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RESEARCH PAPER

Poloxamer Thermogel Systems as Medium for Crystallization

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ABSTRACT

Purpose To prepare a thermoreversible gel system able to work as a medium for crystallization at around 20°C, allowing easy retrieval of crystals by simply decreasing the gel temperature. Lactose was selected has model substance for crystallization.

Methods Water solutions with different% of poloxamer 407, α-Lactose monohydrate, and ethanol were prepared and analysed by rheology to understand how the different components alter the gelling temperature. The systems with the required characteristics for lactose crystallization were prepared and the crystals recovered by cooling and then filtering the dispersion.

Results Rheological analysis showed interaction between the poloxamer and lactose. Increasing the quantity of poloxamer or lactose lowered the gelation temperature while the addition of small amounts of ethanol had a modest effect on the same property. These data were used to identify the ideal concentration of the components in order to prepare a system matching the features of our purpose. Such system yielded high quality crystals, with well-defined geometry and narrow particle size distribution.

Conclusion Poloxamer is a very interesting polymer in that it is able to generate a reversible gelling medium from which crystals can be harvested by filtering, without the addition of any chemicals to promote the sol–gel transition.

KEY WORDS crystallization · lactose · poloxamer · rheology · thermogel

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ABBREVIATIONS

CI	Carr index
D_{50}	median diameter
DSC	differential scanning calorimetry
G′	elastic modulus
G″	viscous modulus
IQR	interquartile range
LSS	lactose stock solutions
PEO	polyethylene oxide
PPO	polypropylene oxide
PSS	poloxamer stock solutions
δ	phase angle
η*	complex viscosity
ρ_b	bulk density
ρ_t	tapped density

INTRODUCTION

In the manufacturing of drugs or excipients, crystallization is the most common procedure in the final phases of purification and separation, defining both chemical purity and physical properties (e.g. particle size, shape, and crystal structure of the materials produced). It is not merely a simple intermediate step in chemical production, but has to be considered a crucial phase in determining the processability, bioavailability, and stability of the final material (1).

While crystallization from solution is currently the most commonly used methodology, it can have several drawbacks, among them difficulties in producing crystals with narrow particle size distribution and low particle aggregation. One of the alternative methods is crystallization in a gel matrix. The technique, which originated at the end of

19th century, when the German chemist and photographer Liesegang observed precipitation of salts in gelatine (2). was popular in the 1960s and 1970s as an easier way to obtain perfect, defect-free crystalline substances (3). In fact, gel matrix often affords an ideal environment for crystal growth, because the gel network is strong enough to sustain and protect the crystals, but not so rigid as to prevent their growth; moreover, the mass transfer of crystallizing molecules proceeds in steady way by diffusion, and secondary nucleation is strongly reduced. As a consequence, the harvested crystals have low aggregation, narrow particle size distribution, and high homogeneity in terms of shape and surface texture (3–5), making them better quality than crystals obtained from classical procedures. The only work where crystals obtained from gel were used for a pharmaceutical application, more precisely in the field of dry powder inhalers, reported that they performed much better than materials crystallized from solution (6).

Crystallization in gel was the object of a large number of publications up to he 1980s, well reviewed by Arora (3). Many of them investigated the growth mechanism of crystals or the effect of the variables involved, but most of the papers did not report any procedure for crystal recovery, which was probably obtained through manual removal of each single crystal, as suggested by Robert (4). In the pharmaceutical field, the only works concerning the gel crystallization were published in 2000 by Zeng (5,6), who solved the crystal harvesting problem by using a reversible gel. In particular, the authors used a carbopol polymeric dispersion characterized by reversible sol–gel transition according to the pH. Although pH reversible gels offer a good solution for gel crystallization, an interesting alternative could be found in temperature reversible gels, principally because they do not require addition of any chemicals (acid and base) to the system to promote the sol transition. An ideal thermogel system should be in the gel phase around room temperature and switch steeply to a liquid dispersion upon a small change of temperature, preferably toward lower temperatures to avoid resolubilization of the crystals. The ideal candidate may be Poloxamers (also known as Pluronic), which are triblock copolymers of polyethylene oxide(PEO)-polypropylene oxide(PPO)-polyethylene oxide (PEO). Some of these polymers, very well known and characterised (7–13), can dissolve in water and ethanol medium, generating clear dispersions that can gel when the temperature is increased over a specific value, called the gel point. Such systems are very versatile from this point of view; in fact, the gel point is strongly dependent on the poloxamer type (molar mass and PEO/PPO ratio) and concentration, the type of solvent, and the type and concentration of other materials that may be present (14), so that the gel point can be adjusted to the desired value simply by selecting the right amount and type of each of the components.

The purpose of the present study was to develop a thermogel system able to work as a crystallization medium, one that gels at a temperature of 18–25°C and liquifies at a lower temperature, so that the crystals can be harvested easily. Lactose was selected as a model substance for the crystallization process, as it is a very well characterized pharmaceutical excipient that allows rapid analysis and interpretation of data obtained.

The work was organized into three phases: an initial characterization of the water/poloxamer/lactose system, in order to understand how the different components influence the gel point, an optimization phase to select the best conditions for the crystallization process, and a final part where the harvested crystals were characterised and compared with the starting and control samples.

MATERIALS AND METHODS

Materials

Poloxamer 407 (Acef, Italy; molecular weight 12.6 kDa and PEO/PPO ratio 2:1) and α-Lactose monohydrate (Pharmatose 150 M and Pharmatose 50 M, DMV International, The Netherlands) were used as received. Absolute ethanol was of standard reagent grade. Deionised water was produced with a laboratory deionizer (Osmo Lab UPW 2, Gamma 3, Italy).

Samples Preparation and Crystallization Set-Up

Concentrated solutions of Poloxamer 407 (Poloxamer stock solutions, PSS) were prepared by dispersing the polymer in the required amount of degassed and deionised water using the "cold" procedure (14). PSS were stored at 4–5°C for at least 48 h before use. Concentrated solutions of Pharmatose 150 M (Lactose stock solutions, LSS) were instead prepared by dissolving the disaccharide in the required amount of degassed and deionised water at 70°C.

Immediately after preparation, the LSS were left at room temperature until they reached the temperature of 25°C, and then added to the PSS kept in an ice bath. Moreover some final solutions were prepared by adding ethanol to the PSS-LSS solutions, in order to obtain a four-component system. The final solutions were mixed for 10 min while still in ice bath and then stored in an incubator at a specific temperature at which the solutions gel. The concentrations and amounts of PSS, LSS and ethanol were defined in order to obtain final solutions with concentrations ranging between 12% and 34% W/W for poloxamer, 0–26% W/W for lactose and 0–12.2% W/W for ethanol.

After a predetermined period of time (4, 14, and 24 h) in the incubator, the gels were cooled down in an ice bath for

5 min and then filtered under vacuum. The crystals recovered were washed with cold (5°C) absolute ethanol and then dried in the oven at 50°C for 3 h. The drying conditions were selected in order to obtain a final moisture content (determined by a Moisture Analyzer Scaltec SMO 01) similar to that of commercial lactose (4–5% W/W). The dried crystals were finally collected in closed vials and stored in a dessicator over calcium chloride.

At the same time, two control systems without polymer were prepared: water-lactose and water-lactose-ethanol, named respectively control water (C_{H20}) and control Ethanol (C_{Et}). In these systems the lactose concentration was 40% and 30% respectively, concentrations which allowed crystallization in times comparable to those of gelled systems. Moreover, for the C_{Et} the ethanol amount was the same (12.2%) as that of the gelled system. The control systems were prepared by dissolving lactose at 70°C under constant stirring and then leaving the solutions at ambient conditions up to 24 h, always under constant stirring, in order to avoid the phenomenon of caking. All the successive steps were the same as those of the gel systems.

Rheological Characterization of the Poloxamer Systems

Rheological analyses were performed using a stress control rheometer (Stress-Tech, Reologica) equipped with cone-plate geometry (4/40), automatic gap, and operating in the oscillation mode.

All the gel systems were analysed after preparation using a temperature sweep test, performed by stressing the samples at constant frequency (1 Hz) and pressure (10 Pa), while the temperature increased from 5 to 30°C (or to 40°C if no transitions were observed) at a rate of 1°C/min. Before each test, samples were left to equilibrate in the rheometer geometry at 5°C for 5 min. Each samples was analysed in triplicate.

The test made it possible to quantify the variation of the main rheological parameters such as elastic modulus (G′), viscous modulus (G″), phase angle (δ), and the complex viscosity (η*) as a function of temperature.

Characterization of the Lactose Crystals

DSC Analysis

Thermal analysis was carried out in a Pyris 1 DSC (Perkin-Elmer, Norwalk, USA), equipped with an intracooler (intracooler 2P, Perkin-Elmer, Norwalk, USA) in an inert nitrogen atmosphere.

A small amount (2–4 mg) of the samples was placed in an open aluminium pan and analysed, using an empty open pan as reference, from 25 to 250°C at a scan rate of 10°C/min.

The instrument was calibrated following the manufacturer's procedure using indium and zinc as standards.

All runs were performed at least in triplicate.

Image Analysis

Morphological characterization of the particles was performed using an optical microscope (MT9000 polarizing microscope, Meiji Techno Co. Ltd, Japan), equipped with a 3 Mega Pixels CMOS camera (Invenio 3S, DeltaPix). The images acquired (2048×1536 pixel) were subsequently analysed through the use of an image analysis software (Image Pro Plus, Media Cynernetics Inc.).

The software was calibrated for the various objectives used by means of a specific glass slide with a 5 mm graticule (S2-StageMic, Graticules LTD, UK). Pictures acquired using the 2.5X, 10X and 20X objectives (Meiji Techno Co. Ltd, Japan) possessed magnifications, expressed as pixel height, of 2.577, 0.643 and 0.318 μm respectively.

Length (L), the maximum distance between two points on the perimeter, and Breadth (B), the distance between two perimeter points linked by a line perpendicular to the length, were measured for each particle, while the particle diameter was determined as the average between the length and the breadth. The particle shape was quantified by applying the elongation ratio (also known as aspect ratio in the case of analyses of particle sphericity) (15), calculated by the ratio between length and breadth.

At least 30 randomly selected particles were analysed for each batch, randomly selected, and the average size was reported as the median value (D_{50}) of the particle size distribution, while the data dispersion was expressed as the interquartile range (IQR). Median value and IQR were also chosen to describe the elongation ratio data.

Density Measurements

True density of the samples was measured using a helium pycnometer (AccuPic 1330, Micromeritics). For every analysis, each sample was measured 10 times after 30 purging cycles.

The bulk (ρ_b) and tapped (ρ_t) densities of samples were determined by pouring a pre-weighted amount of sample in a cylinder and measuring the volume occupied initially and after 500 taps respectively (after 500 taps the powder volume remains constant). Carr index (16) was estimated from the bulk and tap densities according with the following equation:

$$CI = \frac{\rho_t - \rho_b}{\rho_t} \cdot 100$$

Density measurement were also performed on Pharmatose 50 M, a coarse grade of lactose, in order to compare a

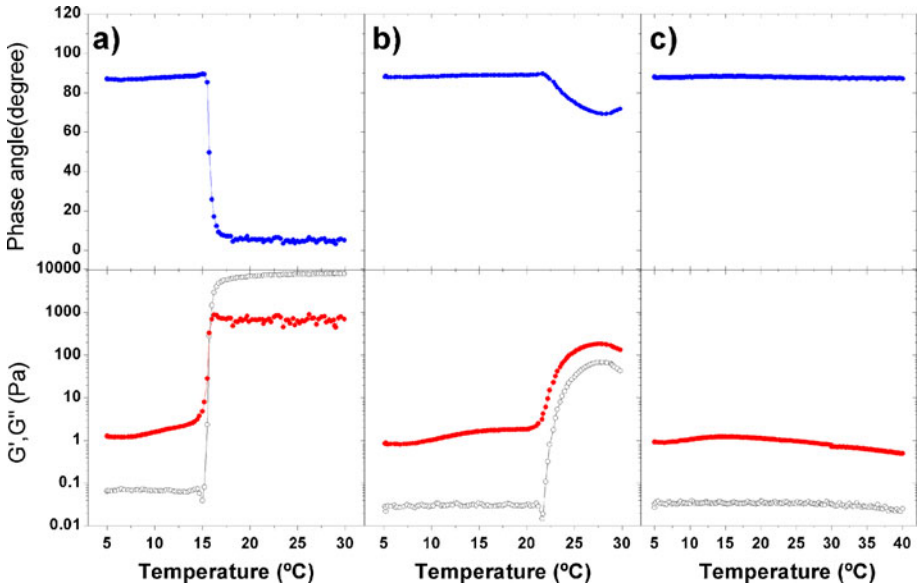

Fig. 1 Temperature sweep traces for (**a**) gelled systems, (**b**) partially gelled systems and (**c**) no gelling systems. Blue circles refer to phase angle, white circles to elastic modulus (G′) and red circles to viscous modulus (G″).

commercial lactose of similar particle size with crystals obtained from the poloxamer gel.

Bulk and tapped densities were determined in triplicate.

RESULTS AND DISCUSSION

Screening and Optimization of the Crystallization Systems

The first part of the work focused on the rheological characterization of water/poloxamer/lactose dispersions, in order to identify the optimal concentration range of the three components able to generate an appropriate gelled system for crystallization, that is, a system that contains enough lactose for crystallization, and that is a gel around 20°C and a sol at lower temperature. The temperature sweep test determined the gelation temperature (gel point) and quantified the variation in sample elasticity. The sol/gel transition, characterised by a drastic increase in the elastic and viscous moduli and by a drastic decrease of the phase angle, is shown in Fig. 1a. The gel point is the temperature at which the phase angle drops to a value of 45° and the two moduli present similar values.

The behaviour of water/poloxamer systems has been object of many scientific investigations, and it is well known that the gel point increases as the poloxamer 407concentration decreases (12,17,18). At the same time, much can still be learned about effects of adding a third component. Before analysing how the addition of lactose affected the gel point, it is interesting to observe that not all the systems analysed had the same behaviour in term of gelling performance. In particular, we observed three different kinds of systems: gelling, partially gelling, and no gelling.

Gelling systems were characterized by a steep change of all the rheological parameters across the gelling point. The phase angle shifted from 85° to 10° while the two moduli shifted from a low temperature condition at which the viscous modulus was higher than the elastic modulus, to a high temperature condition at which the opposite situation held (Fig. 1a). These results indicate that such systems change from a predominant liquid-like behaviour to predominant solid-like behaviour. When examined visually over the gelling temperature, these systems look like a strong transparent gels that do not flow if the container is tipped.

The systems with no gelling showed relatively constant rheological parameters at the temperatures analysed (for these samples the temperature range was extended up to 40°C), with

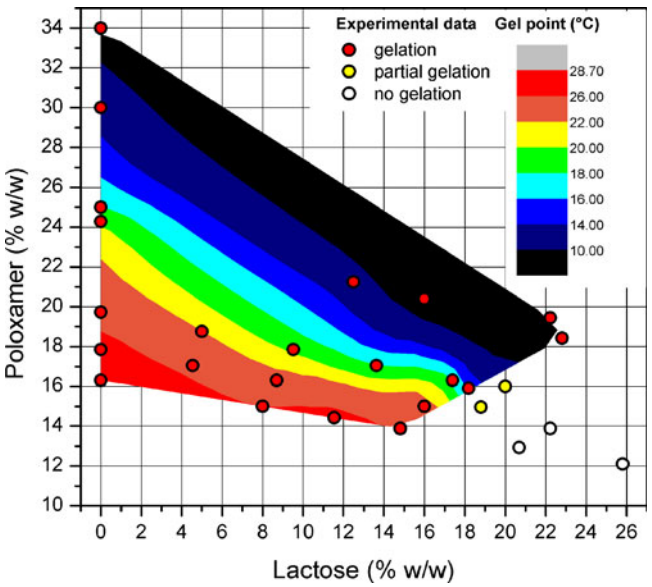

Fig. 2 Effect of poloxamer and lactose concentration on the gel point.

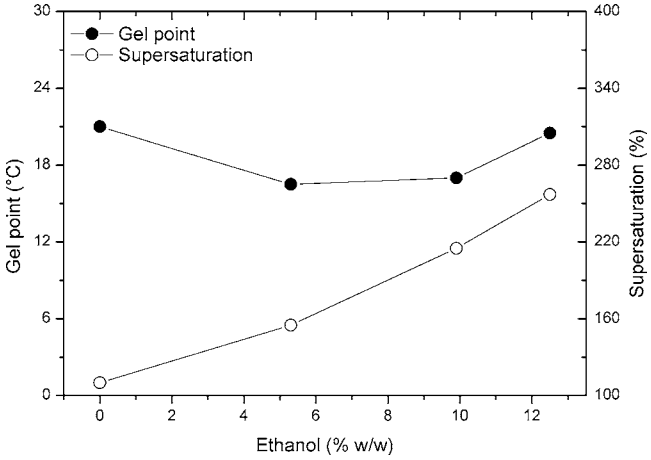

Fig. 3 Effect of the ethanol concentration on the gel point and on the lactose supersaturation level.

moduli values typical of the liquid-like behaviour (Fig. 1c). To the eye, all the systems looked like a transparent liquid.

Partially gelling systems are an intermediate state between those of the two previously described systems. While all the rheological parameters suddenly changed around a "pseudo gelling point", we observed neither the drop of the phase angle to values below 45° nor the cross of the two moduli; the viscous modulus always remained at higher values than the elastic modulus (Fig. 1b). These results suggest a change of the systems from a more or less liquid condition to a much more viscous but still liquid condition. To the eye, these systems looked like transparent gels above the "pseudo gelling point", but they flowed immediately when the container was tipped

The influence of the system composition on the gel point was analysed using a contour plot (Fig. 2) built with a specific algorithm based on the triangulation method (19). The graph shows that the gel point is strongly dependent on the poloxamer and lactose concentration; in particular, it decreases as the concentration of the two components increases. The results clearly indicate that lactose interacts with the poloxamer/water system, influencing its gelation properties. This is also evident when one considers the position of partial gelation and no gelation systems in the graph: all are located at high lactose concentrations. The effect of lactose is particularly useful for our purpose, since it makes it possible to obtain systems that can gel at around 16–20°C using low poloxamer concentrations. However, if a lactose concentration higher than 18% is used, systems gel only partially or do not gel at all.

Poloxamer-lactose interactions can be explained considering the mechanism of poloxamer gelification. As the temperature of the system increases, the poloxamer molecules aggregate to form micelles which in turn interact to form the gel network. Both micellization and gelation can be considered as consecutive and superimposed dehydration processes (20), so that any solute able to interact with water or enhance the solubility of the poloxamer blocks can affect the behaviour of the self-aggregation (21).

The same systems considered for gel point analysis were also studied in term of complex viscosity in the temperature range below the gel point, in order to understand which systems are more suitable for the filtration process. As expected, results (not shown) showed an increase of viscosity as the poloxamer and lactose concentration increased; however, the viscosity values were much less variable compared to gel point values. All the systems with a gel point around 16–20°C had viscosity values similar to those of less concentrated systems. Marked change in complex viscosity was observed only for systems with high poloxamer concentration (>28%) or high lactose concentration (>20%).

In the light of the rheological results, we can say that the most appropriate systems for our aim are those with the highest lactose concentration, which gel at a temperature of 16–20°C and liquify at lower temperatures. These systems can be prepared with poloxamer in the concentration range of 15–16% and lactose in the range of 17–18%.

When systems meeting these parameters were left in the incubator at controlled temperature (around 2°C over the gel point), the lactose crystallization was unsatisfactory. The systems showed poor primary nucleation and absence of secondary nucleation, thus the only effect visible was the growth of a few crystals suspended in the gel, which were able to reach remarkable size after 3–4 days in gel. These

Table I Composition of the Different Crystallization Systems Prepared. In the First Column (Batch) the Letter (A or B) Indicates the Ethanol Amount While the Number (4, 14 or 24) Refers to the Incubation Time Expressed in Hours

Batch	Water (%)	Poloxamer (%)	Lactose (%)	Ethanol (%)	Incubation temperature (°C)	Incubation time (h)
A-4 h	57,0	15,7	17,4	9,9	19	4
A-14 h	57,0	15,7	17,4	9,9	19	14
A-24 h	57,0	15,7	17,4	9,9	19	24
B-4 h	54,7	15,7	17,4	12,2	23	4
B-14 h	54,7	15,7	17,4	12,2	23	14
B-24 h	54,7	15,7	17,4	12,2	23	24

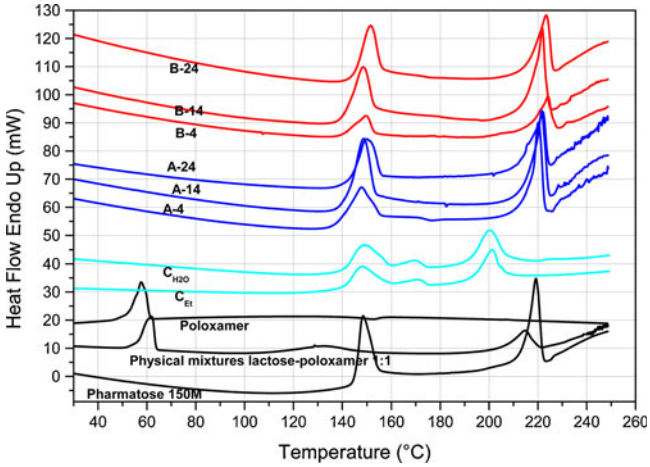

Fig. 4 DSC thermal traces of pharmatose 150 M, poloxamer, their physical mixture and crystals prepared by crystallization from the gel and from the solution. The names refer to the batches prepared according to Table 1.

results were attributed to a low level of supersaturation, (reported as% where 100% corresponds to the solubility limit calculated without considering the poloxamer effect), which was calculated to be around 110%. It is well known that the probability of nucleation increases with supersaturation (22) and, as evident from literature data, a value of 110% is probably quite far from a reasonable value. For example, in the crystallization of lactose from carbopol gels, a supersaturation level at least of 265% was used (5). In order to optimize the poloxamer gel crystallization system it was necessary to increase the supersaturation level. Since it was not possible to increase the amount of lactose (which would have modified the gel point temperature), the only solution was to decrease its solubility, substituting part of the water with a different solvent. Obviously such a solvent has to interact with poloxamer in a similar way to water, without changing the gelling process too much. Ethanol is a solvent able to generate a gel system with poloxamer (14), and lactose is practically insoluble in it (23). To evaluate the feasibility of using ethanol in the systems, we performed rheological analyses on systems containing 15.7% and 17.4% of poloxamer and lactose, gradually increasing the amount of ethanol. The results, reported in Fig. 3, show that the gel point shifted to lower temperatures at 5% of ethanol and then came back to the values of the initial system as the ethanol approached a concentration around 12.5%. In any case, the gel point always remained in the

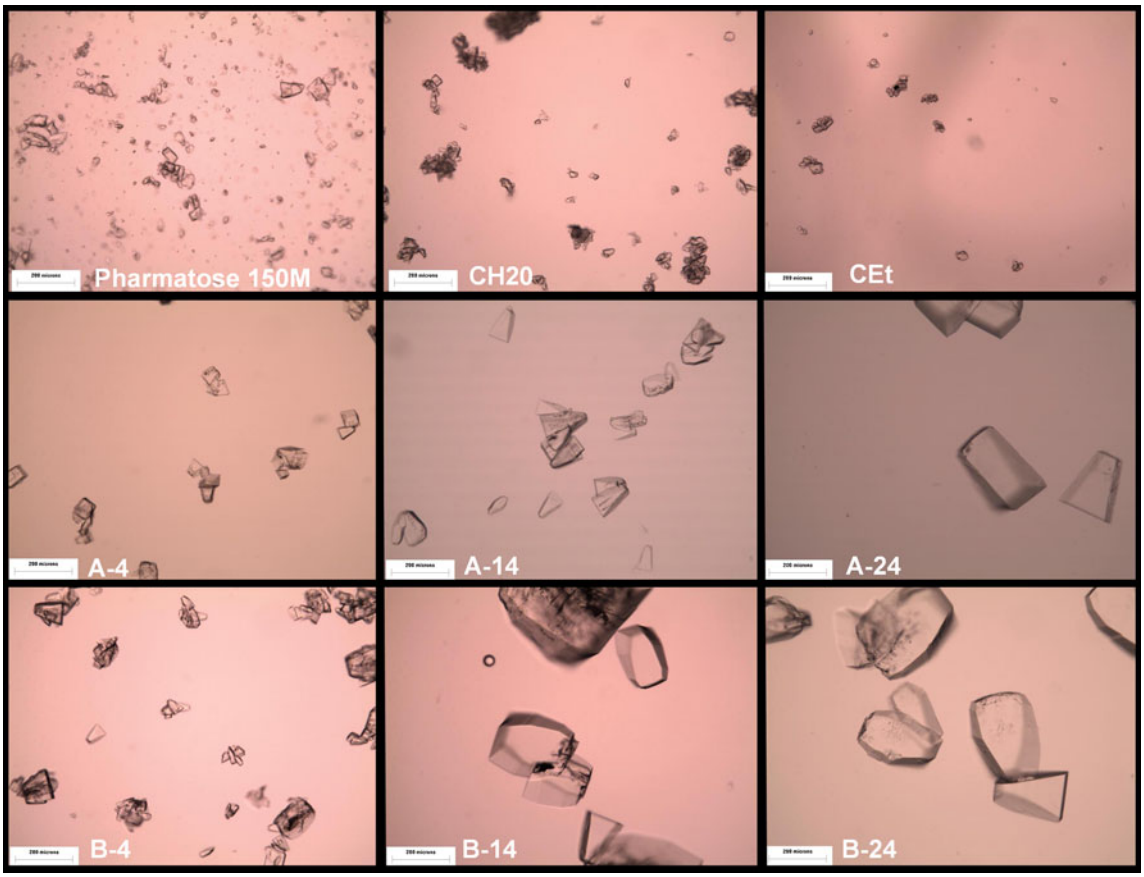

Fig. 5 Images of crystals prepared by crystallization from gel, by crystallization from solution and commercial lactose. All images were acquired using a 10X objective and the bar scale always refers to 200 μm. The names on the pictures refer to the batches prepared according to Table 1.

Table II Image Analysis and Density Results

Batch	D50 (μm)/IQR (μm)	Elongation ratio/IQR	Pycnometric density (gr/cm^3)	Bulk density (gr/cm^3)	Tapped density (gr/cm^3)	Carr Index
Pharmatose 150 M	14.0/10.6	1.6/0.5	1.518 ± 0.002	0.47 ± 0.01	0.73 ± 0.04	36.41 ± 4.29
Pharmatose 50 M	128.2/64.3	1.8/0.4	1.514 ± 0.002	0.49 ± 0.02	0.57 ± 0.03	14.04 ± 2.34
C_{-H20}	14.2/12.0	1.4/0.4	1.478 ± 0.003	0.31 ± 0.00	0.44 ± 0.01	30.07 ± 2.12
C_{-Et}	16.4/8.9	1.6/0.7	1.499 ± 0.005	0.35 ± 0.01	0.51 ± 0.02	30.83 ± 1.12
A-4 h	38.6/7.7	1.9/0.6	1.509 ± 0.002	0.45 ± 0.02	0.54 ± 0.00	17.31 ± 2.60
A-14 h	78.9/17.7	2.3/0.6	1.498 ± 0.002	0.50 ± 0.02	0.58 ± 0.02	14.18 ± 1.07
A-24 h	230.1/65.4	1.9/0.6	1.506 ± 0.002	0.67 ± 0.01	0.65 ± 0.00	12.31 ± 0.18
B-4 h	37.4/8.0	2.4/0.4	1.495 ± 0.002	0.46 ± 0.02	0.55 ± 0.01	16.36 ± 1.10
B-14 h	156.7/31.1	2.0/1.2	1.498 ± 0.002	0.51 ± 0.01	0.59 ± 0.02	13.56 ± 1.62
B-24 h	168.8/52.7	2.0/0.5	1.492 ± 0.002	0.53 ± 0.02	0.61 ± 0.00	13.11 ± 3.44

range 16–20°C when the ethanol concentration was less than 12.5%. Therefore, the addition of ethanol does not change the gelling properties of the system too much, but makes it possible to increase the supersaturation level up to 260% (Fig. 3). The supersaturation calculus was based on data found in the literature for lactose solubility in hydro-alcoholic media (24). Based on these results, two different systems were prepared for lactose crystallization, according to the concentrations and conditions reported in Table 1. Ethanol addition dramatically improved the performance of the systems in terms of nucleation, allowing harvest of a good quantity of crystals.

Characterization of the Lactose Crystals

DSC Analysis

Calorimetric analysis made it possible to identify the polymorphic forms of the crystallized lactose. DSC analysis was first performed on the starting materials, poloxamer and lactose, and on their 1:1 physical mixtures (Fig. 4). Poloxamer showed a thermal trace with a single endothermic peak identified as the melting event, while the starting lactose presented two endothermic transitions, corresponding to the dehydration of the water of crystallization at around 144°C and to the melting of the α-form at around 223°C (25), confirming that it is the α-form monohydrate. The physical mixtures did not show any evidence of incompatibility or interaction between the two solid materials. All the crystals obtained in gels presented similar thermal traces (Fig. 4), characteristic of the α-form monohydrate, without traces of the β-form, amorphous form, or poloxamer. Instead, controls prepared with constant stirring showed a further exothermic peak at around 175°C (Fig. 4). Such a peak, attributed to the crystallization of amorphous lactose (5,25), suggests that these samples were probably a mixture of α and amorphous lactose. Moreover, their melting peaks were shifted to lower temperature, around 200°C. While the shift of the α-lactose melting peak to lower temperatures has been previously reported, the reasons are still unclear, though it has been observed to be dependent on the thermal history and sample pre-treatment (26).

Microscopic Analysis

The morphology of the crystals was observed by microscopy. Pictures of the crystals obtained from gel, control samples, and commercial lactose are reported in Fig. 5. All samples possessed the typical tomahawk shape of α-lactose crystals (27), with an elongation ratio between 1.4 and 2.3 (Table 2). However, when compared with the control or commercial crystals, all samples crystallized from gel were characterized by a better defined geometry, especially when the crystals

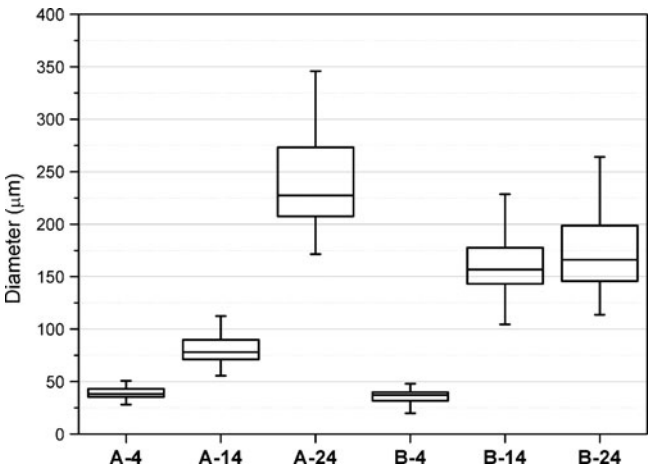

Fig. 6 Box plot of the particle size distributions of the crystals prepared by crystallization from gel. The x-axis refers to the batches prepared according to Table 1. In the box plot the box horizontal borders represent the 25th and 75th percentile, the horizontal lines in the middle of the box represents the median value of the distribution and the two whiskers the 5th and 95th percentile respectively.

had enough time to grow, as in the samples recovered after 14 or 24 h. The different batches also presented different size, as evident in the pictures and from data reported in Table 2. The two controls had similar size, with values comparable to those of the commercial sample used as starting materials, suggesting that the different conditions of crystallization from solution did not overly influence the final result. However, for the samples crystallized from gel, the results were totally different, with size growing as incubation time increased. In order to better analyse particle size data, it is useful to plot them using a box chart, where the different distribution parameters can be easily compared (Fig. 6). In the A samples, as the incubation time increased, the size of crystals grew and distribution widened, evident both by the interquartile range and by the two whiskers. On the other hand, in the B sample, there was an increase of both size and distribution only up to 14 h, after which the process was completed. Moreover, after an incubation time of 24 h, the A crystals were characterized by bigger size and higher variability. These results suggest that crystallization kinetics differ according to the differences in the crystallization systems, i.e. at the supersaturation level. It appears that for the lower supersaturation level (sample A), the nucleation process occurs slowly and is partially superimposed with the crystal growth, while for the higher supersaturation level, the nucleation is much faster and almost temporally separated from the crystal growth. In the latter case, the growth occurred on nuclei with homogeneous size, generating samples with a narrower particle size distribution. This theory is supported by the results obtained in the systems prepared without ethanol, where the nucleation was poor and slow, generating very large crystals together with very small particles.

Density Measurements

Pycnometric density values did not show significant variation in the different batches produced or in the two grades of marketed lactose, confirming the DSC result of no evidence of poloxamer in the samples crystallized from gel medium. On the other hand, bulk density, tapped density, and Carr index varied among the different batches. However, the results cannot be attributed to the crystallization medium, but are dependent exclusively on the size of the different samples, as evident from the data of Pharmatose 50 M, a commercial grade with size distribution similar to that of B-14 and B-24.

CONCLUSIONS

This work concerns the development of a thermoreversible gel system that serves as a medium of crystallization that allows easy recovery of the crystals. The Poloxamer 407 was chosen as the main component, since it is capable of generating reversible thermogelling systems in water, where the gelling temperature can be controlled and modified by adjusting its concentration and those of any additives added.

Rheological analysis showed that lactose, selected as a model for crystallization, markedly influenced the properties of the poloxamer gel. Therefore, it was possible to prepare a crystallization system that gelled at room temperature and liquified below 18°C by simply adjusting the poloxamer/lactose ratio. In addition, it was observed that small amounts of ethanol did not unduly alter the gelling properties of the system, but changed the solubility of the solute, thus making it possible to prepare systems with different levels of supersaturation.

Like all gel systems for crystallization described in the literature, the poloxamer systems were suitable for the preparation of high quality crystals, with the added benefit, in this case, that crystals can be easily recovered simply by lowering the temperature by a few degrees and filtering, without addition of any chemicals to promote the sol–gel transition. This aspect is particularly important if the substances to be crystallized are sensitive to the presence of chemicals, such as acids or bases used in the crystallization from carbopol gel.

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