer (1 × 3 cm) which was situated 2 cm above the bottom of a 500 ml beaker. The

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ABBREVIATIONS: θ_r, angle of repose; θ_s, angle of slide; A, area of the projected image of a particle; C# lactose, sieved 63–90 μm fraction of Carbo # lactose; Carbo # lactose, lactose prepared from carbopol gels before sieving; C_C, Carbopol concentration; C_L, lactose concentration; Control 1, sieved (63–90 μm) fraction of lactose prepared under stirring from initial concentration of 33%, w/w; Control 2, sieved (63–90 μm) fraction of lactose prepared under stirring from initial concentration of 43%, w/w; DSC, differential scanning calorimetry; d_{sv}, surface volume mean diameter by optical microscopy; E, elongation ratio of the projected image of a particle; F_{shape}, shape factor; $F_{surface}$, surface factor; RDC, relative degree of crystallinity; SEM, scanning electron microscopy; SSA, specific surface area; t_C, crystallization time; TGA, thermal gravimetric analysis; XRPD, X-ray powder diffractometry.

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required amount of Carbopol 934 (B. F. Goodrich Chemical Co., Cleveland, Ohio, USA.) with an average molecular weight of approximately 3,000,000, was added into the vortex. When all the Carbopol was dispersed, the liquid was allowed to stand overnight in the dark. A cloudy, colloidal solution with a pH of about 3.2 was obtained. A predetermined amount of lactose (Borculo Whey Ltd., Chester, UK) was then dissolved in the Carbopol solution at 90°C under constant stirring at 500 rpm. Sodium hydroxide solution (1 M) was added dropwise to the solution, whilst stirring at about 800 rpm, until a clear homogeneous gel was produced at a pH value of approximately 4.5. The addition of the neutralising agent (NaOH) was continued so as to obtain a pH value of 7 and the gel was then sonicated in a water bath for about 15 min to remove any entrapped air bubbles and insoluble particles. The gel was placed in the dark until the majority of the crystals had grown to the size range of 63–90 μm, monitored using optical microscopy. Then, the gel was adjusted to pH 3–3.5 with hydrochloric acid (1 M) to obtain a fluid and the crystals allowed to settle for about 10 min. After decanting the supernatant, the crystals were washed with 60% ethanol twice and absolute ethanol three times. The crystals were allowed to dry at room temperature after which, a small amount of sample (about 0.5 g) was taken from each batch of lactose. The remaining crystals were passed through a 90 μm test sieve (Endecotts Ltd., London, UK) placed over a 63 μm test sieve. The particles were sieved manually and slowly for 1 h so as to limit the rupture of any crystals. The particles were thus divided into 3 size fractions (<63, 63–90 and >90 μm) which were collected and weighed separately. The classified lactose crystals were dried under vacuum at 70°C for 3 h before transferring to sealed vials, placed in a desiccator over silica gel. The Borculo lactose was also subjected to a similar sieving and drying treatment to obtain 63–90 μm fraction, designated as Lactochem®.

Lactose crystallisation from Carbopol 934 gels was carried out under different conditions by altering the crystallisation time and the concentrations of either lactose or Carbopol gel (Table I). Three separate batches of lactose crystals were prepared from Carbopol gels under each of the seven conditions listed in Table I but all of these 3 individual batches were then mixed to prepare final batches of lactose, which were labelled as Carbo 1 to Carbo 7, respectively. The 63–90 μm fraction of batches Carbo 1 to Carbo 7 were labelled as C1 to C7, respectively. Lactose crystals from batch Carbo 1 were further classified into fractions <63; 90–125 and >125 μm. Batch Carbo 7 differed from other batches of lactose in that it was washed directly with 100% ethanol rather than being prewashed with 60% v/v ethanol.

Table I. The Crystallization Conditions, Surface Volume Mean Diameter Measured by Optical Microscopy and Particle Size Distribution Obtained by Sieve Measurement of the Resultant Lactose Crystals

Batch No	Lactose (% w/w)	Carbopol (% w/v)	Crystal time (h)	Mean Size (μm)	% Particle (μm)		
					<63	63–90	>90
Carbo 1	43.0	0.6	72	105.4	5.8	35.4	58.8
Carbo 2	43.0	0.3	24	87.9	10.3	56.5	33.2
Carbo 3	33.0	0.3	24	76.5	12.2	68.7	19.1
Carbo 4	50.0	0.4	48	116.3	8.2	12.6	79.2
Carbo 5	50.0	0.6	72	114.2	1.4	22.3	76.3
Carbo 6	38	0.4	72	93.3	8.5	53.5	38.0
Carbo 7	38	0.4	48	75.4	15.6	73.2	11.2
1st Control	33	0	24	105.3	25.2	12.2	62.6
2nd Control	43	0	12	100.6	24.5	17.9	57.6

Two aqueous solutions of lactose with concentrations of 33% and 43% w/w were prepared at 90°C. After filtration through a Whatman filter paper (<0.45 μm) whilst hot, they were allowed to cool to room temperature to obtain slightly acidic solutions with pH 4–4.5. After neutralization with NaOH solution, the lactose solutions were agitated separately at 500 rpm for lactose to crystallize. Two lactose batches were prepared, which were subjected to a treatment of washing and drying similar to that employed for lactose crystals derived from Carbopol gels. The sieved (63–90 μm) fractions of lactose batches crystallized from initial concentrations of 33% and 43% w/w were designated as control 1 and control 2, respectively.

Morphological Characterization of Lactose Crystals

A small amount of lactose from each batch was viewed by optical microscopy (Labophot-2, Nikon, Japan) and the images of the particles (Nikon camera) were transferred to an IBM compatible computer. Particle images were analysed automatically using analySIS 2.0 software (SIS Image Analysis GmbH, Germany). At least three hundred particles were measured for each batch of lactose. The area of the projected image of each particle was recorded and the surface-volume diameter was calculated as the mean diameter of the powder. The morphology of lactose crystals was quantified by three shape descriptors, derived from the length (L), width (W), perimeter (P) and area (A) of the projected image of a particle and these include the elongation ratio (E: L/W), the shape factor (F_{shape}: $4\pi \times A/P^2$) and the surface factor ($F_{surface}$: $F_{shape} \times (1 + E)^2/(\pi \times E)$). E has a value in the range ≥1, the higher the value the more elongated the particle. F_{shape} is in the range 0–1 and combines properties related to both surface roughness and shape (e.g., a spherical particle with a smooth surface has a value of 1). $F_{surface}$ is a derived factor which also varies from 0–1 but is primarily dependent upon surface roughness alone; particles that are perfectly smooth would have a value of 1 (7).

Particle shape and surface textures were also compared qualitatively by scanning electron microscopy (SEM). Several photomicrographs were produced by scanning fields, selected randomly, using a Philips SEM501B scanning electron microscope (Einhoven, Holland).

The true density of lactose was measured using a Beckman Air Comparison Pycnometer (Model 930, Beckman Instrument, Inc., Fullerton, USA) and the specific surface area was determined using an air permeation method with a Fisher sub-sieve sizer.

Powder Flowability

Angle of Repose

Lactose crystals were carefully poured into a copper tube (2.65 cm × 6.90 cm), which had been placed over a flat base with a diameter of 2.53 cm. After the powder column reached a height of approximately 4 cm, the addition of powder was stopped and the tube was slowly lifted vertically, leaving a

cone of powder. The height of the cone was measured and, the angle of repose (θ_r) was calculated from the tangent (cone height/cone base radius). Each sample was measured at least in triplicate.

Angle of Slide

The angle of slide (θ_s), can be employed to express the flowability of the powder bed (8). A small amount (approximately 10 mg) of lactose crystals was placed on a stainless steel plane (6.55 × 7.00 cm), and this was then tilted by screwing a supporting spindle vertically upwards from below the plane until powder slide occurred. The angle between the tilted plane and the horizontal base, θ_s was measured directly, in triplicate for each sample.

Characterization of Polymorphic Forms

A small amount of lactose crystals (4–5 mg) was placed in an open aluminium pan within the sample chamber of an STA 625 Differential Scanning Calorimeter (TA instruments, Surrey, UK). Thermal gravimetric analysis (TGA) and differential scanning calorimetry (DSC) of the sample were carried out concommitantly at a heating rate of 10°C min^{-1} from ambient temperature to 280°C under N_2 flowing at 50 ml min^{-1}.

The X-ray powder diffraction (XRPD) pattern of lactose was measured at room temperature with a Philips X'Pert Dual Goniometer (Philips Analytical, Holland). The X-ray source was a copper-Kα operated at a voltage of 40 kV and with a current of 50 mA. Samples were back-filled into 16 mm holders. Results were recorded over a range of 2–35° (2θ) with a step size of 0.04° and a count rate of 1 step s^{-1}.

RESULTS AND DISCUSSION

Crystallization of Lactose from Carbopol Gels

Lactose crystals with different particle sizes and size distributions were prepared when different concentrations of lactose and Carbopol gel were employed (Table I). The relationship between the mean diameter of lactose crystals and these preparative conditions can be seen from the following empirical equation generated by a 'step-wise forward algorithm' in multiple regression using Minitab® for Windows software (Version 10.2).

$$\text{Mean particle size } (\mu m) = 2.12\ C_L - 3.9\ C_C + 0.2\ t_c - 4.4\ r^2 = 0.886 \quad (1)$$

where C_L and C_C are the concentrations (% w/w) of lactose and Carbopol gel, respectively; t_c is the crystallization time (h).

Thus, either increasing the initial lactose concentration, reducing Carbopol concentration or extending the crystallisation time period will increase the mean particle size of the lactose crystals prepared. It is widely known that increasing supersaturation increases crystal growth, leading to the preparation of larger crystals. The lack of convection currents in a gel may retard the transfer of lactose molecules from the surrounding solution to crystal surface, reducing the growth rate of lactose crystals. This might explain why the crystals were smaller in the presence of the gels. However, lactose particles prepared from Carbopol gels had consistently smaller fractions of particles less than 63 μm in diameter (Table I) than the controls (Table I). For example, batch Carbo 1 had a mean diameter of 105.4 μm with 5.8% w/w particles <63 μm, which was less than a quarter of the 25.2% w/w particles <63 μm of the 1st control batch that had a mean diameter of 105.3 μm. Carbopol 934 gel is likely to inhibit secondary (heterogeneous) nucleation due to the lack of any external agitation (6). The nucleation suppressing property of gels distinguishes crystallisation in gels from ordinary diffusion methods and is responsible for the production of crystals with relatively uniform size distribution.

Most of the crystals prepared from Carbopol gels had a more regular shape with a smoother surface than the controls (Fig. 1). All the lactose prepared from the gel had a similar shape of an elongated tomahawk, regardless of the conditions of crystallisation. As mentioned previously (13), when crystallisation was carried out under constant stirring, the crystal shape of lactose changed with the initial lactose concentration. The relatively consistent shape of lactose prepared from Carbopol gel suggests that the effect of supersaturation of lactose on particle shape was suppressed in the presence of the gel such that the crystal shape of lactose was practically independent of the initial lactose concentration. Lactose molecules can be expected to migrate freely in the crystallisation media under constant stirring and hence, any change in the supersaturation results in a change in the crystallisation pressure in the vicinity of the growing crystals, which will eventually change the crystal shape. However, the framework of the gels may impose a three-dimensional barrier for the free migration of lactose molecules and consequently, lactose concentrations in the immediate vicinity of the growing crystals might be expected to be lower than the apparent concentration of lactose in the bulk of the crystallisation medium. Therefore, any increase in the apparent supersaturation of lactose may not result in a corresponding increase in the effective concentration driving crystal growth. This would result in a reduction in the sensitivity of crystal habit to lactose concentration.

Of all the batches of lactose prepared from the gels, batches C2 and C3 appeared to have the least regular shape (Fig. 1). These batches were prepared from gels with a concentration of 0.3% w/v. It was observed that after crystallisation, most of the crystals sedimented to the bottom of the container. The sedimented crystals tended to form aggregates that were difficult to disperse into individual component particles. Therefore, in order to obtain crystals of regular shape with a smooth surface, the gel concentrations had to be increased so as to confer the appropriate rheological characteristics to suspend the majority of the crystals. However, higher concentrations of Carbopol gels resulted in slower crystal growth of lactose, extending the time period for the crystals to grow to the desirable size range for these studies (63–90 μm). Furthermore, too high a concentration lead to unnecessarily high rigidity of the gel, which in turn made it difficult to harvest the crystals. Therefore, the polymer concentration had to be carefully controlled and a concentration of approximately 0.4% w/w was thought to be most suitable for the preparation of lactose crystals with the maximum proportion within the size range 63–90 μm.

When lactose batch C7 was examined by SE microscopy, some needle crystals could be seen adhering to the coarser crystals (Fig. 1). These needle crystals were introduced during the washing process since this batch of lactose was washed

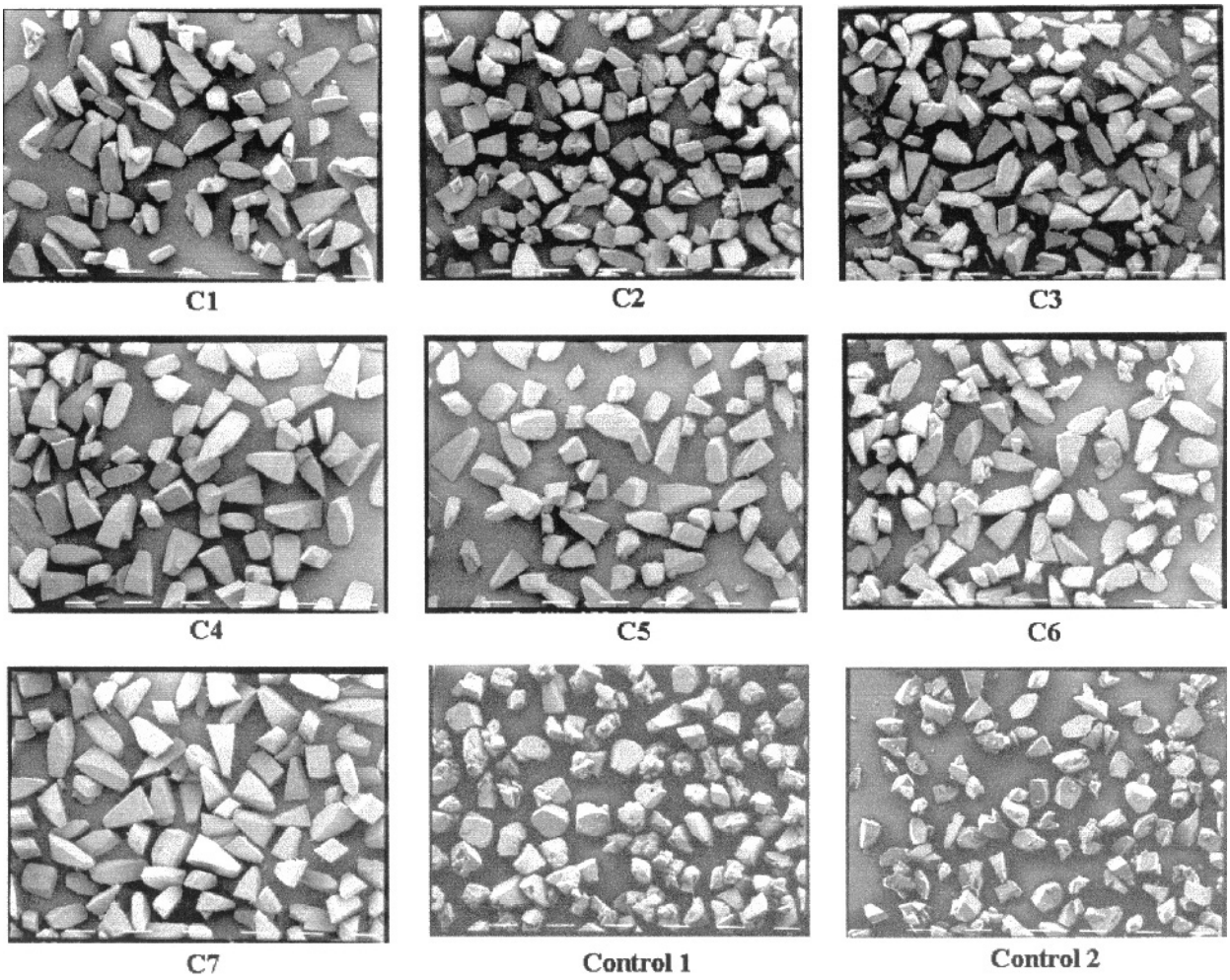

Fig. 1. The SE micrographs of some batches of lactose prepared from Carbopol 934 gels and the controls (Scale bars represent 100 μm).

directly with 100% v/v ethanol without pre-washing with 60% v/v ethanol as employed for the rest batches of lactose. After separation from the mother liquor, the crystals still had traces of the mother liquor adhered to the crystal surfaces. If the mother liquor was placed in direct contact with 100% ethanol, then, any lactose remaining in the solution crystallised so rapidly that only needle crystals were obtained. Therefore, a pre-washing process with lower ethanol concentrations had to be employed so as to remove most of the mother liquor from crystal surfaces without the formation of unwanted crystals. Too low an ethanol concentration should be avoided in the pre-washing process with a view to avoiding lactose dissolution and maintaining the integrity of lactose crystals.

Each batch of lactose had a density (Table II), similar to that of α-lactose monohydrate, 1.54 g cm^{-3} (9). Most of the crystals prepared from Carbopol gels had values of shape factor which were similar to those of the controls. Nevertheless, the standard deviation of the shape factor derived for all crystals prepared from Carbopol gels, which varied between 0.07 and 0.09 (Table II), was significantly lower (ANOVA $p < 0.05$) than those of the controls, suggesting that the former were more uniformly shaped than the latter. The mean elongation ratio derived for all the batches of lactose crystals prepared from the gels was 1.71 ± 0.18, which was significantly higher ($p < 0.01$) than that of the controls. Thus, Carbopol gels may slightly alter the crystal habit of lactose, leading to the production of more elongated particles.

Lactose particles prepared from Carbopol gels generally had a value of 'surface factor' close to unity, indicating these batches of lactose had such smooth surfaces that the surface asperities, if any, were undetectable by the method employed in the current study. Batches C2 and C3 had lower values of 'surface factor' (0.94 and 0.91, respectively) and this was in agreement with the visually rougher surfaces of these batches of lactose as shown in their SE micrographs (Fig. 1). Lactose batch C7 also showed a lower value of 'surface factor' (0.94) and this might be due to the adhered small needle crystals on the surface of the coarser lactose crystals. The rest of the batches of the lactose crystals all showed a 'surface factor' value of 1, which was higher than the values obtained for the control batches. If the Carbopol concentration was sufficient to suspend the majority of the growing lactose crystals (≥4% w/v), then the particle shape and surface smoothness of the resultant lactose crystals appeared to be more or less independent of the crystallisation conditions. This is shown by the lack of significant difference ($p > 0.05$) in either the shape factor or elongation ratio of these batches of lactose.

Different size fractions of Carbo 1 lactose differed slightly

Table II. The Density, Mean Diameter (d_{sv}), Specific Surface Area (SSA), Shape Factor, Elongation Ratio, and Surface Factors of Some Batches of Lactose

Batch No	Density g cm^{-3}	d_{sv} (μm)	SSA (cm^2 g^{-1})	Shape factor	Elongation Ratio	Surface factor
		(n > 300)		(n > 150)	(n > 150)	
Lactochem	1.53	88.7	834	0.74 ± 0.09	1.68 ± 0.36	1.00 ± 0.12
C1	1.54	104.1	636	0.76 ± 0.07	1.58 ± 0.32	1.02 ± 0.08
C2	1.56	101.7	798	0.70 ± 0.09	1.61 ± 0.38	0.94 ± 0.10
C3	1.55	105.2	839	0.68 ± 0.08	1.59 ± 0.35	0.91 ± 0.09
C4	1.54	111.7	680	0.73 ± 0.09	1.85 ± 0.48	1.02 ± 0.11
C5	1.53	105.7	649	0.76 ± 0.07	1.55 ± 0.31	1.01 ± 0.08
C6	1.54	109.4	712	0.71 ± 0.09	2.03 ± 0.40	1.02 ± 0.10
C7	1.55	118.8	742	0.68 ± 0.08	1.78 ± 0.33	0.94 ± 0.09
Control 1*	1.55	100.3	774	0.72 ± 0.09	1.30 ± 0.23	0.93 ± 0.12
Control 2*	1.54	100.6	817	0.72 ± 0.12	1.37 ± 0.22	0.94 ± 0.13

Note: Mean ± SD.
* Was the sieved fraction (63–90 μm) of the corresponding control batch listed in Table I.

in their shape and surface texture (Fig. 2). The <63 μm fraction contained a combination of prismatic, pyramidal and tomahawk shaped particles. The 63–90 μm and 90–125 μm fractions were mostly tomahawk-shaped with similar surface textures whereas particles >125 μm were shown to contain some aggregates.

The crystals <63 μm had the lowest value of elongation ratio, shape factor and 'surface factor', suggesting that particles of this size fraction had the least regular and elongated shape with the most surface asperities (Table III). The 63–90 μm crystals exhibited the highest values for the shape factor (0.76) and a value close to unity for the 'surface factor', indicating that this size fraction had the most regular shape with the least surface asperities. The 90–125 μm crystals had a lower value of shape factor (0.71) but higher value of elongation ratio (2.02) than the 63–90 μm crystals. This was indicative of a less regular but more elongated shape for the former size fraction than for the latter fraction. The 90–125 μm particles also exhibited a 'surface factor' value of unity, indicating this size fraction also had smooth particle surface. However, a further increase in the particle size above 125 μm appeared to reduce the values of all the shape descriptors. Increasing the particle size from <63

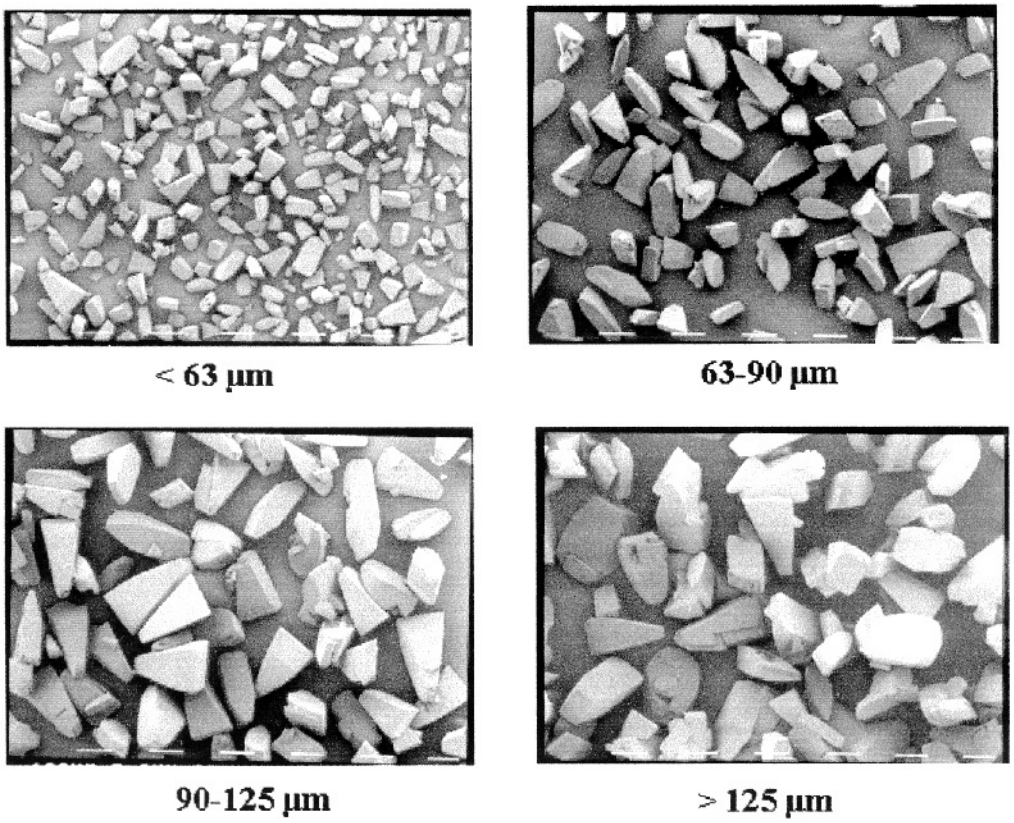

Fig. 2. The SE micrographs of different size fractions of Carbo 1 lactose.

Table III. Some Physical Properties of Different Size Fractions of Lactose Particles Batch Carbo 1

Size (μm)	Density g cm^{-3}	Diameter (μm)	Shape factor	Elongation ratio	Surface factor
<63	1.57	65.6 ± 17.9	0.62 ± 0.15	1.52 ± 0.28	0.82 ± 0.16
63–90	1.54	104.1 ± 19.1	0.76 ± 0.07	1.58 ± 0.33	1.02 ± 0.08
90–125	1.53	174.6 ± 19.6	0.71 ± 0.07	2.02 ± 0.37	1.02 ± 0.09
>125	1.54	211.8 ± 26.9	0.66 ± 0.06	1.83 ± 0.21	0.92 ± 0.08

Note: Mean ± SD, n > 150.

μm through 63–90 μm to 90–125 μm, tended to increase the elongation ratio of the crystals, suggesting larger particles were more elongated than smaller particles. Therefore, similar to growth in aqueous solutions under constant stirring, lactose crystals also grew along their longitudinal axes in Carbopol gels. Further growth of lactose crystals to >125 μm appeared to produce less elongated particles since the crystals >125 μm had an elongation ratio of 1.83 ± 0.21, which was significantly ($p < 0.01$) lower than 2.02 ± 0.37 for the crystals 90–125 μm. This phenomenon suggests that although lactose crystals grow more along their length than along their width, the bias toward longitudinal axes might decrease when the crystals exceed a certain limiting diameter.

Flowability of Lactose Crystals

Lactose particles prepared from Carbopol gels showed more consistent values of θ_r (40–46°) and θ_s (40–48°) in comparison to the controls and this might have been due to more effective control of the particle morphology of the former particles (Table IV). Further, the crystals prepared from Carbopol gels appeared to exhibit superior flowability than the controls since they generally had smaller values of θ_s than the latter lactose. The better flowability of lactose crystallised from Carbopol gels may have largely been due to the smoother surface of these crystals since such particles would have a smaller internal friction during flow (8). Further, the angle of slide was shown to be significantly ($p < 0.01$, paired t-test) higher than the angle of repose for all samples taken from the same batch. The angle of repose differs from the angle of slide in that the former is determined by the least stable particles whilst the latter depends largely on the average conditions for the bulk of the powder (8). Therefore, the angle of slide may correlate more closely with flow properties than the angle of repose.

Table IV. The Angle of Repose (θ_r) and Angle of Slide (θ_s) of Different Batches of Lactose Crystals

Batch No	θ_r (°)	θ_s (°)
C1	46 ± 1	48 ± 0
C2	40 ± 0	43 ± 1
C3	41 ± 2	45 ± 1
C4	40 ± 1	45 ± 2
C5	42 ± 2	48 ± 1
C6	41 ± 0	43 ± 1
C7	43 ± 1	40 ± 1
Control 1	56 ± 2	> 90
Control 2	43 ± 1	50 ± 2
Lactochem	48 ± 2	50 ± 1

Note: Mean ± SD, n ≥ 3.

Characterization of Polymorphic Forms

Lactose prepared from Carbopol gels showed TGA (Fig. 3) and DSC (Fig. 4) traces typical of α-lactose monohydrate. The TGA showed a weight loss between approximately 120°–190°C, due to the dehydration of water of crystallisation, and a weight loss at 200°–250°C, due to lactose decomposition (10). The DSC showed an endothermic transition starting at about 130°C, corresponding to dehydration of water of crystallisation, and an endothermic peak at about 217°C which is the melting endotherm of α-lactose monohydrate (11). A small exothermic peak was observed at about 177°C, which was attributed to the crystallisation of unstable anhydrous α-lactose arising from the dehydration of α-lactose monohydrate during the DSC scan (12). However, the peak may be a result of a large irreversible exotherm combined with a smaller reversible endotherm (13). The exothermic event has been attributed to the crystallization of amorphous lactose and the heat of crystallization, calculated from the integrated area of the peak, can be used to assess the amorphous content of the crystals (14). The DSC traces of crystals prepared from the gel showed a smaller exothermic peak at 177°C, suggesting that the crystals might contain less amorphous content than the those prepared under constant stirring.

All batches of lactose exhibited an X-ray powder diffraction pattern (XRPD) (Fig. 5), similar to α-lactose monohydrate (13,15). Different batches showed slightly different peak intensities, which might be indicative of different degrees of crystallinity. However, it is not possible to calculate accurately the absolute degree of crystallinity by the XRPD patterns obtained in the current work but the relative degree of crystallinity (RDC) of different samples of the same crystal form may be qualitatively compared by their peak intensity at the same diffraction angle. RDC is proportional to the ratio of the peak intensity of a given sample of a single polymorphic form to that of another specimen of the same polymorph (16). Lactochem contained smaller particles which were significantly more elongated than the component particles of two control batches (Table II) but the three batches produced similar XRPD patterns (Fig. 5). Thus, the subtle difference in the particle size and morphology of the different samples might not contribute to a marked difference in the XRDP. The obviously higher peak intensities of C1 and C2 lactose could therefore be attributed to a relatively higher crystallinity of these lactoses as compared with either the Lactochem or control lactoses.

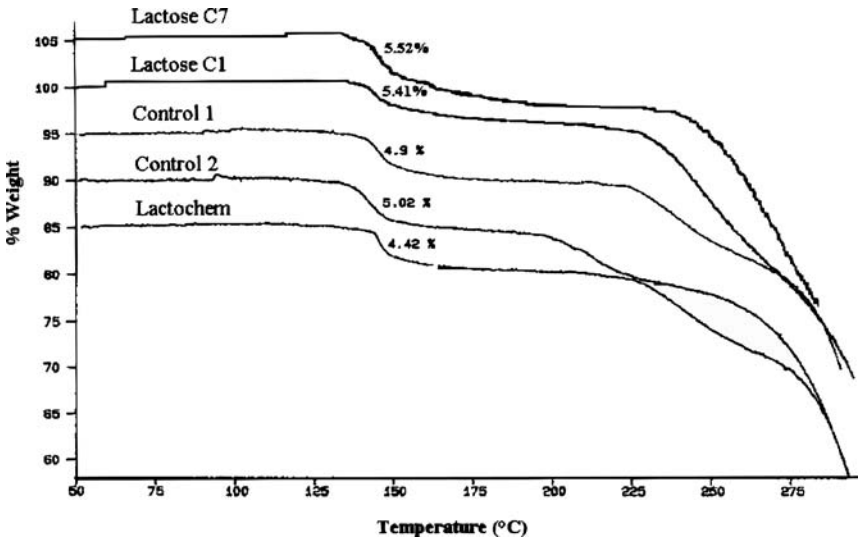

Fig. 3. The TGA thermogram of some batches of lactose crystallized from Carbopol gels and the controls.

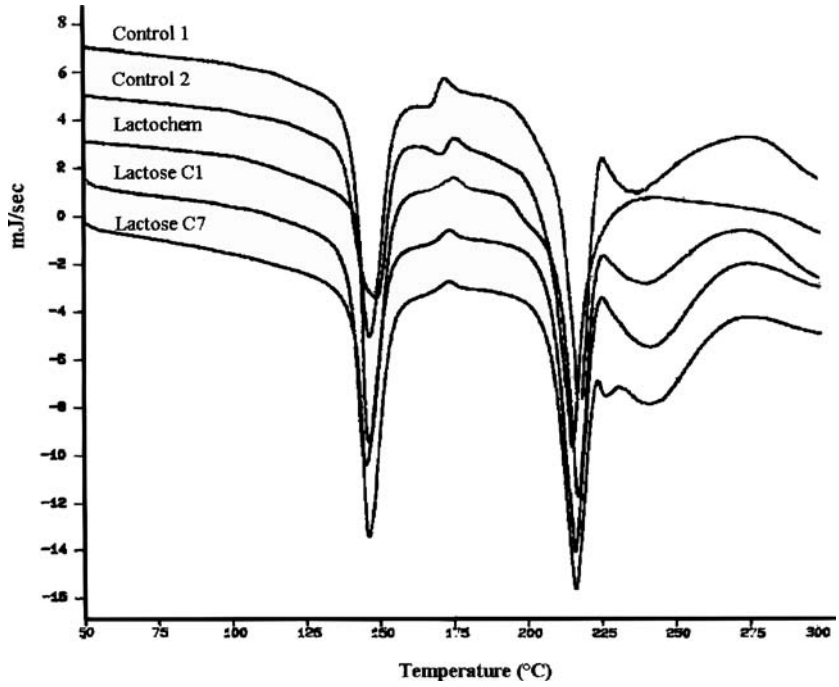

Fig. 4. DSC thermograms of lactose prepared under constant stirring (the controls) and from Carbopol gels as well as the commercial α-lactose monohydrate (Lactochem).

CONCLUSION

The gel framework acts like a three-dimensional crucible in which the crystal nuclei are delicately held in the position of their formation while growth proceeds without the intervention of convective movement of the solute. The crystallization from the gels occurred at a slower rate than in the case of crystallization under mechanical stirring. It is known that the growth rate of a crystal determines the number of defects built into the crystals since the higher the growth rate, the more crystal defects are likely to form in the crystal lattice (17). All these effects may have contributed to the preparation of α-lactose monohydrate crystals of narrow particle size distribution, well-defined, elongated shape with improved surface smoothness and flowability.

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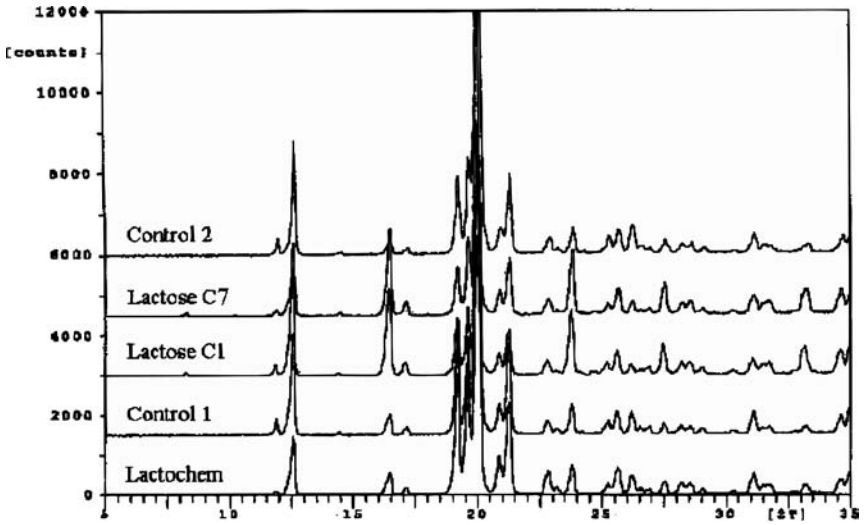

Fig. 5. The X-ray powder diffraction patterns for different batches of lactose crystals.

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