Development of a continuous process to produce the 1:1 β/α mixed lactose crystal

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Preyas Anantpure

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ABSTRACT

A new lactose crystal was formed at Massey University in 1997 while studying the effects of superheated steam on the production of β-lactose. The crystal typically had 50-52% β-lactose content and an X-ray diffraction pattern that did not match with either β-lactose or α-lactose monohydrate, and so it was thought to be an entirely new lactose crystal. Preliminary work was then done at Massey University to determine the conditions under which the crystal could be produced. The new crystal was produced in a batch process in a superheated steam environment between the temperatures of 125°C to155°C and at very fast drying rates.

The present work attempts to develop a continuous process to produce this new lactose crystal. During the late stages of the project it was found that a similar crystal was already documented in the literature and its crystal structure defined. So the crystal found at Massey University could not be termed as a new crystal. The crystal found in the literature was formed by a high thermal treatment to solid-state α-lactose monohydrate and amorphous lactose and had a β/α anomeric ratio of 1:1. The present work attempts to develop a continuous process to produce the 1:1 β/α mixed lactose crystal from a liquid state and in a superheated steam environment.

A roller drier was thought to be the best option to produce the new crystal in a continuous process. Different arrangements were developed to create the required conditions under which it was expected that the 1:1 β/α mixed lactose crystal would be produced. Lactose solution sprayed on the roller drier using spray nozzles at temperatures of 125°C to 155°C and flow rates in the range of 110ml/min to 40ml/min with varying drum speeds consistently produced 85% β-lactose. Lactose solution was smeared on the drum surface which also produced about 80% β-lactose. Lactose solution that was sprayed over a tray which was designed to allow only small amount of the solution (about 3ml/min) to pass through produced about 58% β-lactose. X-ray diffraction showed that the crystal was a mixture of 1:1 β/α mixed lactose crystal and β-lactose crystal. This confirmed that, to produce the 1:1 β/α mixed lactose crystal very low flow rates were required (1.5ml to 3ml/min flow rate). It was observed that the 1:1

β/α mixed lactose crystal was formed when the lactose solution formed a rubbery amorphous lactose solution and then quickly crystallized in the superheated steam environment. To confirm this hypothesis, spray dried amorphous lactose was crystallised over the roller dried inside the superheated steam environment at 125°C, 135°C and 145°C. The resulting product was a mixture of the 1:1 β/α mixed lactose crystal and β-lactose crystal. To produce an amorphous phase from the solution, the solution was injected in air for a few seconds before introducing it into the superheated steam environment. Lactose solution at 90 °C injected onto the roller with a temperature of 145°C for 10 sec in air and 15 minutes in superheated steam produced a crystal having a structure different to that of a β-lactose crystal or α-lactose crystal and it had a similar X-ray diffraction pattern to that of the 1:1 β/α mixed lactose crystal documented in the literature and the crystal formed at Massey in 1997. It was also shown that in the absence of superheated steam, β-lactose crystals were formed.

It was clearly shown that a noticeable amount of the 1:1 β/α mixed lactose crystals are formed in products having β-lactose contents below 60%.

The formation of 1:1 β/α mixed lactose crystal was found to be very problematic and thus the results were not repeatable. Further investigation should be carried out with better control of all the parameters. Moisture content (m_c) was thought to be a contributing factor that needs to be investigated further.

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CHAPTER 1

PROJECT OVERVIEW

A new lactose crystal was formed at Massey University, Palmerston North in 1997 by (Paterson & O'Donnell, 1997) while studying the effect of superheated steam on crystallization of lactose. This new crystal contained both α and β-lactose anomers with a typical β-lactose content of 51-52% giving a β:α ratio of 1.08:1. It was found that the new crystal was produced under a superheated steam environment between temperatures 120°-155°C and above an initial drying rate of 0.35 gm/min/10ml. The present work attempts to develop a continuous process to produce the new lactose crystal.

Lactose is usually produced by crystallization from a lactose solution below 93.5°C followed by separation and flash drying, producing α-lactose monohydrate crystals with a coating of amorphous lactose, or by crystallization above 93.5°C on a roller dryer producing a β-lactose crystal product with up to 30% α-lactose incorporated into the β-lactose crystal structure. Amorphous lactose is produced when lactose solution is spray dried.

It was hypothesized that the new crystal could be produced by rapid crystallization at temperatures above 120°C. To create conditions for rapid crystallization it was proposed to initiate very fast drying producing amorphous lactose that would crystallize in a superheated steam environment to form the new crystal.

The objectives of the present research work were:

- Literature search to confirm that the crystal form found by (Paterson & O'Donnell, 1997) has not been documented before.
- Design and develop a process to obtain the required conditions to produce the new crystal continuously and verify the hypothesis made above.
- Produce 10 kg of the new crystal.
- Provided sufficient quantity of crystal was produced, determine the properties of the crystal- amorphous lactose content, dissolution time,

solubility limits, crystallinity, density, melting point, sweetness, crystal size and carry out tabletting of the crystals.

- Use the results to compare the properties to those found by (Buma, 1978), (Lerk *et al.*, 1984 (a)), and (Paterson & O'Donnell, 1997).

Unfortunately the attempts at developing a continuous process failed due to some unknown factors which were producing a mixture of new crystal and β-lactose. Thus further investigations into the production of the new crystal are recommended. But the new crystal was produced once in a very small quantity. The X-ray diffraction pattern showed a different crystallographic structure than that of β-lactose and α-lactose, and so it was concluded that this was a new lactose crystal. This thesis covers the process followed and modifications made to the set up during the project.

Firstly Chapter 2 covers the literature review. This was carried out to ensure that no process had been developed before to produce the new crystal. The literature search covered:

- Carry out a literature search to ensure that the crystal itself had not been discovered before.
- Different methods to produce lactose crystals or lactose additives.
- Detailed search of patented methods to produce lactose crystals or lactose tablet additives.
- The work done on the development of the new crystal at Massey University. The conditions required to produce the new crystal and the methods used to determine the properties of the new crystal.

Chapter 3 describes the step-by-step development of the continuous process. It includes the materials and methods, the results and discussions and the reasoning behind the changes made to the set up.

Chapter 4 ends the thesis with the conclusions and recommendations.

CHAPTER 2

LITERATURE REVIEW

2.1 *INTRODUCTION*

To understand the nature of the new lactose crystal, it was important to first understand the basic forms of lactose and other properties that might help in the formation of the new crystal, namely crystallization of amorphous lactose. The purpose of literature search was to confirm whether or not the crystal had been found before and no other process had produced the new lactose crystal. This chapter reviews the various forms of lactose and how they are produced, surveys alternate production methods and reviews the previous work conducted at Massey University on the new crystal.

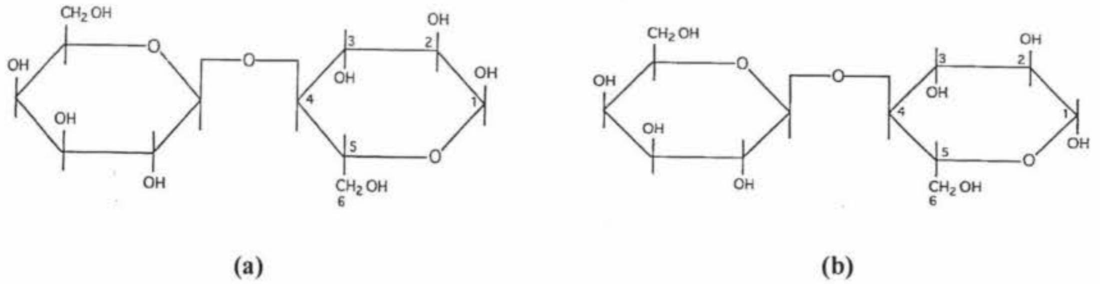
2.2 *LACTOSE*

Lactose (4-o-β-D-galactopyranosyl-D-glucose) (Webb & Johnson, 1965), or milk sugar, is the major carbohydrate in the milk of most mammals. Lactose is the predominant solid in milk. Commercially, lactose is isolated from whole or de-protenised whey, obtained as a waste product from cheese and casein processing.

2.3 *BASIC FORMS OF LACTOSE*

Lactose mainly exists in either of the two crystalline forms: α-hydrate or β-anhydride or as an amorphous "glass" mixture of alpha and beta lactose. Several other forms may be produced under special conditions as shown in Figure 2-5.

Lactose consists of a galactose ring and a glucose ring linked by a β-1-4 glycosidic bond (Fox & McSweeney, 1998). The hemiacetal group of the glucose moiety is potentially free (i.e. lactose is a reducing agent) and may exist as an α or β anomer (Fox & McSweeney, 1998). Alpha and beta lactose are isomers that differ in the orientation of the hydroxyl group on the carbon C [1] (Fig 2-1 a & b).



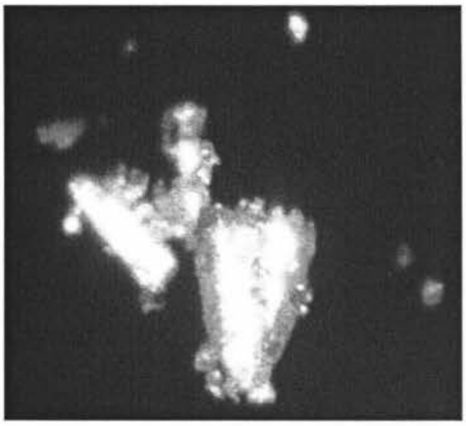
(a) (b)

Figure 2-1: Alpha Lactose (a) and Beta Lactose (b).

Crystalline forms have a definite molecular structure, where as amorphous lactose has a disordered molecular structure. Four other crystalline forms of lactose have been reported in literature. Hargreaves (1995) lists these as a 3:5 β/α ratio, a 2:3 β/α ratio, a 1:4 β/α ratio and a stable anhydrous α-lactose.

2.3.1 α- Hydrate

Ordinary commercial lactose is α-lactose monohydrate, or simply α-hydrate. It is prepared by concentrating an aqueous lactose solution to super saturation and allowing crystallization to take place at a moderate rate below 93.5°C. Commercially produced α-lactose contains about 90-92% α-lactose, 5% water and remaining β-lactose. That α-hydrate is a stable form, is indicated from the fact that the other forms change to α-hydrate in the presence of small amounts of water below 93.5°C. It has a specific optical rotation of $[\alpha]^{20}_{D} = 89.4°$ and a melting point of 201.6°C (Webb & Johnson, 1965). The crystals are not hygroscopic and are sparingly soluble and cause a sandy mouth feel. α-lactose monohydrate crystals have a typical tomahawk shape. Picture 2-1 shows the α-lactose crystals as seen under a polarised microscope.



Picture 2-1: Typical tomahawk α-lactose crystals as seen under polarised microscope (100x).

2.3.2 α- Anhydride

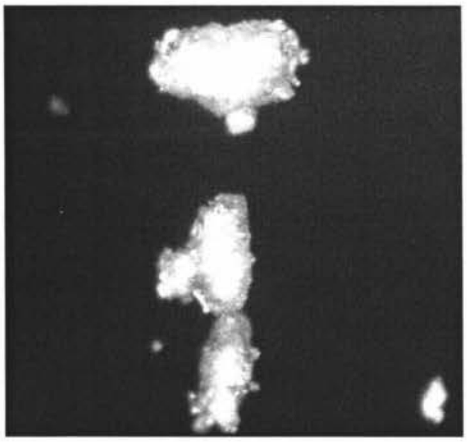
The water of crystallization can be removed from alpha-hydrate crystals under various conditions. These crystals are produced when α-hydrate crystals are heated above 100°C under vacuum. The product is stable in dry air but is highly hygroscopic. Its melting temperature is 222.8°C (Webb & Johnson, 1965).

Thermal treatment in a moist atmosphere at temperatures over 110°C, or desiccation with suitable liquids, such as dry methanol, may result in a non hygroscopic product, generally called stable anhydrous α-lactose (Lerk *et al.*, 1984 (a)).

2.3.3 β- Anhydride

When crystallization of a supersaturated lactose solution takes place above 93.5°C, the crystals formed are that of β-anhydride. These anhydrous crystals have a melting point of 252.2°C and when dissolved in water have a specific rotation of $[\alpha]^{20}_{D} = 35.0°$ (Webb & Johnson, 1965). β-lactose as a crystal only exists as the anhydrous form. If sufficient water is present β-lactose crystals will dissolve and mutarotate to α-lactose and subsequently incorporate water to crystallize as α-lactose monohydrate (Angberg *et al.*, 1991). β-lactose is sweeter and more soluble than α-lactose (Webb & Johnson, 1965). Picture 2-2 shows β-lactose crystals under a polarised microscope. The highly crystalline nature is clearly seen in the picture.

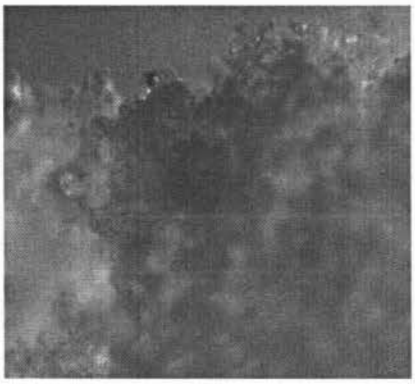
Commercially available β-lactose is produced by extrusion or roller drying and typically contains about 80% of the β anomer and 20% of the α anomer, although commercial grades with higher β-content are available (Bronlund, 1997).



Picture 2-2: β-lactose crystals as seen under polarised microscope (100x).

2.3.4 Amorphous Lactose

When lactose solution is rapidly dried, the viscosity increases so much that the lactose molecules do not get enough time to crystallize. Amorphous lactose does not have a definite structure and may be considered as a solid solution in which α and β-lactose are present in their equilibrium ratio at the temperature of drying (Buma, 1970). Lactose glass is stable if protected from moisture. It is very hygroscopic and quickly takes up moisture from the surrounding air and becomes sticky. Under these conditions of crystallization, if enough water is present, part of the moisture will be retained as the water of crystallization in the α-hydrate form and part will be released, as α-hydrate is not hygroscopic. Thus, milk powder exposed to air absorbs moisture for a while and then gives up moisture again. Products containing crystalline α-hydrate are not as hygroscopic as products containing amorphous lactose. Picture 2-3 shows amorphous lactose under polarised microscope.



Picture 2-3: Amorphous lactose as seen under polarised microscope (100x).

2.4 *MUTAROTATION*

The conversion of α-lactose to β-lactose and β-lactose to α-lactose in solution is called mutarotation (Figure 2-2). The configuration around C [1] of glucose is not stable and can readily change (mutarotate) from α to β form and vice versa. When either form is dissolved in water, there is a gradual change over of one form to the other until equilibrium is reached. Regardless of the form used in making the solution, the rotation will change until the specific optical rotation is $[\alpha]_D^{20} = 55.3°$ at equilibrium (anhydrous weight basis). This is 37.3% in the α form and 62.7% in the β form at 20°C and equilibrium ratio of $62.7/37.3 = 1.68$. The rate of reaction is slow at low temperatures but increases as the temperature rises, becoming almost instantaneous above about 75°C. Mutarotation plays an important role in the solubility behaviour of lactose.

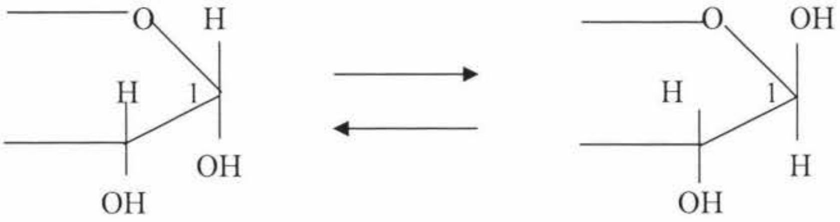


Figure 2-2: Mutarotation.

2.5 *SOLUBILITY OF LACTOSE*

The solubility of α-lactose is different to that of β-lactose (Figure 2-3). The solubility curves meet at 93.5°C. α-lactose is less soluble below 93.5°C, and above 93.5°C, β-lactose becomes less soluble. Thus crystallization above 93.5°C produces β lactose while crystallization below 93.5°C produces α-lactose.

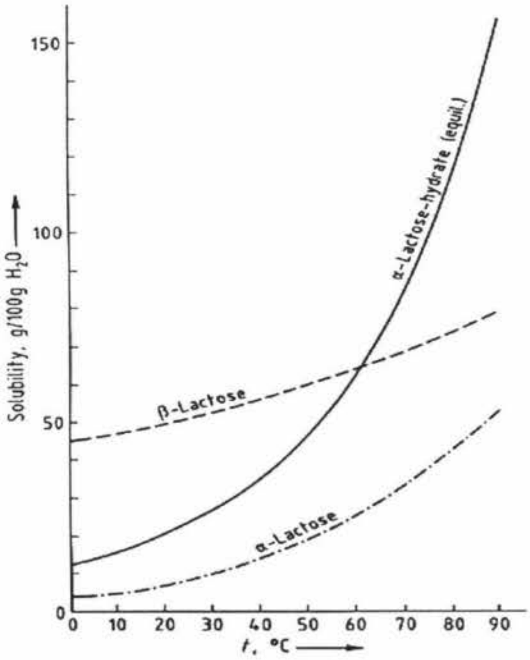


Figure 2-3: Solubility of lactose as a function of temperature (Gerhartz, 1988).

Table 2-1 below gives the solubility of lactose in water at different temperatures.

Temperature (°C)	Solubility (g of lactose/g water)	β/α ratio	Reference
0	11.9	1.61	
15	16.86	1.60	
20	19.10	1.59	(Lowe, 1993)

25	21.81	1.58	
30	24.81	1.56	
40	32.75	1.54	
50	43.46	1.52	
60	58.40	1.50	
70	78.26	1.47	
75	90.40	1.46	
80	104.60	1.45	
89	138.7	-	(Visser, 1982)
93.5	143.9	-	

Table 2-1: Solubility of lactose at different temperatures.

When α-lactose is added in excess to water with agitation a definite amount dissolves rapidly after which an additional amount dissolves slowly until final solubility is attained. However the initial solubility is the true solubility of α-lactose as the increased solubility is due to mutarotation. As mutarotation occurs, the solution becomes unsaturated with respect to α- lactose and thus more α-lactose dissolves. This continues until equilibrium is reached and no more α-lactose can dissolve, which defines the final solubility limit (Nickerson, 1974).

2.6 *CRYSTALLIZATION*

2.6.1 Basic Concept

Crystallization refers to the formation of crystals from a solution. In order for crystallization to take place, the solution must be supersaturated. The concept of supersaturation can be extended to two zones: metastable zone and the labile zone. The metastable zone occurs in the first stage of supersaturation before nucleation begins. Nucleation can be due to primary nucleation or secondary nucleation. In primary nucleation solute particles cluster together and instantly crash out of the solution. Secondary nucleation requires seeding. The contact can be between the solution and other crystals, a mixer blade, a pipe or even the wall of the vessel (http://www.cheresources.com/cryst.shtml, 2004).

Nucleation occurs readily in the labile zone, but the crystals can grow and crystallize out of the solution both in the labile and metastable zones.

2.6.2 Crystallization of lactose

With lactose there is the additional factor of mutarotation. The overall lactose crystallization process proceeds as shown below:

Step 1 Step 2

β- lactose $\leftrightarrow$ α-lactose $\leftrightarrow$ α- lactose hydrate crystals

If mutarotation (step 1) is slower than crystallization (step 2), the α-lactose ratio will be lower than the equilibrium value of 37% α-lactose at 20°C and the rate of crystallization will be controlled by the mutarotation reaction. Conversely, if crystallization is slower than mutarotation then the values of α and β- lactose will be close to their equilibrium ratios in the solution.

2.6.3 Crystallization of amorphous lactose

Amorphous lactose is formed when an aqueous lactose solution is dried rapidly. Above the amorphous lactose glass transition temperature (T_g) the amorphous glass is transformed into a viscous rubber. Most physical changes in amorphous materials result from a dramatic decrease of viscosity and increase of molecular mobility in the rubbery state above T_g. Crystallization of amorphous lactose can release water that was absorbed from the surrounding air decreasing the T_g and increasing the rate of crystallization (Roos & Karel, 1992). Amorphous lactose may crystallise to several different crystal forms, as α-lactose monohydrate, anhydrous β-lactose, stable and unstable anhydrous α-lactose and anhydrous mixture of α and β-lactose depending on the temperature and water activity conditions (Jouppila *et al.*, 1997) and a 1:1 β/α mixed lactose crystal formed under high temperature conditions (Lerk *et al.*, 1984 (a), Lerk *et al.*, 1984 (b) and Willart *et al.*, 2004). The process of formation of the 1:1 β/α mixed lactose crystal is given in detail in sections 2.8.2, 2.8.3 and 2.9.2. The rate of crystallization of amorphous lactose is moisture and temperature dependent (Roos & Karel, 1992).

2.7 *DIFFERENT PROCESSES TO PRODUCE LACTOSE*

There are a number of processes used to produce lactose. Batch crystallization and spray drying are the most common processes.

2.7.1 Batch Crystallization

In processes commonly carried out by the industry, a whey solution is concentrated by evaporators to 60% to 65% total solids and cooled slowly batch wise in large tanks for crystallisation of lactose. Passing it through two stage decanters separates the lactose from the whey concentrate. After separation, lactose is dried in a flash drier followed by a fluidised bed drier to a moisture content of 0.1%-0.5%. This process produces lactose powder with about 95% α-lactose monohydrate crystals (Bylund, 1995).

2.7.2 Spray drying

Spray dried lactose was introduced to the pharmaceutical market in the 1960's as an excipient that enables direct compression of formulations in a simple manufacturing process (Gunsel & Lachman, 1963). Bolhuis *et al.* (2004) gives a good description on the recent developments in spray-dried lactose and its tabletting properties.

Spray dried lactose is produced by spray-drying an aqueous solution of lactose having a suspension of α-lactose monohydrate crystals. The resulting product is sieved to yield a fine powder, which is important for achieving the appropriate flow properties of spray-dried lactose. The β/α ratio in spray dried lactose depends on the outlet temperature of the spray drier (Buma, 1970). The compaction properties of spray-dried lactose are described in section 2.12. An example of spray-dried lactose is the "Supertab" lactose that is a mixture of alpha lactose monohydrate crystals and amorphous lactose produced by Fonterra at Kapuni, New Zealand.

Patented methods to produce lactose crystals found in literature are-

2.7.3 Method of treating lactose (Nezbed, 1974)

A patented method of interest found in the literature was the use of a roller drier to produce a particular type of lactose crystal, suitable for use in forming tablets by direct tabletting process.

Nezbed (1974) described a method to produce lactose crystals having 50% amorphous lactose and having at least 65% β-lactose out of which at least 20% by weight had to be crystalline. All the α-lactose was in amorphous form. The aqueous solution contained 40%-60% lactose by weight. According to the patent, 40% lactose solution should be desirably stored above about 60°C and 60% lactose solution above about 71°C. The lactose solution was sprayed on the drum –10 ft long and 3-½ ft diameter, at a rate of 906 kg/hr, which corresponds to a feed rate of 0.185 kg/m^2. The drum was maintained at a temperature of about 210°F to 300°F (99°C-149°C) and was rotated at 8 rpm. The lactose remained on the drum for about 6 seconds and was then scraped off by a blade (the lactose was allowed to be in contact with the drum for a period sufficient to remove the water). The solution was sprayed on the drum at a pressure of 20 psig (1.3 bar) using 5 to 9 spray nozzles. The spray pattern was flat, and covered the entire length of the drum. The lactose obtained from the drum had about 0.3% moisture content and was in the form of small flakes. The flakes were screened to provide a lactose product having an average size of 60 mesh or smaller. It has been found that 60 mesh or smaller particle size provides a lactose product that is particularly suitable for direct tabletting procedures. The lactose crystals produced by the above conditions had 74.3% β-lactose of which 36.1% was crystalline. The lactose product had 25.7% amorphous alpha lactose.

2.7.4 Method of seeding lactose crystals to initiate crystallisation (Credoz & Beuneu, 1983)

The following method was developed to produce α-lactose monohydrate. The percentage of crystallized lactose obtained from lactoserum can be substantially increased without noticeably increasing investment costs or energy consumption. The first phase of crystallization was a continuous crystallization stage wherein seeds of crystallization were added to the lactoserum to initiate crystallization and to concentrate the lactoserum. The concentrated lactoserum was brought to a supersaturated state and maintained at this stage by evaporation to obtain a mixture of mother liquor and lactose crystals, which was then subjected to two centrifugal drying stages to obtain a first portion of large lactose crystals and a second portion of such crystals grown by cooling.

2.7.5 Evaporation and cooling of the viscous lactose solution (Henningfield & Dinesen, 2003)

This method was patented by Henningfield & Dinesen (2003) for producing α-lactose monohydrate crystals using the evaporation and cooling technique. This method comprised of heating the lactose solution above 40°C but below the maximum temperature for crystallization of α- lactose monohydrate from the liquid (between 50-

90°C), simultaneously agitating it to increase the viscosity and then cooling and drying it. The drying equipment might be a fluidized bed. The slurry after the evaporation step had a solids content of 87%, moisture content of 13% and 85% of the lactose was crystalline α-lactose monohydrate. The moisture content after the final drying process was 2%.

2.7.6 Flash drying and pre-cooling of the concentrated solution to produce lactose crystals (Getler, 2004)

This method was patented to process whey solution to produce α-lactose monohydrate. The whey solution was first heated by a heat exchanger to at least 90°C, to reduce the risk of crystallisation in the heat exchanger (Masters, 1991) [cit. in (Getler, 2004)]. The solution was then transferred to a flash dryer. Some part of the liquid was then recycled and some transferred to a cooling vessel. The solution was transferred directly to an air/fluid bed drier. The concentration of the liquid concentrate from the first unit may be 66%, and from the second unit 73% starting with 58% in the liquid product.

It was also assumed during this work, that only a fraction of the paste comes into contact with the walls of the cooler causing a rapid formation of a high number of seed crystals. Further, it was assumed that the seed promoted the formation of lactose crystals during the subsequent drying process.

2.8 *FORMS OF LACTOSE CRYSTALS FOUND IN LITERATURE HAVING SIMILARITIES TO THE NEW CRYSTAL*

2.8.1 Lactose obtained by crystallization from methanol

Buma (1978) dissolved spray-dried lactose and ground α-lactose monohydrate in almost water free methanol. Rapid filtration and then drying at 50°C yielded crystalline lactose crystals consisting of almost equal proportions of α and β-lactose. The β/α ratio of spray dried and ground α-lactose was 54/46 and 45/55 respectively. Both samples of lactose had a density of 1.59-1.60 g/cm^3 and the sedimentation analysis showed that there was only one type of particle present with this density in both the cases. From the specific gravity measurements Buma (1978) concluded that the crystalline lactose did not consist of α-lactose monohydrate and β-lactose, but crystals consisting of α and β-lactose.

2.8.2 Alterations of α-lactose during Differential Scanning Calorimetery

This is a short communication by Lerk *et al* (1984 (a)), that reports the occurrence of changes in the solid state during differential scanning calorimetry of α-lactose. DSC was done on α-lactose monohydrate, stable anhydrous α-lactose and unstable anhydrous α-lactose at a heating rate of 10°C/min. All the three samples showed an endothermic transition at about 140°C. But the melting endotherm of the unstable anhydrous α-lactose was preceded by an exothermic peak. This exotherm was studied by heating the samples at different temperatures and studying the crystal structure by X-ray diffraction. The β-lactose content was determined by GLC (Gas Liquid Chromatography). The results showed a conversion of the unstable α-lactose at 180°C into a product with a crystallographic structure different from both the hydrous and anhydrous α-lactose and from β-lactose crystals. X-ray diffraction analysis showed that the conversion product was similar to the lactose crystal reported by (Buma, 1978).

GLC analysis of the product produced at 180°C had a α-lactose content of 42%. Lerk *et al.* (1984 (a)) characterized this β/α lactose compound as having β/α ratio of approximately 1:1.

X-ray diffractions done on samples heated at a rate of 2°C/min also detected the same 1:1 β/α mixed compound at 200°C.

The structure of the 1:1 β/α compound was studied by X-ray diffraction by Lefebvre *et al.* (2005) and they demonstrated that the 1:1 β/α mixed compound was not a mixture of the two crystalline forms but a new crystal form containing the two anomers, confirming the conclusion made by (Buma, 1978).

2.8.3 Transitions of Lactose by Mechanical and Thermal Treatment

Lerk *et al.* (1984(b)) studied the thermal characteristics of amorphous lactose, intensively ground α-lactose monohydrate and β-lactose. DSC curves were obtained at a heating rate of 10°C/min using thermal analyser. X-ray diffractions were taken on samples, both prior to and after thermal treatment by heating to about 180°C followed by immediate cooling to room temperature. The non-thermally treated but intensively ground samples showed no or a very weak diffraction pattern, which shows the formation of amorphous lactose (amorphous forms exhibit very weak diffraction patterns). This indicated that the intense grinding resulted in un-crystallization of both α-lactose monohydrate and β-lactose. X-ray diffraction of the products obtained by heating the intensively ground (i.e. the un-crystallised) α-lactose and amorphous lactose to 180°C corresponded with the crystalline β/α mixed lactose compound. The un-crystallized β-lactose crystallized to β-lactose on heating.

To investigate the formation of the β/α mixed lactose compound from thermally treated amorphous lactose, additional experiments were done to study the changes in β-lactose content by way of heating amorphous lactose at different temperatures. Six batches of amorphous lactose having different β/α ratios prepared by spray drying and freeze-drying were heated to different temperatures and then cooled to room temperature. Determination of the β-lactose content of all the products showed the final product having a β/α ratio of about 1:1 (Lerk *et al.*, 1984(b)). X-ray diffractions of the samples heated to about 200°C corresponded to the crystalline 1:1 β/α compound.

Lerk *et al.* (1984(b)) concluded that α-lactose monohydrate looses its water of crystallization and like β-lactose changes into an amorphous phase due to intensive grinding. Thermal treatment at temperature of about 180°C results in crystallization of the amorphous phase into a crystalline β/α compound.

2.9 *PROCESSES FOUND IN LITERATURE PRODUCING CRYSTALS SIMILAR TO THE NEW CRYSTAL*

2.9.1 Patented method for producing a crystalline tabletting additive, thus obtained and use thereof (Kussendrager & van den Biggelaar, 2002)

Kussendrager & van den Biggelaar (2002) patented a method for producing a crystalline tabletting additive, which had a stable mixture of α and β-lactose crystals.

The lactose used in the method was spray-dried amorphous lactose. The spray-dried lactose was subjected to fast crystallization (for a short time between 5 to 10 minutes) and under agitation to a temperature between 30°C -100°C at a relative humidity between 60% and 25%. The humidity selected had no direct proportion to the temperature. The agitation was provided by a fluidized bed or mechanical form. By this method it was claimed that almost all the amorphous lactose that was initially present in the spray dried lactose was converted to a stable crystalline mixture of α and β-lactose.

This tabletting additive (α/β mix crystal) was called a stable crystalline mixture, as the analysis showed that the additive did not take up any additional moisture. Amorphous lactose is highly hygroscopic and in the presence of moisture crystallises to α-lactose. This affects the disintegration properties and the bioavailability of the active ingredient thus altering the performance of the tablet. It was claimed that this additive has better tabletting properties than the spray dried lactose and that the tabletting additive was insensitive to lubrication. The DSC thermogram of this tabletting additive showed a peak at 230°C which corresponded to the melting point of a pure α/β crystal. The various conditions of air temperature and humidity under which the spray-dried lactose was treated were – 25°C at 51% RH, 75°C at 25% RH, 60°C at 35% RH, 40°C at 55% RH.

2.9.2 Solid state Amorphization of Lactose by Ball Milling

Willart *et al.* (2004) studied the possibility of formation of pure glassy amorphous lactose by ball milling and then heating the product to re-crystallize it. The theory proposes that the extrinsic static disorder induced by milling adds to static disorder associated with the thermal vibrations, causing the softening of elastic constants to a critical value.

Ball milling was carried out in a dry nitrogen atmosphere to eliminate the formation of amorphous lactose at ambient humidity. It was found that the humid conditions (without nitrogen atmosphere) caused mutarotation converting about 15% of the sample to β-lactose. It was thought of producing pure amorphous α-lactose powder by eliminating mutarotation in the absence of humid air during ball milling under dry nitrogen.

Pure α-lactose powder was obtained by dehydration of the crystalline α-lactose monohydrate by blowing dry gaseous methanol through 20gm of a α-lactose monohydrate for three hours, and then ball milling carried out for 23 hours. A sharp exotherm during DSC analysis at a heating rate of 2°C/min showed a re-crystallization at about 160°C, which also suggests the formation of an amorphous phase during the milling process. A heat capacity (C_p) jump before the exotherm also characterised a glassy character of the amorphous phase. Thus amorphous lactose was formed during milling which crystallised at about 160°C.

Powder X-ray diffraction was done on crystalline α-lactose, α-lactose sample milled for 23 hours, and on the sample obtained by heating the milled sample at 170°C at the same rate of 2°C/min as in the DSC runs. The re-crystallized milled product had a completely different crystalline structure than α-lactose monohydrate, unstable α-lactose and β-lactose crystals and were similar to the β/α compound reported by Lerk *et al.* (1984 (a)).

Nuclear Magnetic Resonance (NMR) analysis showed that the re-crystallized product had the α and β anomer in equal proportion (that is, 50% β-lactose). Starting with 1% β-lactose content at the beginning, the 4% β-lactose content in the milled amorphous lactose suggests that the mutarotation was due to the water present in the α-lactose monohydrate and not due to milling.

2.10 *PRELIMINARY WORK ON PRODUCING THE NEW LACTOSE CRYSTAL*

Paterson & O'Donnell (1997) investigated the concept of using superheated steam to produce β-lactose crystals. The superheated steam-drying concept was proposed as a way of eliminating the formation of amorphous lactose on the surface of the α-lactose monohydrate crystals during drying under normal air. The new method reliably produced a product with 90% β-lactose content, provided the temperature was below 125°C, and the drying rate was not too fast. However, Paterson & O'Donnell (1997) also found an entirely new crystal form of lactose that was produced in the superheated steam environment at temperatures of 125° C and above as shown in Figure 2-4 and at drying rates above a critical value of 0.2 g/min/10ml. The X-ray diffraction pattern was entirely different from that of α-lactose monohydrate or β-lactose crystals. Polarimeter results showed that these crystals typically had 51-52% β-lactose content giving aβ:α ratio of 1.08:1.

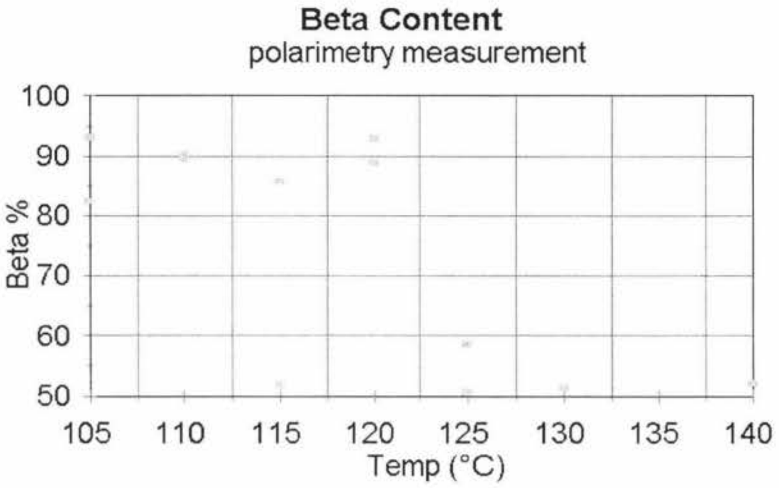


Figure 2-4: Graph of β-lactose content versus Temperature (Paterson & O'Donnell, 1997).

The pressure cooker pot used for producing the new crystal was put over a heating plate and steam was created by boiling water inside it. Heating coils connected to the body and the lid of the hot pot provided superheat to the steam.

Further work was carried out by Le Lievre (1998) and by Marshal (2000). Le Lievre (1998) was able to produce the crystal only once. The new crystal was formed at a temperature around 120°C, and drying rate above 0.3gm/min/10ml. The new crystal had a β-lactose content of 46%, which was less than that of the crystals produced by Paterson & O'Donnell (1997). The anomeric ratio of the crystal was 46:54 (β:α).

The lactose solution was dried on a suspended plate inside the pressure cooker. Marshal (2000) showed that the new crystal could be produced above a drying rate of 0.35g/min/10 ml with the temperature ranging from 120°C to 140°C.

Dhanjee & Paterson (2000) conducted further work on producing the new crystal. They successfully produced the new crystal four times but at different drying rates- 0.40 gm/min/10ml at 125°C, 0.34 gm/min/10 ml at 135°C, 0.36 and 0.56 gm/min/10 ml at 140°C. They therefore could not establish a relation between the drying rate, the temperature of the super-heated steam and the formation of the 50% β-lactose crystal. They suggested that the lack of relation could have been due to the fluctuation in the temperature of the suspended plate in the cooker upon injection of the lactose solution.

Table 2-2 below compares the characteristics of the crystals obtained by Buma (1978) and Dhanjee & Paterson (2000).

Properties	Buma (1978)		Dhanjee & Paterson (2000)
	Spray dried	Ground α- lactose	
Total moisture content	0.1%	0.97%	0.443% & 0.480%
Crystallinity	100%	100%	100%
Density	1.59-1.62 g/cm^3	1.59-1.60 g/cm^3	-
α/β ratio	46:54	55/45	48:52
Free moisture content	-	-	0.095% & 0.140%
Melting temperature	-	-	212-216 ^{0}C

Table 2-2: Comparison of crystals obtained by (Buma, 1978) and (Dhanjee & Paterson, 2000).

Coghill (2001) produced the new 50% β-lactose crystals at drying rates between 0.2 and 0.27g/min/10ml, and temperatures between 110°C and 130°C. Quite a few crystals were produced with 60%-70% β-lactose content at drying rates between 0.27 and 0.35g/min/10ml. These crystals were found to be a mixture of the new crystal and β-lactose anhydride. The drop in temperature upon injection of the lactose solution was studied in particular and the importance of achieving a steady state was recognised.

Clarke (2002) observed a temperature lag that occurred once the lactose solution was injected over the suspended plate. Drying rates with and without the plate were studied and it was found that higher initial drying rates were obtained when the solution was injected on the bottom of the pressure cooker instead of the suspended plate. The 50% β-lactose crystal was produced at temperatures 120°C and 130°C and high initial drying rate of 4.5gm/min/10 ml and about 7gm/min/10ml. In both the cases the solution was spread all over the bottom, which also eliminated the temperature lag. High initial drying rates were thought to be a key factor.

More recently, Ecroyd (2003) used the same procedure as Clarke (2002), but in a new stainless steel pressure cooker as the old aluminium cooker cracked during modifications. Ecroyd (2003) achieved consistent production of the new crystal by slow and even injection, resulting in a high drying rate. The 50% β-lactose crystal was successfully produced at drying rates between 2gm/min/10ml and 10.4g/min/10ml and temperatures between 120°C and 166°C.

Figure 2-5 below gives the interpretation of the way the new crystal might be produced.

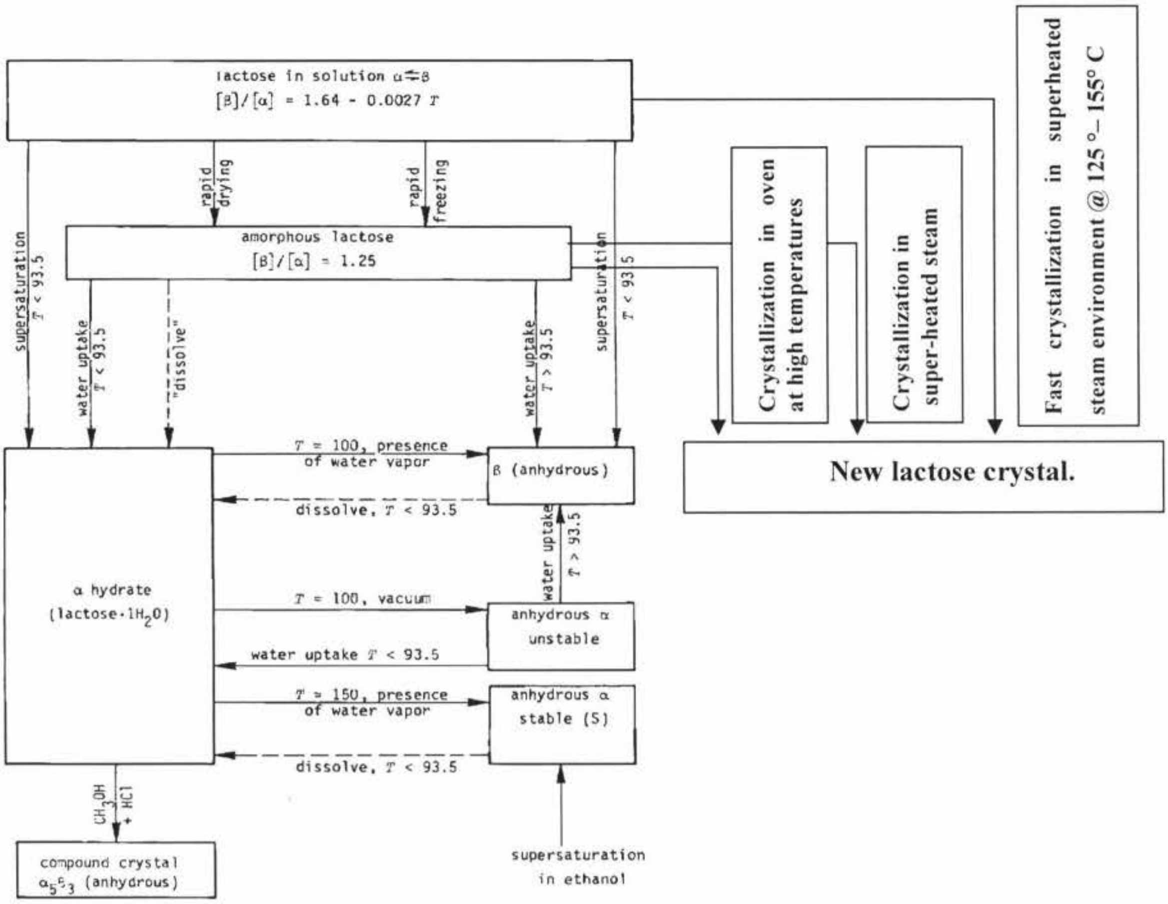


Figure 2-5: Interpretation of the process for production of the new crystal.

Modification of lactose (adapted from (Walstra & Jenness, 1984)).

2.11 PARAMETERS USED TO CHARACTERIZE THE NEW CRYSTAL

All the previous studies on the production of the new crystal used the following methods to characterize the new crystal.

2.11.1 Anomeric ratio

The β/α ratio of the lactose crystal was determined by measuring the anomeric ratio. The initial anomeric ratio was determined by back extrapolation of the ratio to the point of initial powder dissolution. The same method was used to determine the optical ratio of lactose by Buma & van der Veen (1974). Alternative methods include gas-liquid chromatography (GLC) and high-resolution proton and carbon-13 magnetic (NMR) spectroscopy (Hargreaves, 1995).

The polarimeter method gives the anomeric ratio of known concentrations of lactose solution. Since the method described assumes a two-component system (α and β) the presence of significant quantities of other crystals will change the optical rotation of the entire solution. Thus, pure lactose solutions are important. The optical rotation expressed by a solution of both anomers is the linear summation of the rotary power of each anomer weighted by the relative concentration of each Hargreaves (1995).

Gas liquid chromatography (GLC) provides an efficient means of separating carbohydrates such as lactose (Hargreaves, 1995). Each anomer expresses different retention times when separated over a column distance of two meters. As pure lactose does not readily volatise at normal column injection temperatures (200°C-300°C), samples must be derivatised to a more volatile compound, typically with trimethylsilylated (TMS) ether. GLC also requires the use of the solvent dimethyl sulphoxide (DMSO) to inhibit the mutarotaion of lactose in solution (Buma & van der Veen, 1974).

Hargreaves (1995) found that high resolution NMR spectroscopy was well suited to lactose characterisation. There was no need for time consuming derivatisation and unlike polarimetry, samples did not have to be accurately weighed. How ever this method is complex and expensive.

The polarimeter was chosen for use in this work as the method is cheap, the equipment was available and it is well established in the literature. Hargreaves (1995) also found out that it is an accurate method for characterising the anomeric composition of lactose powders.

2.11.2 Moisture content

Moisture can be thought as being chemically bound or physically adsorbed to a crystal (Bronlund, 1997).

2.11.2.1 Chemically bound moisture

Chemically bound water is normally called water of crystallisation. In α-lactose monohydrate, one molecule of water is present for every molecule of α-lactose. This is further distinguished as being lattice water, as it is required in the crystal lattice to maintain the integrity of the crystal structure. External energy is required to remove this bound moisture. Total moisture content (which includes chemically bound water and physically adsorbed water) can be measured by several methods, including chemical titration, azeotopic distillation and oven drying.

The Karl Fischer technique is an example of chemical titration (Anderson & Berline, 1973). Using this method the entire sample is dissolved and all the moisture is released. The amount of moisture is then determined by titration. Anderson & Berline (1973) found that titrations with pure α-lactose monohydrate powder consistently yielded the theoretical value of 5%.

Toluene distillation is an example of azeotropic distillation (Anderson & Berline, 1973). Della Monica & Holden (1968) found that toluene distillation could be used for determination of moisture in dried whole milk.

Oven drying at 120°C can be used to determine the total moisture content by determining the weight of the sample before and after drying. Drying is complete when there is no further weight loss.

Dhanjee & Paterson (2000) used the Karl Fischer method to successfully determined the total moisture content of the new crystal as 0.443% and 0.480%.

2.11.2.2 Physically adsorbed water

Adsorbed moisture is present on specific sites on the particle surface to form a monolayer and subsequent additional layers. The water molecules can be attached to the crystal surfaces by van der Waals forces or hydrogen bonding (Bronlund, 1997). This is called the "free" moisture.

The most widely accepted method to determine "free moisture" is the vacuum desiccation over phosphorous pentoxide for at least a month. This method is not applicable for routine industry based measurements as it a very time consuming procedure.

As temperature increases more and more bound moisture is removed. Thus oven-drying methods are not repeatable. Bronlund (1997) found that vacuum dried samples at 60°C for three hours gave sensible results for the free moisture content in line with the phosphorous pentoxide desiccator method. This indicates that at 60°C only the free moisture is removed. Dhanjee & Paterson (2000) used the method described by Anderson & Berline (1973) and Bronlund (1997) to determine the free moisture content. Dhanjee & Paterson (2000) found the free moisture content of the 50% β-lactose crystal as 0.095% and 0.104%.

2.11.3 Crystallinity

There are various methods available to determine the crystallinity of lactose powder. These include X-ray diffraction, differential scanning calorimetery (DSC), spin-lattice relaxation time measurement, relative humidity measurement and infra-red spectra.

X-ray diffraction is the most widely used method to determine the crystallinity. Paterson & O'Donnell (1997) have conducted powder X-ray diffraction on several different lactose crystals, including the superheated steam produced crystal. Thus it is advantageous to use the same method for analysis.

Differential scanning calorimetry (DSC) detects the subtle endothermic shift in specific heat capacity around T_g. Hargreaves (1995) found that characterisation of a binary mixture of amorphous and crystalline lactose could be achieved by spin-lattice relaxation time measurements. This method was found to be accurate, however it is also complex and expensive

Hargreaves (1995) analysed the crystalline structure of alpha lactose, conventional beta lactose and amorphous lactose. α-lactose monohydrate showed significantly different crystal ordering. But the two forms of β-lactose, which have unique crystal structure showed no significant differences. Because of the insensitivity of CP-MAS to differences in crystalline structure between β-lactose species, this method was not pursued as a characterisation methodology.

2.11.4 Density

According to Buma (1965), density can be measured by gas or liquid displacement techniques. Buma (1978) used the centrifugation in carbon tetrachloride/liquid paraffin solution method and an air pycnometer method for measuring the density of the lactose crystal produced from methanol.

The sedimentation method involved centrifuging (using a Gerber-type centrifuge) powder samples suspended in carbon tetrachloride/liquid paraffin mixtures of varying density and plotting the sediment volumes against the densities of the liquid mixtures. The intersection of the sedimentation curve with the density axis gave the true density of the powder. A condition of the method used was that no powder dissolved during centrifugation (Buma, 1965).

The pycnometric method involved air displacement to determine the mean particle density. Using a commercially available air pycnometer, a powder sample of known weight was used and the powder volume could be read from a digital counter.

Dhanjee & Paterson (2000) had some difficulties with the liquid displacement method using a volumetric flask because the amount of powder produced was small. It also gave an error of about 12%. Dhanjee & Paterson (2000) also found that the method of using a flask and a ground glass fitting with a glass tube attached to collect the displaced fluid proved inaccurate.

2.11.5 Melting point

Le Lievre (1998) and Dhanjee & Paterson (2000) used the Digital Melting Point Apparatus, Electrothermal Engineering Ltd to determine the melting point of the new crystal produced. Dhanjee & Paterson (2000) found the melting point of the new crystal to be 212°C-216°C.

2.11.6 Rate of dissolution

The dissolution of lactose is of industrial importance to many processors. Most users of lactose require it to be dissolved in water quickly and easily before utilisation. The rates at which the various forms of lactose dissolve are different. Paterson & O'Donnell (1997) proposed that because the new crystal was very near to the α/β equilibrium ratio it would dissolve much faster than α-lactose monohydrate at room temperatures.

Hodges *et al.* (1992) described a method for measuring the dissolution of lactose powder in water. This method was used by Dhanjee & Paterson (2000) to determine the rate of dissolution and it was found that solutions above the α-lactose solubility limit at 20°C can be achieved quickly, and are not limited by the mutarotation reaction.

2.12 *EXCIPIENTS & TABLETTING PROPERTIES*

Excipients for granulation can be divided into two categories: bulking agents and functional additives (Parikh, 1997). The bulking agents or fillers also serve a function in that they form the core or structure of a dosage form. Bulking agents are generally inert and inexpensive. Functional additives include binders, disintegrants, lubricants, colorants and stabilizing agents. Choice of the excipient depends on several factors; namely, the drug used, process involved, the formulator, and the cost of the excipient.

The common filler used is lactose, although other sugars, dicalcium phosphate, starch, pre-gelatinized strach, and microcrystalline cellulose (MCC) are also used (Parikh, 1997). Starches and MCC are also used as disintegrants in tablets.

Lubricants are not added until just before tabletting of the granules. The most commonly used lubricant is magnesium stearate. Other lubricants include calcium stearate, stearic acid, wax, hydrogenated vegetable oil, talc and starch (Parikh, 1997). Binders used in granulation consist of a wide variety of sugars and polymers. Sugars include sucrose, glucose and sorbitol. Examples of natural polymers are acacia, alginic acid, sodium alginate, gelatine and starch (Parikh, 1997).

To this day, lactose remains one of the most popular excipients for active pharmaceutical ingredients whose dose makes them suitable for direct compression (Bolhuis *et al.*, 2004). Spray dried lactose has been principally used for this purpose. Lactose is used in tablets and particularly in medicinal, nutritional and therapeutic tablets as it dissolves rapidly, has less flavour or odour, is not excessively sweet, and does not give bad physiological effects. Crystals of α-lactose monohydrate that are large enough to flow reasonably well are not particularly compressible (Vromans, 1987) [cit. (Bolhuis *et al.*, 2004)]. According to (Vromans, 1987), the product containing finer lactose fractions formed stronger compacts under the same compaction force. Bolhuis *et al.* (2004) also found that even with the same amount of amorphous lactose in both the samples, the one with finer lactose fraction produced 30%-50% harder tablets.

Tablets formed by the wet granulation process dissolve less rapidly than tablets formed by direct tabletting and are less desirable when used in tabletting of medicinal preparations (Nezbed, 1974).

Inference:

During the late stages of the project, a few articles were found as mentioned in section 2.8.2, 2.8.3 and 2.9.2 that discussed the occurrence of the 1:1 β/α mixed lactose crystal, that was similar to the crystal found by (Paterson & O'Donnell, 1997). So the crystal described by (Paterson & O'Donnell, 1997) cannot be called a new lactose crystal.

Lefebvre *et al.* (2005) have studied the structure of the crystal. Henceforth the new lactose crystal will be described as a 1:1 β/α mixed lactose crystal.

The articles found in the literature have discussed the formation of the 1:1 β/α mixed lactose crystal from solid-state α-lactose monohydrate and amorphous lactose, while (Paterson & O'Donnell, 1997) managed to form the crystal from the liquid state.

From the previous work done on the formation of the 1:1 β/α mixed lactose crystal, it can be said that 1:1 β/α mixed lactose crystal should be obtained at temperatures between 120°C-150°C with high initial drying rates. Slow injection and spreading of the lactose solution evenly over the drying surface should give high initial drying rates.

After considering the methods to produce the 1:1 β/α mixed lactose crystal on a continuous basis, a roller drier was thought to be the most feasible option, as the conditions required to produce the 1:1 β/α mixed lactose crystal were achievable. It would be relatively easy to produce a superheated steam environment and high initial drying rates at the required temperature.

CHAPTER 3

TRIALS & RESULTS

Step by step development of the continuous process

3.1 *INTRODUCTION*

The 1:1 β/α mixed lactose crystal was consistently produced by previous researchers in a batch process using the hot pot. To produce the 1:1 β/α mixed lactose crystal in a continuous way, the same conditions obtained in the hot pot had to be obtained in the continuous process. Even though the rates of drying and temperature range were roughly known from the previous work, it was accepted that exactly the same drying rates would not be achieved during the continuous process. The only known and common parameters between the two processes were the operating temperatures, use of superheated steam and concentration of the solution. The higher and lower limits of all the other parameters had to be determined by doing trials, interpreting the results and then making modifications to the process.

3.2 *PREVIOUS WORK*

All the previous work on the 1:1 β/α mixed lactose crystal used the hot pot set up shown in Figure 3-1. Boiling the water inside the hot pot generated steam. Superheat was provided to the steam by heating coils connected to the body of the hot pot.

The pot was placed on a weighing scale. After providing superheat to the steam, the system was allowed to stabilize to the required temperature. 120gm α-lactose monohydrate was completely dissolved in 100 ml distilled water at 90°C. 10 ml of the solution was injected with a syringe into the superheated steam environment generated inside the hot pot. The run was stopped after it was observed that there was no further decrease in the weight. The drying rate was found by plotting the decrease in weight of the lactose solution against time.

The 1:1 β/α mixed lactose crystal was produced over a range of drying rates and temperatures. There was no clear relationship between the temperature, the drying rate and the β-lactose content in the product.

Figure 3-1: Equipment used for production of the 1:1 β/α mixed lactose crystal (Hot Pot).

3.3 *PRESENT WORK*

From the literature it was clear that the best conditions to produce the 1:1 β/α mixed lactose crystal would be between the temperatures 120°C-155°C with high initial drying rates. Slow injection and spreading of the lactose solution evenly over the drying surface by spray nozzles would give high initial drying rates.

Taking into account the conditions needed to produce the crystal in a continuous process, a roller dryer was thought to be an ideal option. It was also relatively easy to produce the superheated steam environment over the roller drum.

A small size laboratory roller drier was available which was used to develop the process.

The makers of the roller drier, Richard Simon & Sons Ltd, Nottingham, were contacted for the specifications. The specifications were important to find out the pressure handling capacity, calculate the rate of evaporation, and heat loss from the system.

The specifications were:

Material of roller drums: Cast Iron.

Pressure handling capacity: 80 psi (5.5 bar) [about 155°C].

Thickness of each drum: 0.5 inch.

Length of each drum: 8 inch.

Diameter of each drum: 8 inch.

3.3.1 Variables in the process

The process variables that the process depended on were identified as follows.

- **Temperature of the drum surface:** The 1:1 β/α mixed lactose crystal was produced between 120°C –155°C.
- **Speed of the drum:** This factor determines the time the solution would remain in the steam environment. A slow drum speed meant that the crystals could be re-wetted from the spray and a fast drum speed meant that the solution might not crystallize in the steam environment or might not crystallize at all and would result in amorphous rubber lactose.
- **Flow rate of the solution (rate of application of the lactose solution):** This determines the rate of evaporation. The rate of application should be low enough so as to get a high rate of evaporation and allow enough time for the solution to completely crystallize in the superheated steam environment.
- **Temperature and concentration of the solution:** The solubility of lactose is temperature dependent (section 2.5). The concentration used in previous studies was 120gm/100ml water. At very low concentrations a lot of water needs to be evaporated and at very high concentration the solution tends to become supersaturated quickly and crystallize in the spraying set up.
- **Superheated steam environment:** The steam inside the box had to be superheated. The temperature of the environment should be the same as the temperature of the roller drum.

3.3.2 Basic set up of the rig

3.3.2.1 High pressure steam piping for the roller drier

The piping and fittings for the roller drier were old and had a few leaks. New suitable fittings, such as valves, steam trap, strainer, and steam separator were acquired. All the old piping for the roller drier was replaced by new ½" piping and the fittings fitted in suitable places. As the temperature required for the experiments was between 120°C-155°C, a high-pressure steam point (0-7 bar) was located in the laboratory and additional piping completed to extend it to the roller drier. A pressure sensor was connected just after the pressure reducing valve.

The experimental rig is shown in Figure 3-2 and Figure 3-3 is a schematic layout of the experimental rig.

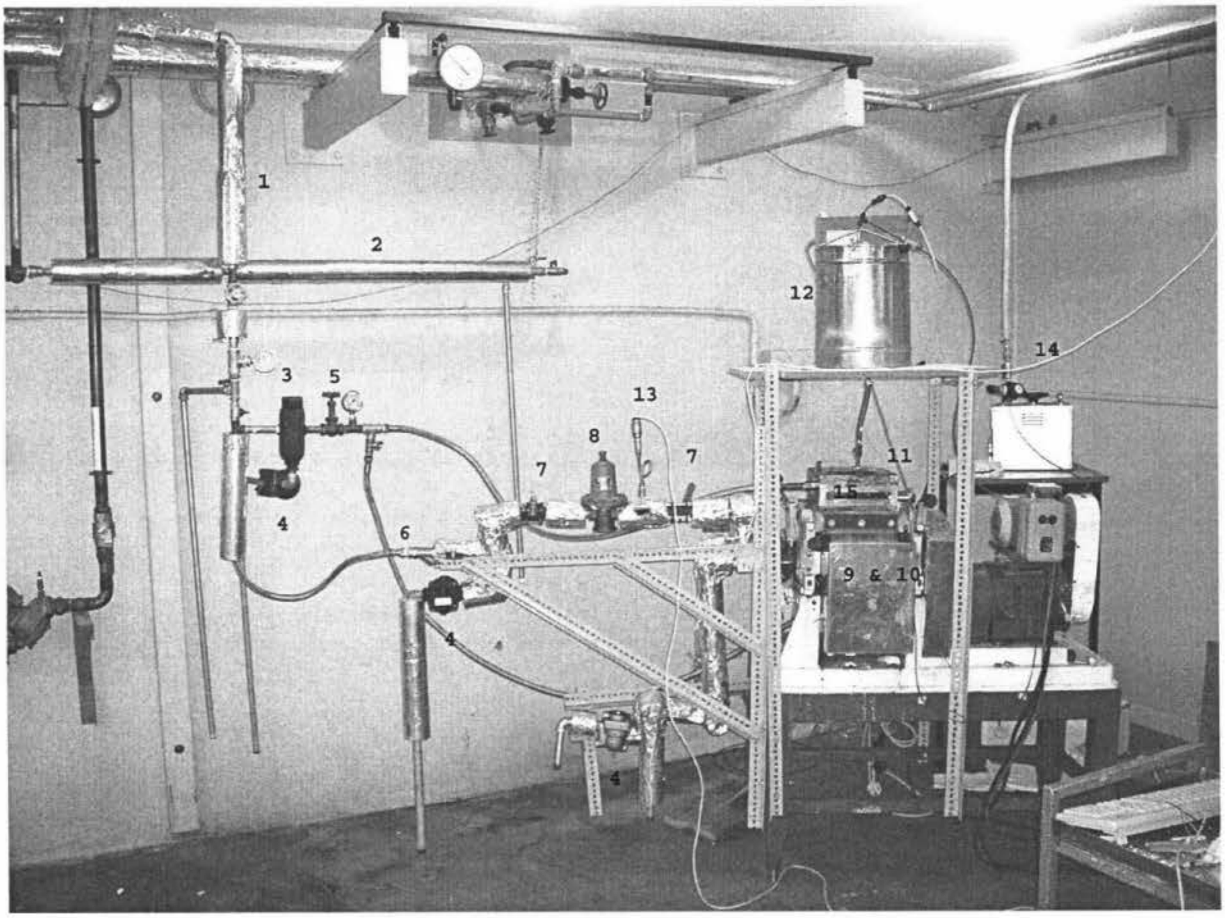


Figure 3-2: Experimental rig.

1: High Pr. steam line (0-7 bar), 2: Low Pr. steam (0-2bar), 3: Steam separator, 4: Float trap, 5: Globe valve, 6: Strainer, 7: Ball valve, 8: Pressure reducing valve, 9: Collection tray, 10: Roller drier, 11: Steel box, 12: Water bath with vertical cylinder and temperature controller, 13: Pressure sensor, 14: Air Pressure regulator, 15: Spray nozzle inside the steel box.

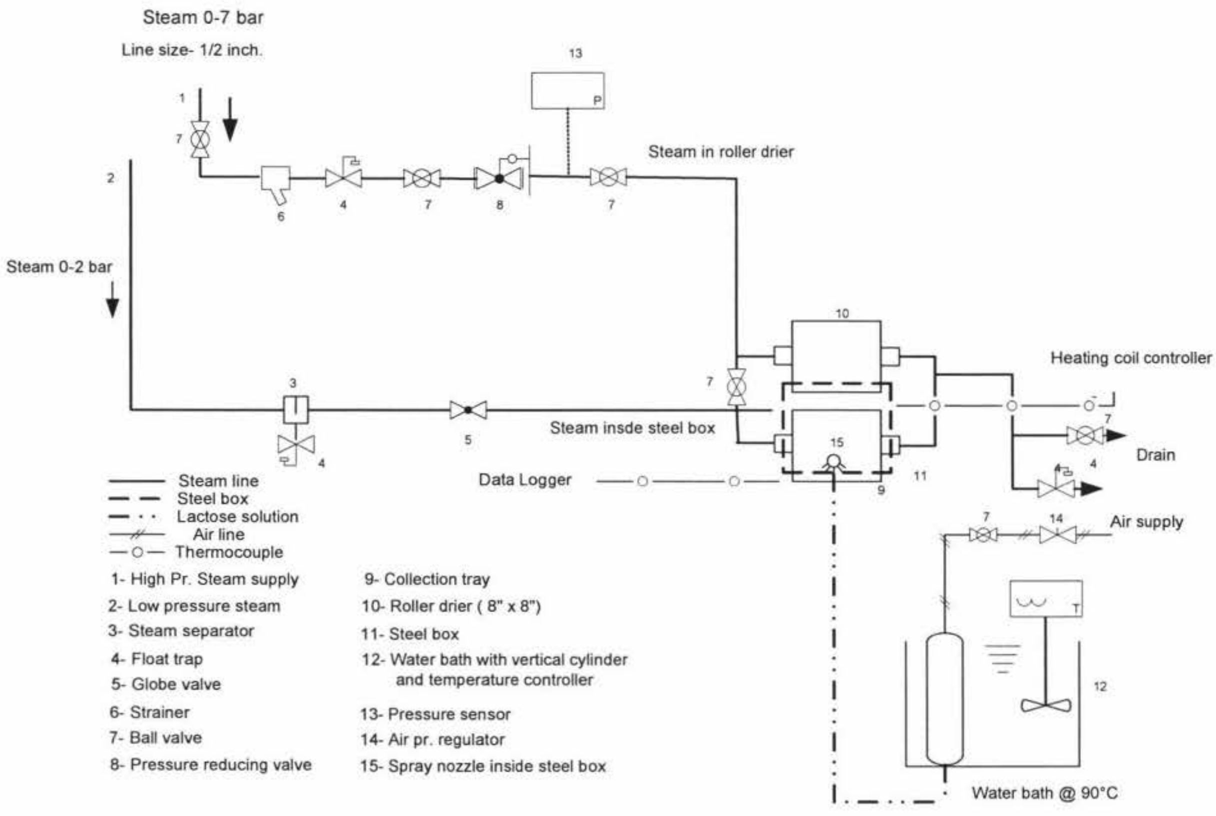


Figure 3-3: Schematic layout of the experimental rig.

3.3.2.2 Superheated steam environment

A steel box was fabricated to fit over one roller drum as shown in Figure 3-4 (a). The steel box had a steam inlet to constantly supply steam and maintain the steam environment over the drum. A heating coil was connected inside the steel box to provide additional heat to create a super heated steam environment. The inside of the box is shown in Figure 3-4 (b). The steam line that supplied steam to the box had a steam separator to ensure that the steam supplied inside the box was dry.

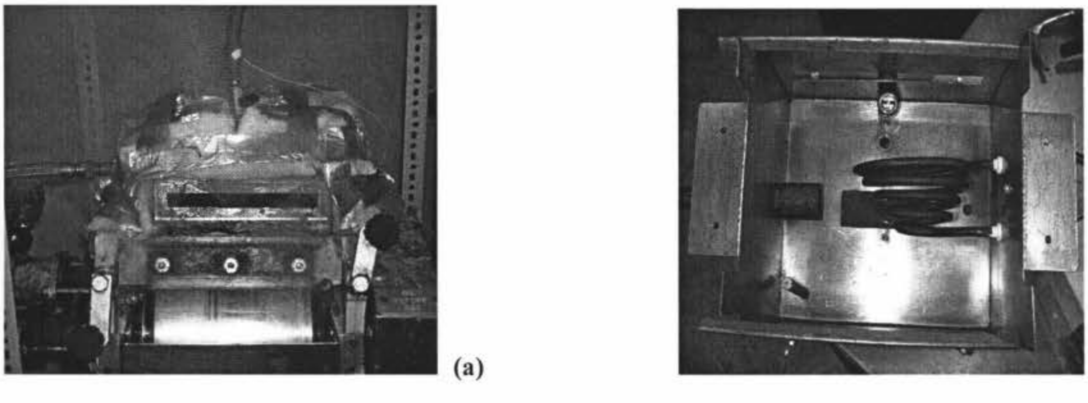

(a) **(b)**

Figure 3-4: (a) Steam environment over the roller and (b) Box internals: steam inlet, heating coil, spray nozzle & temperature sensor

3.3.3 Different setups for application of lactose solution

It was desired to have high drying rates and an even spread over the drum surface. It was recognised that high drying rates are possible at low flow rates, but the flow rate that would produce the 1:1 β/α mixed lactose crystal was unknown.

The following gives the various ways lactose solution was applied to the drum surface.

3.3.3.1 Spray Nozzles

Spray nozzles were thought to be an ideal option for even spreading of the lactose solution at low flow rates. Nozzles were acquired from Spraying Systems Co. Lactose solution had to be applied over the drum at 90°C and so a water bath was used to maintain the solution temperature at 90°C. A vertical cylinder (which could be air pressurised) was fixed inside the water bath to hold the lactose solution (Figure 3-5).

Figure 3-5: Water bath & cylinder to hold the lactose solution.

The bottom of the cylinder was connected to the spray nozzles. Air pressure controlled the flow rate through the nozzle. The specifications of the nozzles used are given in Table 3-1 below. The spray nozzles were selected according to the type of spray and the flow rate required. A schematic layout of the set up for spray nozzle is shown below in Figure 3-6.

Nozzle specifications	TP730023	TPU650017
Operating pressure	1bar-35 bar	2 bar- 35 bar
Capacity (l/min)	0.05 – 0.31	0.05 – 0.23
Spray angle (°)	50° - 97°	44° - 86°
Orifice diameter (mm)	0.30	0.28
Spray pattern	Flat	Flat

Table 3-1: Specifications of the nozzles used.

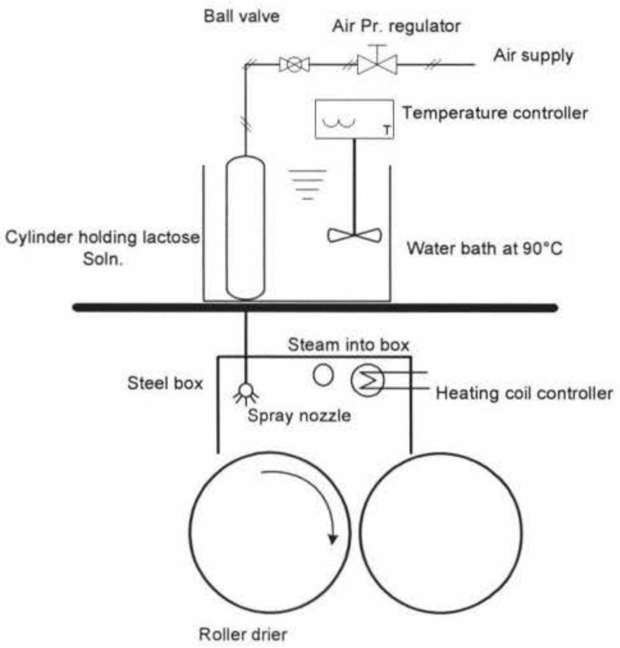


Figure 3-6: Set up for spray nozzle.

3.3.3.1.1 Experimental

An ideal experimental run would start by heating the roller drum to the required temperature. A Fluke made temperature sensing probe used for measuring the surface temperature of curved surfaces was acquired for that purpose. Steam was introduced into the steel box above the drum and additional heat was provided by the heating coil fixed inside the box. The roller drier was set to the required speed. The temperature of the roller drier and the temperature of the superheated steam environment were kept the same by setting the temperature controller set point to match the drum temperature. The water bath was heated to 90°C-91°C. A 54.5-wt % concentration (120gm/100ml water) lactose solution was separately made at 90°C and kept ready. After the system was stabilized, lactose solution was filled into the cylinder. The cylinder was sealed and pressurised to the required air pressure. As soon as the inlet valve to the spray nozzle was opened, the lactose solution would start spraying on the drum surface. The dried lactose product was collected and stored in sealed plastic bags. Samples were immediately tested for the β/α content by polarimeter.

3.3.3.1.2 Polarimetric measurement and anomeric calculations

Polarimetric measurements were carried out on an Optical Activity ADP 220 Polarimeter with a 20 cm water-jacketed sample tube. The temperature of the sample tube was maintained at 20°C by circulating water through a water bath. Polarimeter readings were made at 589 nm wavelength.

The water bath was heated to 20°C, and temperature of the distilled water equilibrated in the water bath. The sample tube was flushed three times with distilled water and filled by removing all the air bubbles in it. The polarimeter was calibrated to zero reading before each analysis by using distilled water.

A 5 gm lactose sample was accurately weighed into a 100ml volumetric flask and about 10-20 ml distilled water added to it. The flask was then filled up to the mark. The flask was shaken vigorously to dissolve the entire lactose sample as quickly as possible, as solvation delay displaces the curve to longer times and raises the intercept (Hargreaves, 1995). Polarimeteric readings were commenced as quickly as possible after the 10-20 ml water had been added. This is because mutarotation starts as soon as the sample comes in contact with water. The sample tube was flushed by the solution three times and then filled by removing all the air bubbles. The sample tube was then put inside the polarimeter and the lid put over it. The readings were taken for 2 hours. Lactose powder can be ground so that it dissolves quickly, but care must be taken as excessive grinding may alter the composition of some powders (Hargreaves, 1995).

The remaining solution in the flask was kept for 24 hours and a polarimeter measurement made to get the equilibrium optical rotation as R_∞.

Optical rotation is dependent on solute concentration and polarimeter cell length. These dependencies may be normalised (equation 3.1) to yield the specific optical rotation at fixed temperature and wavelength. It is therefore important that the concentration of lactose in solution is accurately known.

The specific equilibrium rotation $[R_\infty]$ is given by equation 3.1 (Hargreaves, 1995).

$$[R_\infty] = \frac{100R_\infty}{Lc}$$

Equation 3.1

Where,

L = length of the polarimeter cell in decimetres (2 dm).

c = anhydrous concentration of lactose in g/100ml.

$[R_\infty]$ = The specific optical rotation at time t= ∞ = 55.48° for pure lactose.

R_∞ = Polarimeter reading at equilibrium.

After finding the anhydrous concentration c from equation 3.1, the specific optical rotation at different times can be found out from equation 3.2 below.

$$[R_x] = \frac{100R_x}{Lc} \qquad \text{where } x = t, \infty$$

Equation 3.2

Where, R_x is the polarimeter reading at any time t.

The specific optical rotation at the moment of solvent contact $[R_0]$ is found from the y-intercept of the plot $Ln([R_t] - [R_\infty])$ versus t at time t=0. $[R_0]$ is found out by extrapolating the plot $Ln([R_t] - [R_\infty])$ V*s* t, back to Time (t) = 0.

The anomeric composition of the actual lactose sample is given by Equation 3.3.

$$\alpha = \frac{([R_0]-[\beta])}{([\alpha]-[\beta])} X100\%$$

Equation 3.3

Where,

$[\alpha]$ = 91.1 and $[\beta]$= 33.5 are the specific rotations of pure alpha and beta lactose,

α = The amount of anhydrous α-lactose in α- lactose monohydrate (%).

Thus

β- lactose content of the sample (%) = (100 - α).

3.3.3.2 Trials with Nozzle TP730023

Water trials were completed to determine the flow rate through the nozzles at different air pressures.

Table 3-2 below gives the flow rates at different air pressures

Nozzle TP730023			
Air Pressure	2 bar	3 bar	3.5 bar
Flow rate	82 ml/min	100 ml/min	108 ml/min

Table 3-2: Flow rates for the nozzle TP730023

The speed of the drum was set to 1 min/rev. It was assumed that the superheated steam environment was available only during one quarter of the roller drum because the roller was open to air after the roller completes one-quarter of a revolution.

Trials with nozzle TP730023 were completed at drum and superheated steam temperatures of 125°C, 135°C and 145°C and drum speed 1 min/rev.

Results:

The results for the trials are given in Tables 3-3 to 3-5.

Nozzle TP730023 Temperature- 125°C & drum speed 1 min/rev			
Flow rate	82 ml/min	100 ml/min	108 ml/min
β- lactose content (%)	68.1%	77.3%	69.9%

Table 3-3: Result for the nozzle TP730023 at 125°C.

Nozzle TP730023 Temperature- 135°C & drum speed 1 min/rev			
Flow rate	82 ml/min	100 ml/min	108 ml/min
β- lactose content (%)	85.4%	85.4%	84.6%

Table 3-4: Result for the nozzle TP730023 at 135°C.

Nozzle TP730023 Temperature- 145°C & drum speed 1 min/rev			
Flow rate	82 ml/min	100 ml/min	108 ml/min
β- lactose content (%)	85.9%	86.2%	86.4%

Table 3-5: Result for the nozzle TP730023 at 145°C.

Discussion:

Table 3-3 shows that at 125°C there was no relation between β- lactose content and flow rate and trials at 135°C and 145°C (Tables 3-4 & 3-5) consistently produced a crystal with about 85% β-lactose. The solution appeared to crystallize in the super heated steam environment. β-lactose might have nucleated out of the solution as the temperature of the drum was higher than 93.5°C and the rate of drying was not high enough. It was decided to try lower flow rates to achieve still faster drying rates. In an effort to slow the rate of application it was decided to smear the lactose solution on to the surface of the dryer.

3.3.3.3 Smearing trials

The lactose solution was smeared over the drum surface using the system as shown in Figure 3-7 and 3-8 below. Pieces of sponge were kept inside a small rectangular metal case as shown in Figure 3-7. The pieces of sponge absorbed the solution coming in and the piece of sponge hanging out of the case smeared the solution onto the drum. Though the flow rate of the solution going into the metal case was known, the actual rate of application could not be determined.

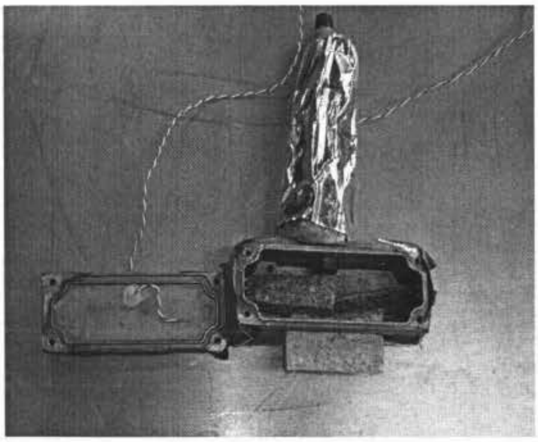


Figure 3-7: Smearing trial set up showing the internals of the metal case.

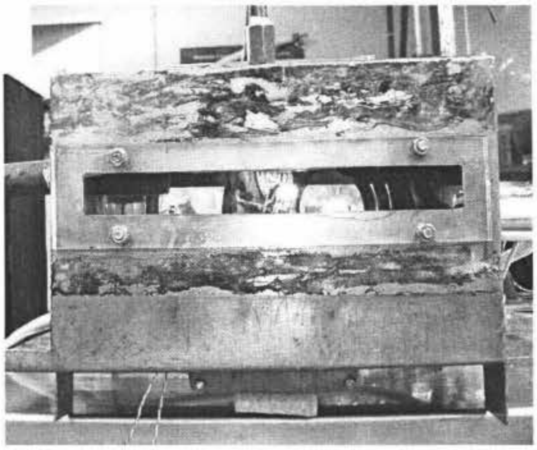


Figure 3-8: Smearing trial set up.

A schematic layout of the set up is shown below in Figure 3-9

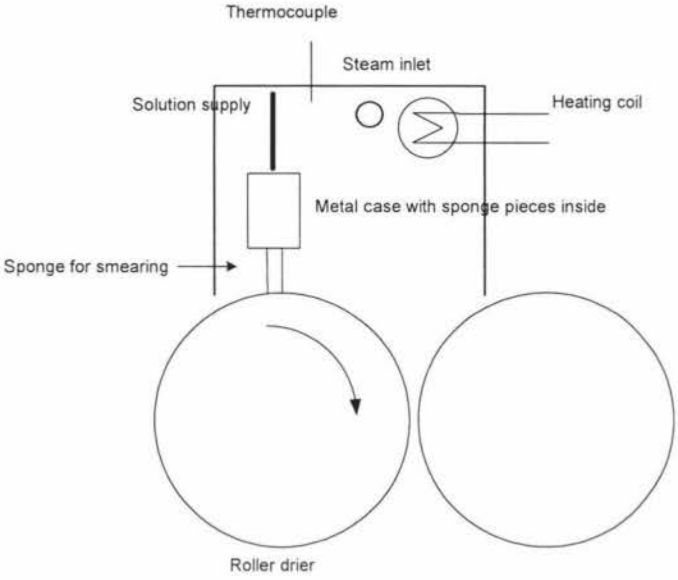


Figure 3-9: Schematic layout of the smearing set up.

Part 1: Different concentrations

The concentration of the solution was reduced to check whether it has any effect on the process. If concentration is reduced the solution would require more time to go into the super saturation state and thus require more time to crystallize.

Two different concentrations were tested: 33.33-wt % concentration (50gm/100ml water) and 50-wt % concentration (100gm/100ml water). The trials were completed at 125°C, 145°C and 155°C. The speed of the drum was set at 1min/revolution.

Results:

Results are given below in Tables 3-6 to 3-8.

Smearing Trials Temperature- 125°C	
	β- lactose content (%)
33.33% concentration	85.2%
50% concentration	85.8%

Table 3-6: Results of the smearing trial at 125°C.

Smearing Trials Temperature- 145°C	
	β- lactose content (%)
33.33% concentration	81.8%
50% concentration	84.3%

Table 3-7: Results of the smearing trial at 145°C.

Smearing Trials Temperature- 155°C	
	β- lactose content (%)
33.33% concentration	82.7%
50% concentration	79.1%

Table 3-8: Results of the smearing trial at 155°C.

Discussion:

Due to the surrounding superheated steam, the solution inside the metal case was boiling and β- lactose was thought to be nucleating inside the sponge. Thermocouples were connected inside the body and it was found that the temperature inside the metal pipe and case was between 110°C-114°C. This could explain the high β- lactose content.

Part 2: Metal pipe and case insulated and temperature monitored.

The metal pipe and the case were insulated and thermocouples were connected to the inside of the case and the pipe that supplied the solution. Trials were completed at 125°C and 145°C at 54.5wt % concentration. The temperature inside the case containing the sponges was between 93°C-98°C and the temperature inside the metal pipe supplying the solution to the sponges was between 91°C-96°C.

The results are as given in Table 3-9

Smearing Trials Concentration- 54.5 wt %	
Temperature	β- lactose content (%)
125°C	86.6%
145°C	83.5%

Table 3-9: Results of the smearing trials after temperature monitored.

Discussion:

The solution was drying just inside the steam environment. Insulating and maintaining the temperature below the boiling point did not stop the β-lactose product forming. Again, it was assumed that the reason β-lactose was forming was because the evaporation rate was not fast enough.

3.3.3.4 Calibration of the polarimeter

The polarimeter was calibrated against mixes made up from high purity α-lactose monohydrate and high purity β-lactose. β-lactose was made by heating a lactose solution in a beaker with constant stirring at 95°C. The α-lactose content in the α-lactose monohydrate obtained from Fonterra, Kapuni after considering the 5% water of crystallisation was 98% α-lactose. The pure β-lactose produced had 93% β-lactose content. β-lactose and α-lactose were analysed on the same polarimeter as used for all the runs. The calibration was checked by mixing powders in proportion to give approximately 25%, 50% and 75% β-lactose content mixtures. The approximate amounts of α-lactose monohydrate and β-lactose added to get the respective mixtures are given in Table 3-10

	Mixture components		
Component added	25% β-lactose	50% β-lactose	75% β-lactose
α-lactose monohydrate	18.696 g	12.554 g	6.196 g
β-lactose	6.304 g	12.554 g	18.804 g

Table 3-10: Mixture components for 25%, 50%, and 75% β-lactose content mixtures.

These samples were then tested by the polarimeter following the same experimental procedure given in section 3.3.3.1.2. Calculations were performed on all the mixtures to find whether the polarimeter readings agreed with the theoretically calculated values.

The comparison of the values obtained by the polarimeter and calculated values is given below in Table 3-11

Comparison of the polarimeter and the calculated β-lactose contents for different mixes

Mix (%β)	Polarimeter results (%β)		Calculated values (%β)
	Run 1	Run 2	
25%	26.2%	26.2%	25.7%
50%	48.9%	49.3%	48.6%
75%	71.5%	71.2%	71.3%

Table 3-11: Comparison of the Polarimeter and theoretically calculated values for different mixtures.

Sample calculations for 25% β-lactose content mix are given below.

Considering that there is 5% water in α-lactose monohydrate, the actual α-lactose content in the mix was [(18.696 x 0.95 x 0.98) + (6.304 x 0.07)] = 17.84 gm and the β-lactose content was [(18.696 x 0.95 x 0.019) + (6.304 x 0.93)] = 6.2 gm.

This gives the β-lactose content in the 25% β-lactose content mix as 25.7% β-lactose.

The comparison in Table 3-11 shows that the theoretically calculated values agree well with the polarimeter readings for the different β-lactose content mixtures. This confirmed that the polarimeter readings were correct and within acceptable limits. A plot of the polarimeter values Vs the calculated values in Figure 3-10 shows a linear plot which also means that the polarimeter readings are within acceptable limits.

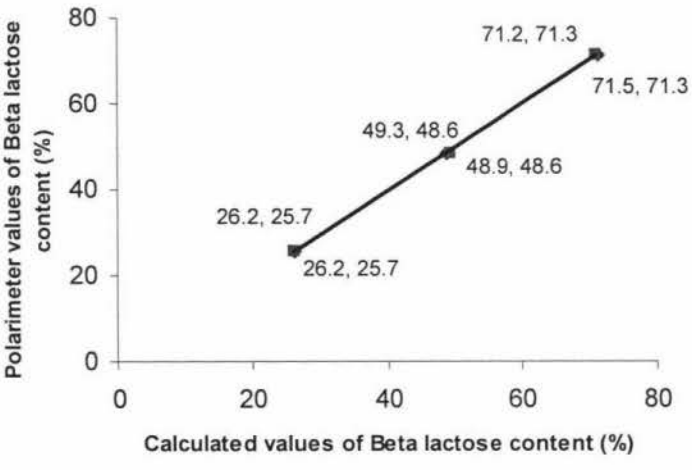


Figure 3-10: Plot of Polarimeter values Vs theoretically calculated values of different β-lactose mixtures.

The graph of Ln [(R(t) - R(inf)] versus Time for Run 1 for the 25% β-lactose content mixture is given in Figure 3-11.

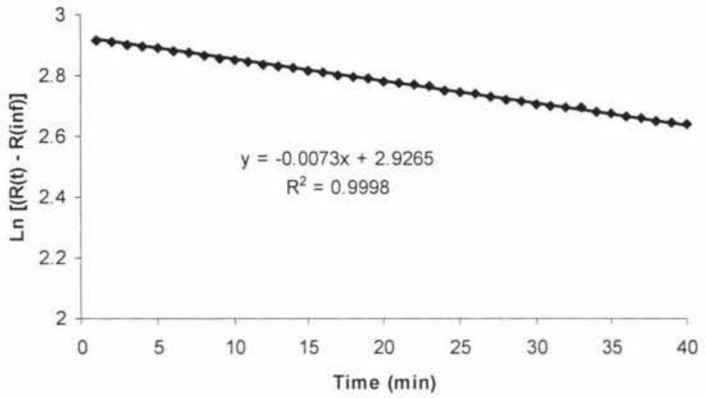


Figure 3-11: Logarithmic plot for run 1 for 25% β-lactose mixture.

The fact that the plots were linear confirms the temperature stability during the runs.

It was decided to set up a system with a lower flow rate to increase the rate of evaporation.

3.3.3.5 Nozzle TPU650017 with needle valve

A small size needle valve was connected in line with the nozzle TPU650017. The needle valve helped in achieving lower flow rates and ensured that the flow was even. Water trials were completed to calibrate the flow rate at different air pressures. Trials with lactose solution were completed to check the flow pattern and to check whether the solution dried inside the steam environment. During some mock trials, it was found that even after the first revolution of the roller drier, some amorphous lactose in the form of a thick rubber was left on the drum surface. This meant that the solution was not getting completely crystallised in the time of one revolution. The results of the trials in which crystallization occurred inside the superheated steam environment are given below.

Results:

The results of the trial with a flow rate of 26.66ml/min and at concentration of 54.5 wt % and drum speed of 1 min/rev are given below in Table 3-12.

Nozzle TPU650017 with needle valve	
Temperature (°C)	β- lactose content (%)
125°C	65.4%
135°C	68.5%
145°C	73.9%
155°C	78.6%

Table 3-12: Results of Nozzle TPU650017 with needle valve.

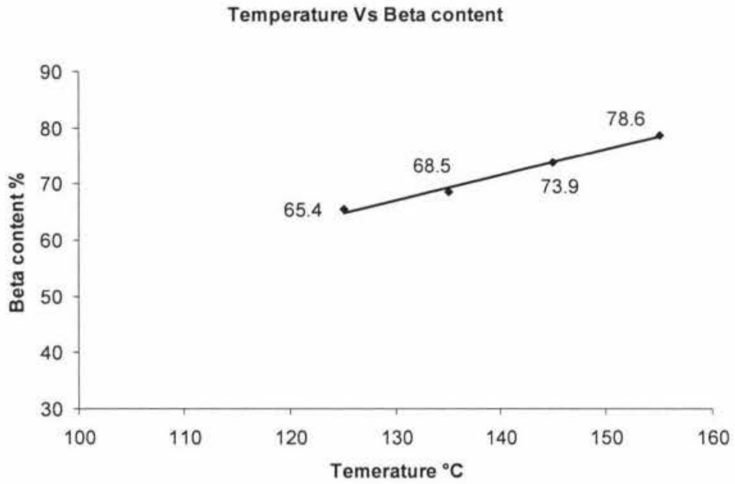


Figure 3-12: Graph of Temperature Vs β-lactose content (Nozzle TPU650017 with needle valve).

Discussion:

A plot of the results (Figure 3-12) clearly shows a trend for β-lactose content that increased with temperature. This was not as expected because higher temperatures should have produced higher rates of evaporation and lower β-lactose content.

The trend was an indication that low flow rates were producing lactose with less β-lactose content. So flow rates lower than 26 ml/min were needed. Also slower drum speeds was thought to be advantageous since the solution would remain in the steam environment for a longer time.

3.3.3.6 Nozzle TPU650017 with collection tray

Now that it was evident that low flow rates were needed and none of the nozzles provided the required low flow rates, a tray was designed which allowed only about 5% of the spray to pass through while collecting and draining the remaining 95% of the solution (Figure 3-13). The tray was fixed inside of the steel box and under the spray nozzle at a certain height so as to get the desired flat spray pattern as shown in Figure 3-14. Flow rates as low as 0.2 ml/min were obtained by this set up. Also a new gearbox was connected to the motor to reduce the speed of the roller drier. The slowest speed the roller drier achieved was 36 min/revolution.

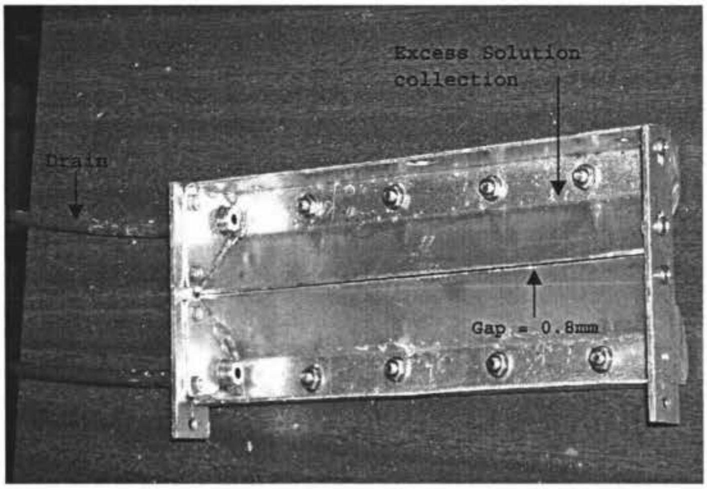


Figure 3-13: Tray for collecting excess solution.

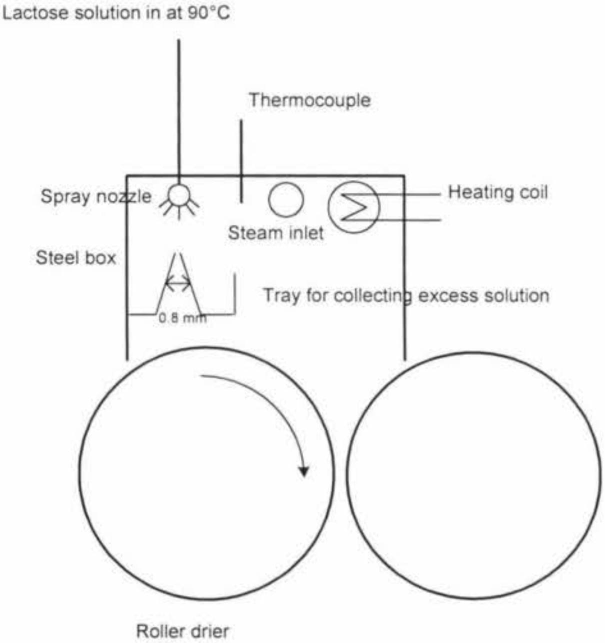


Figure 3-14: Schematic diagram of the set up for Nozzle TPU650017 with collection tray.

Results:

Results of trials for drum speed 8min 37 seconds/rev are given below in Table 3-13.

Nozzle TPU650017 with collection tray Drum speed 8min 37 sec		
Temperature (°C)	Flow rate (ml/min)	β content (%)
125°C	4.5 – 5 ml/min	67.8%
135°C	2.9 – 3.5 ml/min	**57.9%**

Table 3-13: Results for Nozzle TPU650017 with collection tray.

Discussion:

The result at 135°C was the first trial that produced a product with β-lactose content lower than 60%. This was thought to be the 1:1 β/α mixed lactose crystal due to the very low β-lactose content. The disadvantage of this system was that about 98% solution was wasted and the gap between the plates blocked regularly. This showed that to produce the 1:1 β/α mixed lactose crystal flow rates lower than 3ml/min were necessary.

But the process still had to be continuous and obviously waste less solution.

3.3.3.7 Two Fluid nozzle

Usually two fluid nozzles are air atomized and are used mostly in spray driers to get extremely fine droplet sizes. For this particular application, if a continuous low flow is provided at the tip of the two fluid nozzle, then the solution could be atomized at that low flow rate over the drum surface. For this particular application the fluid had to be atomized by steam, as air could not be introduced into the superheated steam environment.

An external mix two fluid nozzle was acquired from Fonterra (Figure 3-15) for doing trials and to check whether a two fluid nozzle would work for this particular application. The fluid comes out of the nozzle tip in the form of drops, which get atomized by the steam flowing past it. The orifice diameter of this nozzle was 0.8mm and the flow from this nozzle was a hollow circular pattern.

A spray is created when steam and the fluid come into contact. The feed is pressurised through the orifice by steam. The gas to liquid ratio is normally greater than 1 (Gottlieb & Schwartzbach, 2004).Two fluid nozzles can be internal mix or external mix types. The common uses of two fluid nozzles are in spray drying and tablet coating. Two fluid nozzles are prone to collect deposits on the nozzle exit orifice, this phenomenon is known as bearding. Thus frequent cleaning is necessary (Schick *et al.*, 2004).

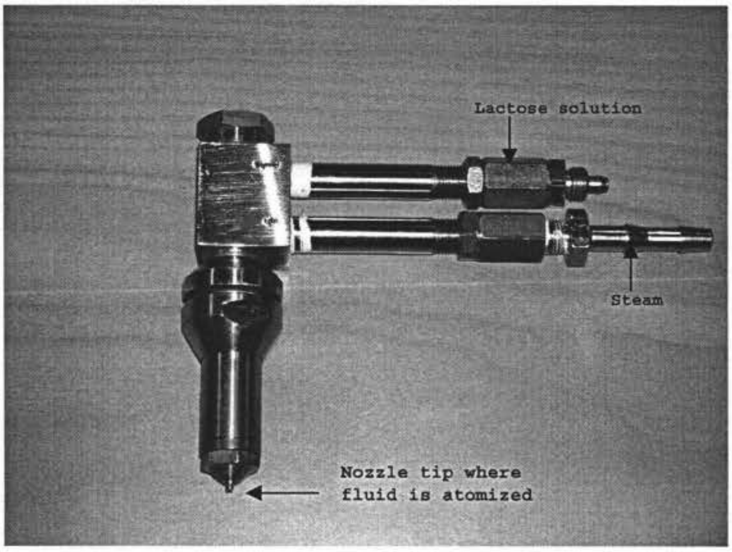


Figure 3-15: An external mix two fluid nozzle.

A peristaltic pump capable of producing a flow as low as 0.1 ml/min was used to feed the lactose solution. The set up of the nozzle was similar to that shown in Figure 3-17, except that due to its long neck, the nozzle tip was further inside the steel box.

Water trials were completed to determine the pump speeds required to produce the low flow rates in the range of 0.1ml/min to 5ml/min.

Lactose trials:

Trial 1: The first trial with this new set up was the repeat of the previous trial that produced 57% β-lactose.

Operating conditions: 135°C, flow rate ≅ 2.5ml/min and drum speed 8min 37 sec.

Results:

The lactose product from the roller drier was collected in two parts. Sample 1 consisted of the powder from the first revolution and Sample 2 was collected after the second revolution.

	2 Fluid Nozzle Trial 1
Sample 1	64% β-lactose
Sample 2	76.4% β-lactose

Table 3-14: Results for Trial 1(2 fluid nozzle).

Discussion:

The samples were collected in two parts to see the effect of nucleation by seeding. As the results in Table 3-14 show, Sample 1 had less β-lactose content than in Sample 2. This meant that after the first revolution the product left on the drum after the knife scraped it was nucleating the β-lactose in the solution. Thus nucleation by seeding seemed to have an affect on the final product.

It was also observed that there was a little amorphous lactose left on the drum after the first revolution. This was the amorphous lactose that had not crystallised.

Thus the result was not replicated by the new setup.

Trial 2: Repeat of Trial 1

Results:

A repeat of Trial 1 at drum temperature 135°C, flow rate ≅ 2 ml/min, drum speed 8 min 37 sec/ rev. The results were similar to Trial 1

	2 Fluid Nozzle Trial 2
Sample 1	69.3% β-lactose
Sample 2	83% β-lactose

Table 3-15: Results for Trial 2 (repeat of Trial 1).

Discussion:

The results show that the process was not repeatable. There were two possible reasons for the high β-lactose content. I) Though the solution was getting dried after the first revolution, the drum speed might be too high and the solution was not getting dried inside the superheated steam environment or II) flow rate might still be high and thus the drying rate was not fast enough. Another observation of interest was that the β-lactose content of Sample 1 in Trial 1 (64%) was slightly lower than Sample 1 in Trial 2 (69.3%), as was the β-lactose content of Sample 2 in Trial 1. This shows how prominent the nucleation factor was.

To get still higher drying rates either the operating temperature had to be increased or the flow rate decreased.

Trial 3: This was similar to Trial 1, but the effects of temperature and flow rate were studied by varying one parameter at a time.

(a) Higher temperature but same flow rate and drum speed- 145°C, 2 ml/min, 8min 37 sec/rev.

Results:

No separate samples were collected. The collective sample was collected after 10 minutes. The product had 81% β-lactose.

(b) Same temperature and drum speed but lower flow rate- 135°C, 1.5ml/min, 8min 37sec/rev.

Results:

The samples were again collected in two parts.

2 Fluid Nozzle Trial 3 (b)	
Sample 1	67.4% β-lactose
Sample 2	82% β-lactose

Table 3-16: Results for Trial 3 (b).

Discussion:

Both the results (Trial 3 a & b) show that the change in flow rate and temperature did not have any effect on the result. There was still a little bit of amorphous lactose left on the drum after the first revolution. The formation of amorphous lactose shows that the rate of drying is very fast, but the amorphous lactose was not getting crystallized in the steam environment. Maybe the drum speed had to be still slower, so as to provide more time for the amorphous lactose to crystallize in the superheated steam environment.

Trial 4: This trial was again similar to Trial 1, but the drum speed was slower. This would give the effect of drum speed on the β-lactose content. Only a combined sample was collected.

Temperature 135°C, flow rate 2ml/min, drum speed 20min/rev.

2 Fluid Nozzle Trial 4	
β-lactose content	79.3%

Table 3-17: Result for Trial 4.

Discussion:

Slowing the drum to 20min/rev also produced 79.3% β-lactose. The solution seemed to crystallize in the steam environment. Very little amorphous glass was left on the drum after the first revolution as compared to Trials 1- 3. The amorphous lactose on the drum meant that the solution was still not getting completely crystallized and importantly not getting crystallized in the superheated steam environment.

It was not clear how much time the solution had to spend in the superheated steam environment. So a comparison with the hot pot was done to check how much time the solution spent in the superheated steam in the hot pot.

Comparison with hot pot:

Hot pot:

Amount of solution injected in the hot pot = 10ml.

Concentration of solution = 120gm/100ml water.

Actual water in 10 ml solution = 4.45ml.

Average drying rate = 0.5ml/min (which meant that water from the solution was evaporated at the rate of 0.5ml/min).

So to evaporate 4.45ml water the time the solution spent in the hot pot was,

$4.45 / 0.5 = 8.9$ minutes $\cong 10$ minutes.

Roller drier:

If flow rate is $\cong$ 1.5 ml/min

Drum speed = 20min/rev (i.e. time spent by solution in super heated steam environment- one quarter revolution is 5 minutes)

Thus, in 5 minutes 7.5 ml solution will be sprayed on the drum. From the hot pot calculations, to dry 7.5 ml solution the speed of the drum should be 30min/rev and not 20min/rev.

This clearly showed that the drum speed had to be much lower in order for all the solution to crystallize completely.

Trial 5: This trial was divided into two parts. The effect of flow rate and drum speed was studied at the same temperature. Total sample was collected.

Part 1: Operating temperature 145°C, flow rate 2ml/min, drum speed 30min/rev.

Part 2: Operating temperature 145°C, flow rate 1ml/min, drum speed 20min/rev.

Results:

2 Fluid Nozzle Trial 5		
		Rates = flow rate / time in sup steam
Part 1	72.5% β-lactose	0.267 ml/min
Part 2	**59.3% β-lactose**	0.2 ml/min

Table 3-18: Results of Trial 5

There is a clear distinction between the two results. The crystals produced in Part 2 were thought to be mainly the 1:1 β/α mixed lactose crystal due to the low β-lactose content.

Discussion:

The results of Parts 1 and 2 clearly show that low β-lactose product was produced when the rate of the process follows the relation between the ratios of flow rate to time in superheated steam as deduced above. Part 1 clearly had more solution per minute spent in the superheated steam environment, and hence it produced more β-lactose.

It was also observed during both the trials that the solution dried completely in the superheated steam environment with virtually no amorphous lactose was left on the drum surface after the first revolution. Due to the very slow drum speed in Part 1, it was observed that the dried product was being re- wetted and that may have been instigating β-lactose nucleation at that temperature. This could be the reason for the higher β-lactose content (72.5%) in Part 1.

Problems with the set up

A number of trials conducted during Part 2, had to be stopped after just about 10 minutes as the nozzle was getting blocked. It was observed that below 2ml/min the nozzle blocked regularly. It was noted that the pipe supplying the lactose solution, the nozzle and sometimes even the fittings blocked regularly. Because of the nozzle design, it had to be fixed inside the steel box at superheated steam temperatures. The nozzle also had a long neck, which meant that the lactose solution was exposed to 145°C for a long time. This caused the lactose solution to boil and crystallize inside the nozzle.

Another reason for the blocking was that due to the very low flow rates (about 1 ml/min), the temperature of the lactose solution dropped along the feed pipe causing the solution to become supersaturated and crystallize inside the pipes or fittings. The solution was spraying seeds of β crystals onto the drum.

It was now clear that to produce lactose crystals having a β-lactose content less than 60%, flow rates less than 1.5 ml/min were required and drum speeds slower than 20min/min.

To avoid blocking of the nozzle a new two fluid nozzle with a suitable small design was procured. The pipes were also heated to around 90°C by heating coils and were insulated to avoid any heat loss and crystallization inside the pipe and fittings.

3.3.3.8 New flat spray two fluid nozzle

The new two fluid nozzle is shown in Figure 3-16. The steam and the solution join inside the fluid cap from opposite directions, and the steam atomizes the fluid through the orifice. It had a flat spray pattern and orifice diameter of this nozzle was 0.78mm.

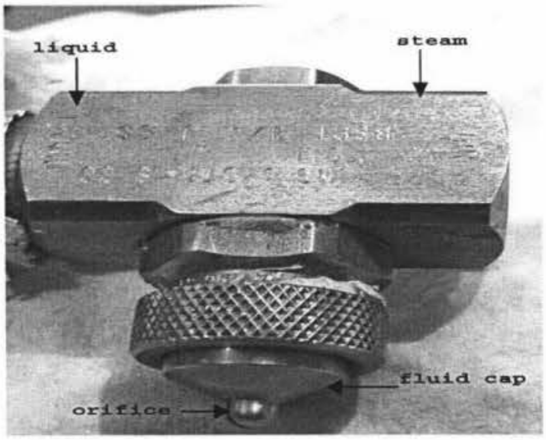


Figure 3-16: The new two fluid nozzle.

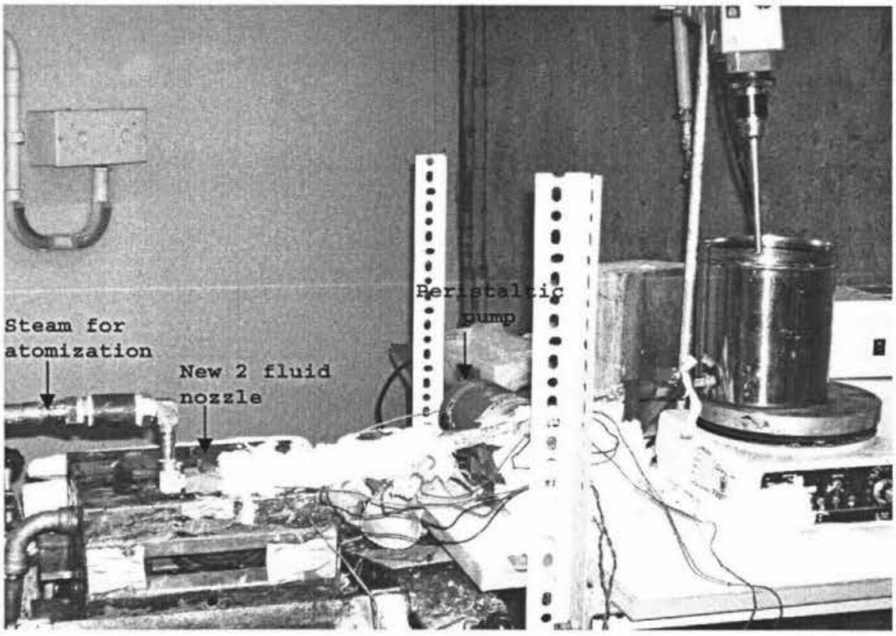


Figure 3-17: Set up of the new two fluid nozzle with peristaltic pump.

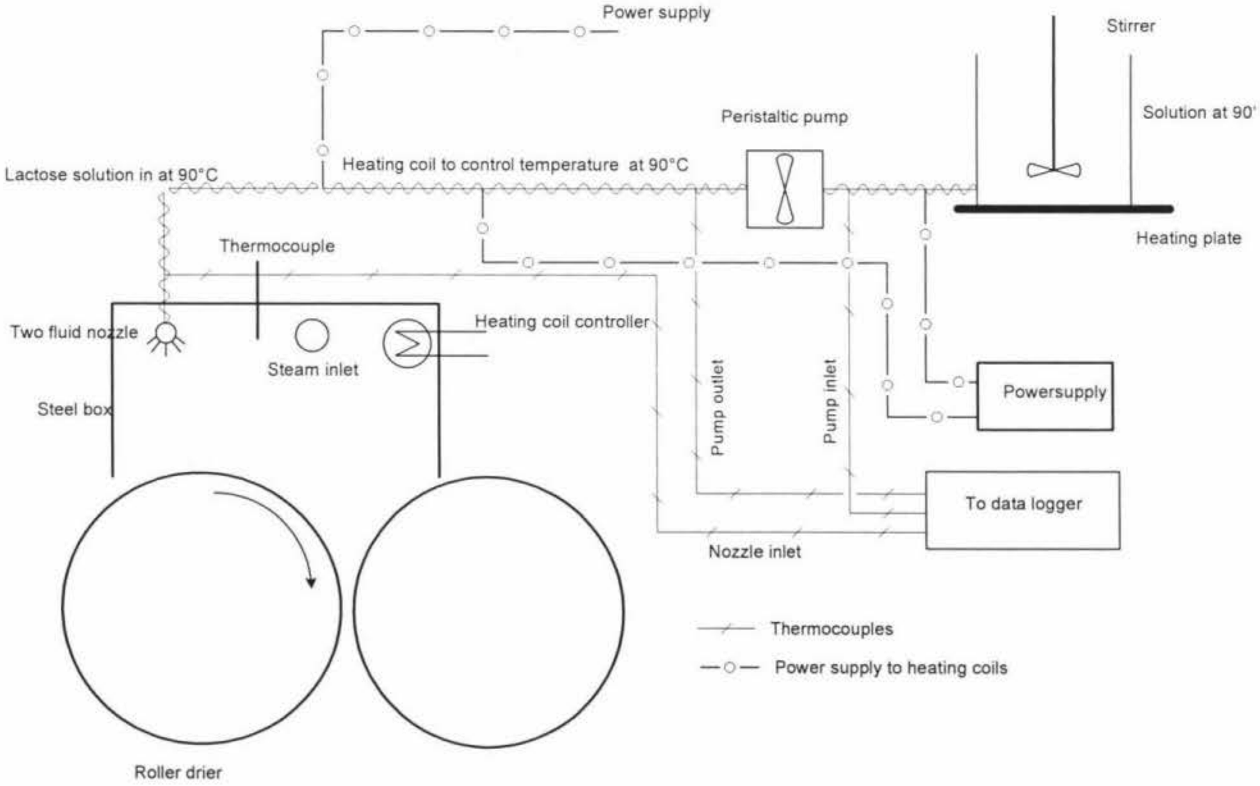


Figure 3-18: Schematic layout of the new two fluid nozzle set up.

The set up was as shown in Figure 3-17 and a schematic layout is shown in Figure 3-18. Lactose solution was made and maintained at about 90°C and pumped to the nozzle by a peristaltic pump. The pipes had heating coils around them and were insulated. The temperature was controlled and logged. With this set up the blocking problems were solved. The nozzle did not block and continuous runs were possible for about one and half hours. A continuous process was now in place, which meant that the first objective of the project was achieved, but the 1:1 β/α mixed lactose crystal still had to be produced in a continuous process.

Water trials were completed to determine the pump speeds required to produce the low flow rates in the range of 0.1ml/min to 5ml/min. Thermocouples were connected at the pump inlet, pump outlet and nozzle inlet and readings were logged every second.

Trial 6: Temperature 145°C, flow rate 0.5ml/min, drum speed 30min/rev, conc.- 120gm/100ml.

The sample was collected in two parts. Sample 1 was the sample after the first revolution and Sample 2 was the sample collected after the second revolution.

Results:

New two Fluid Nozzle Trial 6	
Sample 1	74.25% β-lactose
Sample 2	77.8% β-lactose

Table 3-19: Results for Trial 6.

The temperature profile was as under.

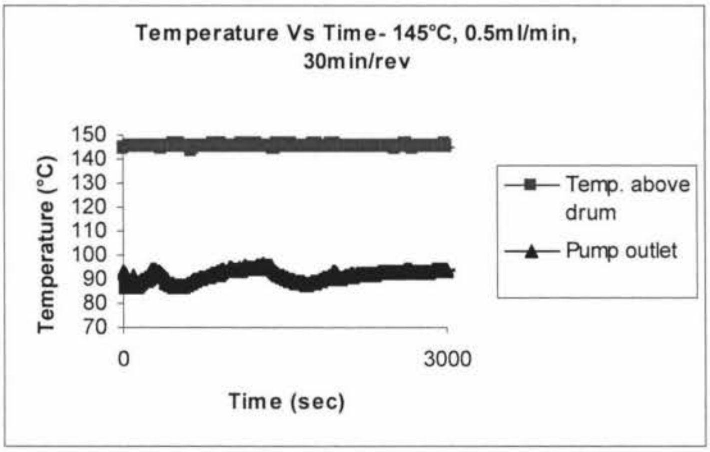


Figure 3-19: Temperature profile for Trial 6 (above drum and pump outlet).

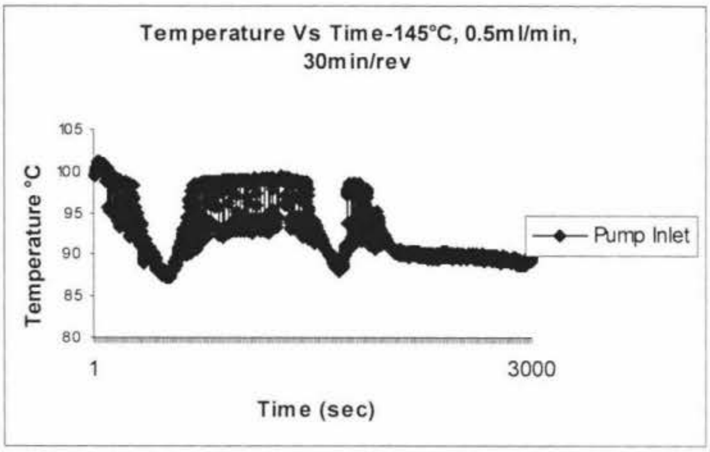


Figure 3-20: Temperature profile for Trial 6 (pump inlet).

Observations and Discussion:

As seen from Figure 3-19 the temperature of the superheated steam (above the drum) was stable, also the temperature at the pump outlet was within acceptable limits-(between 95°C to 85°C). This meant that the solution was getting sprayed at around 90°C. The upper limit of 95°C was set so that the solution does not boil and the lower limit was 85°C because the solubility limit of lactose at 85°C is about 125-130 gm/100ml. As seen from Figure 3-20, there were lot of fluctuations in temperature at the pump inlet. That was because the flow rate of the solution was so low that the heating coils around the pipes overheated the pipes in the process of controlling the temperature. But the average temperature was still within acceptable limits (95°C-85°C). Thus the high β-lactose content was not due to the pre-crystallisation of β-lactose in the pipes.

The solution was observed to crystallize inside the superheated steam environment. During the pervious trials: Trial 5 and the trial with the collection tray set up (section 3.3.3.6), it looked like the solution was getting converted into amorphous rubber phase and crystallizing. So it was assumed that to produce the 1:1 β/α mixed lactose crystal the solution should go through the amorphous phase first. During this present trial the amorphous phase was not observed. It seemed like the solution was crystallizing without going into the amorphous phase. Thus β-lactose might have nucleated out due to some unknown factor.

To find out whether the drum speed was a factor, Trial 6 was repeated but the drum was slowed to 36 min/rev.

Trial 7: Part 1- 145°C, flow rate 0.5ml/min and drum speed 36min/rev.

Part 2- Repeat of Part 1

Trial 7 was carried out at the slowest drum speed possible with the gear- box.

Results:

The samples for Part 1 were collected separately. Sample 1 was the product collected after first revolution and Sample 2 was the product collected after second revolution.

Part 1

	New 2 Fluid Nozzle Trial 7- Part 1
Sample 1	**59.4% β-lactose**
Sample 2	71.8% β-lactose

Table 3-20: Results of Trial 7 (Part 1)

Part 2

	New 2 Fluid Nozzle Trial 7- Part 2
Sample 1	78% β-lactose

Table 3-21: Result of repeat of Trial 7 (Part 2)

Discussion:

An immediate inference from the results of Trial 7- Part 1and 2 was that the process was not repeatable, and the problem with nucleation after the first revolution was prominent. Even though the solution dried in the superheated steam environment, high β-lactose content product was produced.

To get around the problem of nucleation, the knife was still more tightly held against the drum so that it would scrape off almost the entire product from the drum surface. It was also thought that the slow drum speed might be rewetting of the solution causing β-lactose to nucleate out.

Trial 8:

To avoid re-wetting of the solution, the collection tray used earlier was used. Only one tray of the set was used. The speed of the drum was 25min/rev, which was slower than that in Trial 7. The idea behind the half tray was that, it could catch the excess solution that would have fallen on the amorphous lactose formed, thus avoiding rewetting.

Trials were carried out at three temperatures. Table 3-22 shows the results of the samples after first revolution.

Operating conditions: Temperatures 125°C, 135°C, 145°C, flow rate 0.5ml/min and drum speed 25 min/rev.

Results:

New 2 Fluid Nozzle Trial 8- 0.5ml/min & 25min/rev.				
Temperature (°C)	β-Lactose % (Sample 1)	Temperature at Pump inlet °C	Temperature at Pump outlet °C	Temperature at Nozzle inlet °C
125°C	84.9%	98.9°-90.9°C	82°-96.2°C	88.5°-94.5°C
135°C	82.5%	99.4°-89.3°C	87.9°-97.3°C	93.2°-95.5°C
145°C	76.7%	99.6°-92.2°C	88.3-96.6°C	93.7°-96.4°C

Table 3-22: Results of samples after first revolution for Trial 8.

Observations and Discussion:

Similar observations were made during all the 3 trials. Though all the solution dried in the super heated steam environment, only the very first part of the solution formed thick amorphous rubber and then crystallized. The rest of the solution looked like it directly nucleated on the drum surface. This was consistently observed during all the previous trials as well. Thus amorphous lactose was not being formed consistently inside the superheated steam environment, which could explain the high β-lactose contents.

Inference

For an ideal process the speed of the drum should be optimized. Too fast a speed does not give enough time for the amorphous lactose to crystallize, and speeds that are too slow cause rewetting of the amorphous lactose by fresh spray after the amorphous lactose was formed. Also, ideally, the entire product should be scraped off the drum so that there are no seeds for nucleation. It was also observed that sometimes the solution directly nucleated on the drum surface, instead of going to the amorphous liquid phase. This produces product with high β-lactose content.

From all the above trials (Trials 1-8) it can be summarised that the process under these operating conditions and the present set up is not consistent. The operating temperatures were high enough to cause rapid evaporation and convert the lactose solution into amorphous lactose, but this amorphous lactose was getting re-wetted.

It was observed that whenever crystals were formed from the amorphous phase, the product had less than 60% β-lactose content. Thus the chances of forming the 1:1 β/α mixed lactose crystal increased if the solution boiled on the drum surface then went to the amorphous form and then quickly crystallized in the superheated steam. This was the hypothesis made at the beginning of the research and the results and observations support this.

It was now important to establish the hypothesis that crystallization of amorphous lactose inside the superheated steam environment did in fact produce the 1:1 β/α mixed lactose crystal. So a completely new approach was tried where amorphous lactose powder produced by spray drying would be the starting material, instead of a lactose solution.

3.3.4 Conditioning of amorphous lactose

Spray dried amorphous lactose powder was prepared using the conditions given by (Brooks, 2000). The operating conditions of the laboratory GEA Nero A/S spray drier were- feed temperature 80°C, air inlet temperature 200°C, outlet air temperature 96°C. The concentration of the solution was 30gm lactose/100ml water. The amorphous powder was stored at 4°C to avoid crystallization.

Procedure:

The roller drier was heated to the required temperature and a superheated steam environment created inside the steel box. The temperature of the superheated steam environment was kept the same as the temperature of the drum surface. After the system was stabilised, steam was stopped and 5-6 gm of amorphous powder was quickly put on the stationary drum by lifting the steel box. The steel box was then quickly put back and steam introduced into the box. The amorphous powder was kept in the superheated steam environment for 5 minutes, enough time for it to crystallise.

This approach was confirmed when the journal paper by (Lerk *et al.*, 1984(b)) was found during the late stages of the project. The difference between the two approaches was that (Lerk *et al.*, 1984(b)) re-crystallized the spray dried amorphous lactose powder by heating it to 180°C and then cooling it down to the room temperature, and in the present work amorphous lactose was re-crystallized in a superheated steam environment at temperatures lower than 180°C.

Trials were done at temperatures 125°C, 135°C and 145°C.

Results:

The amorphous powder and the conditioned samples were analysed in duplicates by polarimeter.

Conditioning of amorphous lactose powder

	β-lactose content (%)	
	1	2
Amorphous powder	58.9%	59%
125°C	57.8%	57.5%
135°C	57.7%	57.7%
145°C	58.1%	58%

Table 3-23: Polarimeter results for conditioned amorphous lactose at different temperatures.

The temperature profiles of the runs are given below in Figure 3-21 to 3-23.

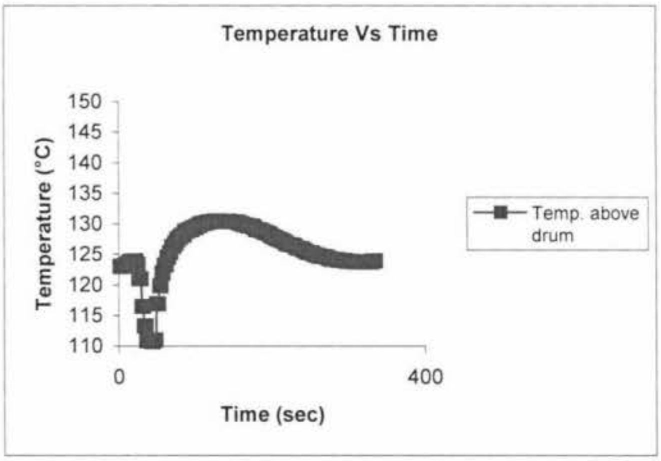


Figure 3-21: Temperature profile for amorphous lactose conditioned at 125°C.

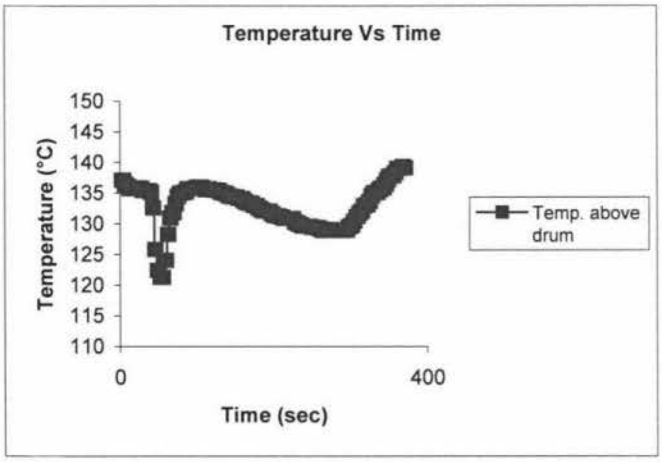


Figure 3-22: Temperature profile for amorphous lactose conditioned at 135°C.

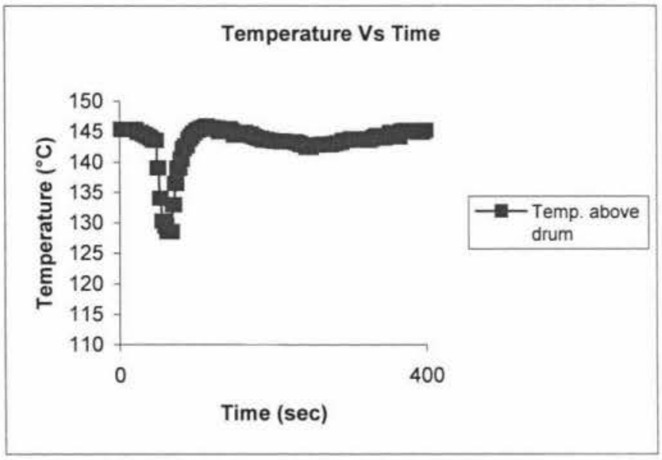


Figure 3-23: Temperature profile for amorphous lactose conditioned at 145°C.

The sudden drop in the temperature was when the steam was stopped so as to put the amorphous lactose on the stationary drum. The time spent between putting the amorphous lactose on the drum and starting the steam again was about 15 sec. The temperature suddenly increases as soon as the steam was introduced.

Observations and Discussion:

As soon as the amorphous powder was put on the drum it absorbed moisture from the surrounding hot air and became sticky. As soon as the steel box was put back and steam was introduced, the amorphous powder started melting and crystallizing. Because the temperature of the superheated steam during all the runs was higher than the glass transition temperature (T_g) of amorphous lactose (≅104°C), the amorphous lactose started to flow and then crystallize.

The β/α ratio in spray dried lactose depends linearly on the outlet temperature of the drier (Buma, 1970). According to the Figure 3-24 (Roetman & Buma, 1974) below, the β/α equilibrium ratio at 96°C (the outlet temperature of the spray drier) is about 1.37. So theoretically the β-lactose content in the amorphous lactose should be 57.8%. The polarimeter readings in Table 3-23 for the amorphous lactose agree with this.

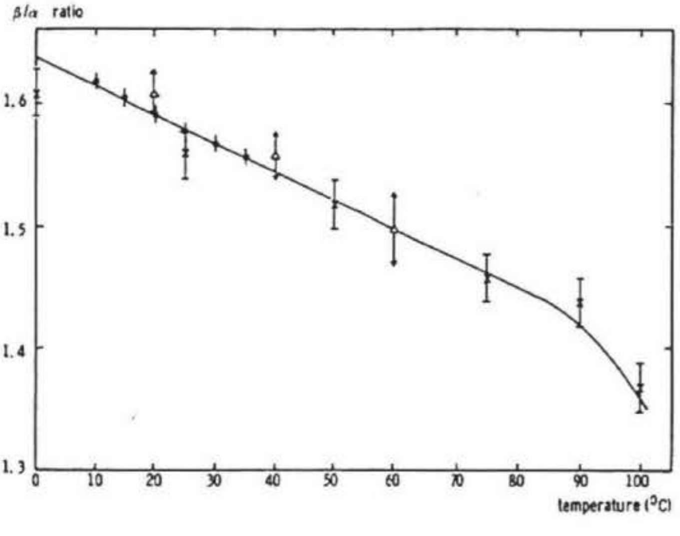


Figure 3-24: Relation between β/α ratio and Temperature (Roetman & Buma, 1974).

From the remaining results of Table 3-23 (125°C-145°C), it can be seen that in the superheated steam environment the amorphous lactose crystallized into a product having anomeric ratio similar to that of the amorphous form. These results were very close to the results of the trials: Nozzle TPU650017 with tray set up (57.4%), Trial 5 Part 2 (59.3%) and Trial 7 Part 1, Sample 1 (59.4%) that were thought to have produced the 1:1 β/α mixed lactose crystal.

Polarimeter results in Table 3-23 show that the β/α ratios of the conditioned amorphous lactose are close to the equilibrium 1:1 ratio. (Lerk *et al.*, 1984(b)) had also produced products having β/α ratio of about 1:1 by heating amorphous lactose at different temperatures and had produced the 1:1 β/α mixed lactose crystal at 200°C.

X-ray diffraction was performed on the conditioned amorphous lactose samples to confirm whether the crystals produced were in fact the 1:1 β/α mixed lactose crystal, or a mixture of the 1:1 β/α mixed lactose crystal and β-lactose crystals.

3.3.4.1 Analysis of the X-ray diffraction patterns for conditioned amorphous lactose

Every crystal has a unique structure and a typical diffraction pattern is produced when X-rays pass through it.

X-ray diffraction was done on a Rigaku MicroMax007 X-ray generator, Rigaku RAxisIV++ image-plate detector, and the data was examined using the Crystal Clear software. Samples of pure β and α-lactose were considered as the control samples. The intensities of the peaks produced by diffractions from the conditioned amorphous lactose samples were matched against the intensities produced by pure β and pure α-lactose monohydrate samples to find out whether the product was the 1:1 β/α mixed lactose crystal or a mixture of crystals.

The diffraction patterns for 1:1 β/α mixed lactose crystal are given in Appendix A. Figure I (a) shows the intensity of the first major peak (19.72) and Figure I (b) shows the intensity of the second major peak (9.75) for the 1:1 β/α mixed lactose crystal.

Figure (II) shows the typical X-ray diffraction pattern developed by β-lactose crystals. The first two peaks generated with intensities 10.95 and 8.49 are the prominent peaks that distinguish the β-lactose crystal. It can be clearly seen that in Figure (II) the two peaks (19.72) and (9.75) are absent. The peak 10.95 is very weak and may not appear sometimes. So the prominent peak for β-lactose is 8.49. The pattern is very clear and spotty. This means that the product is very crystalline.

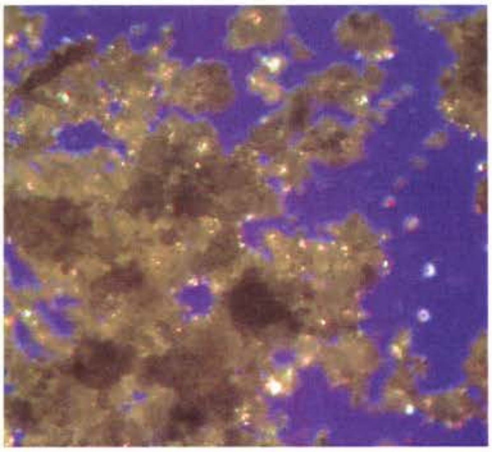
Figure (III) shows the typical X-ray diffraction pattern developed by α-lactose monohydrate crystals. The first two peaks with intensities 7.57 and 7.11 are the prominent peaks that distinguish the α-lactose crystal. Out of the two peaks 7.11 is very prominent so if this peak is present, then it can be said that the product contains some α-lactose crystals. Similar to Figure (II) this pattern is also very clear and spotty.

The "Reference Card" in Appendix A, shows the intensities 19.9 and 9.81 characterising the 1:1 β/α mixed lactose crystal, peak 8.4 characterising the pure β-lactose crystal and peaks 7.41 and 7.016 characterising the pure α-lactose monohydrate crystal as measured on a Philips PW1729 X-ray diffractometer in Landcare Research soil science laboratory (Paterson & O'Donnell, 1997). The "Reference Card" was developed during the previous studies carried out by (Paterson & O'Donnell, 1997) on the development of the 1:1 β/α mixed lactose crystal.

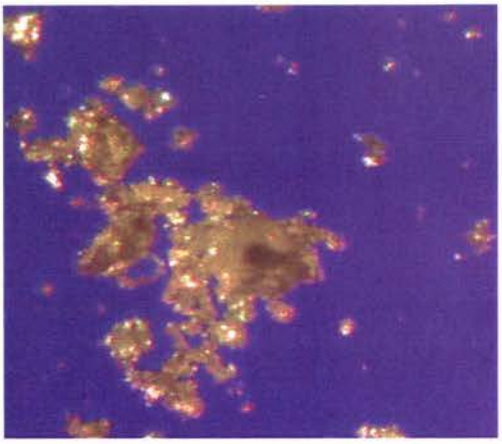
Figure A-1 in Appendix A shows the X-ray diffraction pattern for amorphous lactose conditioned at 125°C. There are two peaks with intensities 19.72 and 9.75 with no other peaks in between. These two peaks are the prominent peaks that characterise the 1:1 β/α mixed lactose crystal. There is also another peak (8.49) prominent for β-lactose crystals immediately after these two peaks. Thus this product is a mixture of the 1:1 β/α mixed lactose crystal and β-lactose crystal. There are no peaks seen that correspond to α-lactose (i.e. 7.57 or 7.11), thus it can be said that there are no α-lactose crystals present in this product. The pattern is also not very clear; this means that the product was not highly crystalline and contains some amorphous phase embedded in it. Pictures taken under the polarised microscope (Picture 3-1) confirms this.

Figure A-2 in Appendix A shows the X-ray diffraction pattern for amorphous lactose conditioned at 135°C. Similar to Figure A-1, this pattern also has the two peaks (19.72, 9.75) that characterise the 1:1 β/α mixed lactose crystal and also the peak (8.49) for β-lactose. The product was not highly crystalline when seen under polarised light (Picture 3-2) and has some amorphous phase in it.

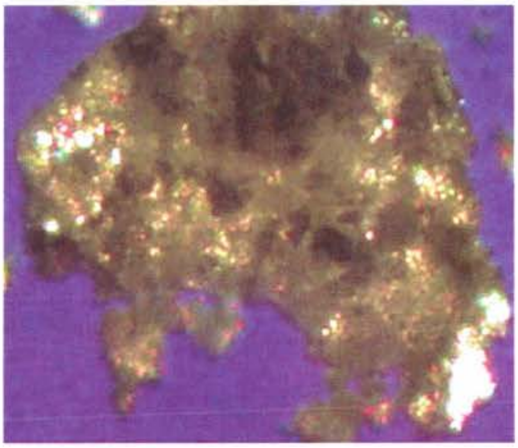
Amorphous lactose conditioned at 145°C had the same type of X-ray diffraction pattern (Figure A-3, Appendix A) as that produced at 125°C and 135°C. Picture 3-3 shows the crystals under polarised microscope. The product looked crystalline with some amorphous coating on the surface of the crystals.



Picture 3-1: Polarised microscope (125°C) (100x).



Picture 3-2: Polarised microscope (135°C) (100x).



Picture 3-3: Polarised microscope (145°C) (100x).

The results of X-ray diffraction for conditioned amorphous lactose are summarised below in Table 3-24.

Results of X-ray diffraction for conditioned amorphous lactose	
Temperature	Product
125°C	1:1 β/α mixed lactose crystal + β lactose
135°C	1:1 β/α mixed lactose crystal + β lactose
145°C	1:1 β/α mixed lactose crystal + β lactose

Table 3-24: Results of X-ray diffraction for conditioned amorphous lactose at different temperatures.

The results clearly show that the products were a mixture of the 1:1 β/α mixed lactose crystals and β- lactose crystals. It can be said that the crystals produced in trials: Nozzle TPU650017 with tray set up, Trial 5 Part 2 and Trial 7 Part 1, Sample 1 which had similar β-lactose contents were also mixtures of the 1:1 β/α mixed lactose crystals and β- lactose crystals.

This shows that the 1:1 β/α mixed lactose crystal is formed when amorphous lactose crystallizes in a superheated steam environment, verifying the hypothesis.

3.3.5 Formation and crystallization of amorphous lactose on the roller drier

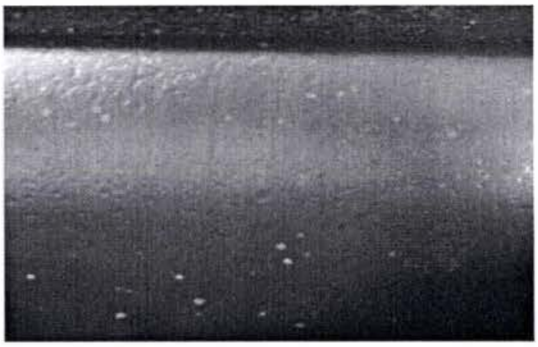
Rapid drying of lactose solution in the presence of air produces amorphous lactose. The drying rate achieved so far in the previous trials was high enough and amorphous was being formed. To produce the 1:1 β/α mixed lactose crystal, this amorphous lactose must nucleate and crystallise inside the superheated steam environment. In all the previous trials it was observed that the drum temperature was high enough to form amorphous lactose, but it was noted that the crystallization of the amorphous lactose inside the superheated steam environment was not consistent.

So it was decided to spray the solution on the drum outside the superheated steam environment, and then introduce the amorphous lactose formed into the superheated steam environment.

3.3.5.1 Hand held spray

A simple hand held spray bottle was filled with lactose solution at 90°C and 54.5-wt % concentration. Solution was sprayed on to the stationary drum at 145°C and kept in air for 2 seconds and 10 seconds. Then the drum was rotated so the solution/amorphous lactose was taken into the superheated steam environment. It remained in the superheated steam environment for 8 minutes. As seen from Pictures 3-4 and 3-5, the drying was not consistent. There was a lot of amorphous lactose left on the drum that had not crystallized at all. The spray was creating very small droplets, which dried so fast that they had insufficient water left in them for nucleation to occur. Thus the amorphous lactose was too thick for the molecules to move past each other to enable crystallization.

This might explain why the drying was inconsistent during most of the previous trials using the spray nozzles.

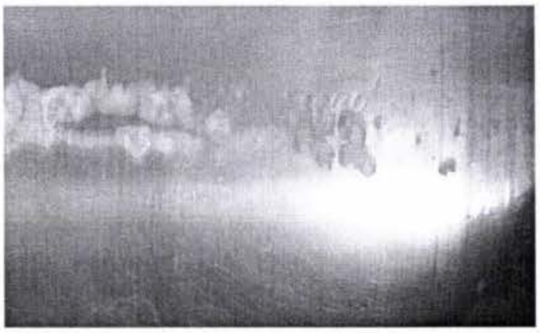


Picture 3-4: Hand spray-2 sec in air, 8 min in in superheated steam.

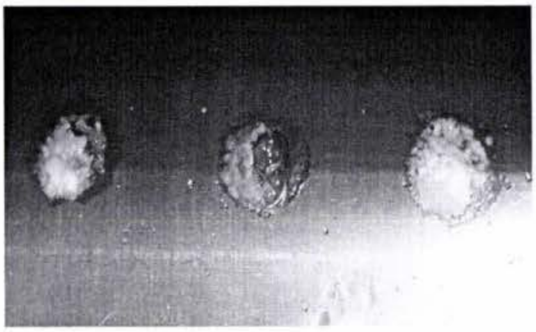
Picture 3-5: Hand spray- 10 sec in air, 8 min super heated steam.

3.3.5.2 Syringe injection

Lactose solution at 90°C was injected from a syringe with the drum temperature of 145°C, and 54.5-wt % lactose solution concentration. In the first trial the solution was injected in a line and in the second trial, three drops of the solution were injected and kept in air for 2 sec and 10 sec and then left in the superheated steam for 10 minutes. It was found that the drops crystallized more uniformly, than when the solution was injected in a line (Picture 3-6 & 3-7).

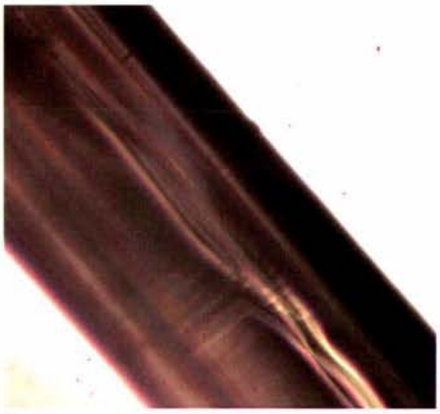


Picture 3-6: Syringe- 10 sec in air, 10 min in superheated steam



Picture 3-7: Syringe- 10 sec in air, 10 min in superheated steam

Injecting the solution one drop at a time was thought to be feasible at that time as it was also easier than spreading the solution in a line. Trials were done to determine how long the solution should remain in air before it started crystallizing. The solution started to crystallize in air after about 30 seconds. Thus it was decided to keep the solution in air for 20 seconds or less. By doing this, the solution got converted into amorphous lactose with medium thickness, which was then introduced into the superheated steam environment. It still had enough moisture content (m_c) to become rubbery and then start nucleating inside the superheated steam environment. To confirm that this solution was in an amorphous state, it was collected and quickly viewed under a polarised microscope (Picture 3-8). As soon as the solution was removed from the drum surface it converted into a brittle glass structure. The dark portion of the picture confirms the amorphous structure. Now that it was shown that drying the solution in air for a short time produced amorphous lactose, it was important to know how much time it should spend in the superheated steam environment to completely crystallize.



Picture 3-8: Solution in air for 10 sec as seen under polarised microscope (100x).

Trials to determine the time needed for the drop to crystallize in superheated steam environment

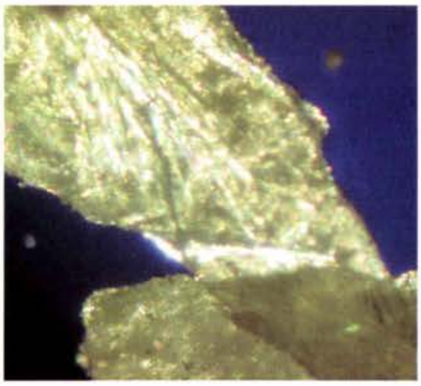
About 0.2 ml of lactose solution at 90°C and at 54.5-wt % concentration (120gm/100ml water) was injected as a single drop on the drum and kept in air and in the superheated steam for the following periods:

I) 135°C, 10 sec in air and 15 min in superheated steam.

II) 135°C, 10 sec in air and 10 min in superheated steam.

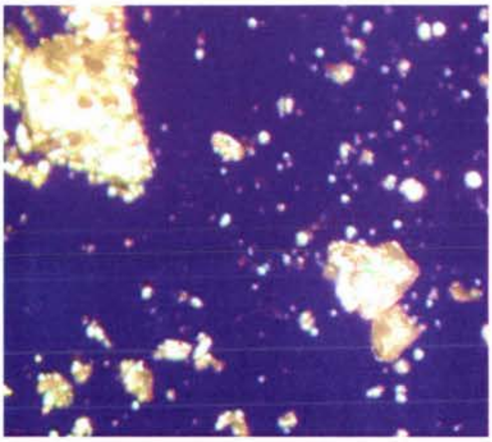
III) 145°C, 5 sec in air and 15 min in superheated steam.

The crystals produced were highly crystalline as seen form Pictures 3-9 to 3-11. There also might be a temperature factor involved. But importantly, it was shown that highly crystalline product was produced even though the solution spent only a few seconds in air.



Picture 3-9: 135°C, 10 sec in air, 15 min in Sup. Steam (100x)

Picture 3-10: 135°C, 10 sec in air, 10 min in Sup. Steam (100x)



Picture 3-11: 145°C, 5 sec in air, 15 min in sup steam (100x)

3.3.5.2.1 Trials with syringe

An ideal run would be to inject a drop (about 0.2ml) onto the stationary drum and keep it in the air environment for a very short time and then introduce it into the superheated steam environment. After 10 or 15 minutes in the superheated steam, the drum was rotated and the product scraped off.

For the purpose of developing a continuous process and to study the effect of the time spent in air, the solution was kept in air for longer times of 20 sec and 10 sec.

Trial 9

135°C, 20 sec in air, 15 min in superheated steam and conc.-120gm/100 ml

Result:

Figure A-4 in Appendix A shows that there are two distinct peaks (19.72, 9.75), representing the 1:1 β/α mixed lactose crystal and a broken peak (8.49) representing β-lactose. The broken peak meant that the β- lactose was less than all the earlier trials. Because only 1 drop was injected at a time, there was not enough product collected to do polarimeter analysis and thus the β/α ratio could not be determined. But it was clear that there was a definite change in the β- lactose content.

Trial 10

135°C, 10 sec in air, 15 min in superheated steam and conc. - 120gm/100ml

Result:

Figure A-5 in Appendix A shows that the broken peak (8.49) is still lighter than in Figure A-4. This meant than the crystal had still less β- lactose and more of the 1:1 β/α mixed lactose crystal.

The crystal observed under the polarised microscope (Picture 3-9 above) clearly showed the high crystalline nature of the crystals. These crystals looked more crystalline than the crystals produce by conditioning the spray dried amorphous lactose.

Trial 11

145°C, 20 sec in air, 15 min in superheated steam and conc.- 120gm/100 ml

Result:

Figure A-6 in Appendix A shows that the peak representing β- lactose (8.49) is very dark, and the two peaks representing the 1:1 β/α mixed lactose crystal (19.72, 9.75) can still be seen. Thus this crystal was made up of the 1:1 β/α mixed lactose crystal and more β- lactose than Trials 9 and 10.

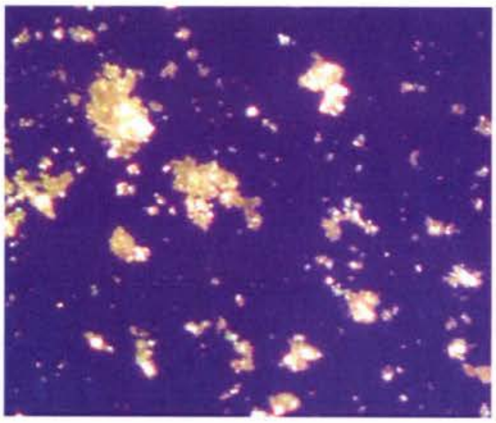
Trial 12

145°C, 10 sec in air, 15 min in superheated steam and conc.-120gm/100ml

Result:

Figure A-7 in Appendix A shows the two peaks (19.72, 9.75) representing the 1:1 β/α mixed lactose crystal, but a peak (8.49) representing β- lactose has almost disappeared except for a very faint grey dot. Thus it can be said that these crystals produced consisted entirely of the 1:1 β/α mixed lactose crystal.

This trial successfully produced the 1:1 β/α mixed lactose crystal, but the β/α ratio could not be found as there was not enough product collected to do the polarimeter analysis.



Picture 3-12: 145°C, 10sec in air, 15 min in superheated steam (100x).

Picture 3-12 taken under polarised microscope shows that the product produced was highly crystalline.

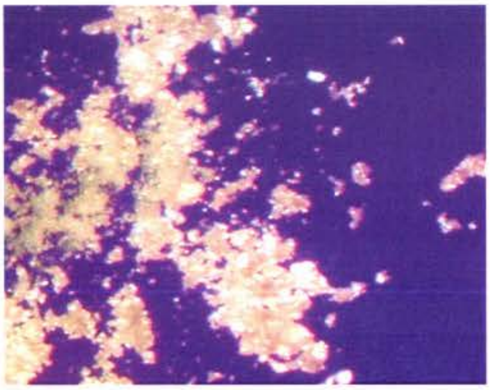
It was clearly shown that the β- lactose crystal content decreased as the time spent in air decreased, finally producing the 1:1 β/α mixed lactose crystal in Trial 12. It was then thought to check the outcome if the solution did not spend any time in air, that is, if it was directly injected into the superheated steam environment, as done in the hot pot trials.

Trial 13

Solution was injected directly on the drum inside the superheated steam environment. 0.2 ml lactose solution with 54.5-wt % conc. (120gm/100 ml) was injected on the drum at 145°C and kept in superheated steam environment for 15 minutes.

Result:

Figure A-8 in Appendix A shows the peak 8.49. This confirmed the presence of β-lactose along with the 1:1 β/α mixed lactose crystal. The dark colour of the peak shows that the amount of β- lactose in the crystal was high. Picture 3-13 under polarised light confirms that the crystals produced were highly crystalline. The high crystallinity was expected as the solution crystallised in a superheated steam environment.



Picture 3-13: Solution injected in superheated steam environment (100x).

Summary of Trials 9-13

Summary of the results of X-ray diffraction of Trials 9-13.

Drum Temperature (°C)	Time in air (sec)	Trial	Result
135°C	20 sec	Trial 9	1:1 β/α mixed lactose crystal + β-lactose
135°C	10 sec	Trial 10	1:1 β/α mixed lactose crystal + less β-lactose
145°C	20sec	Trial 11	1:1 β/α mixed lactose crystal + more β-lactose
145°C	**10sec**	**Trial 12**	**1:1 β/α mixed lactose crystal**
145°C	-	Trial 13	1:1 β/α mixed lactose crystal + more β-lactose

Table 3-25: Summary of the results of X-ray diffraction of Trials 9-13.

Inference

The results of X-ray diffraction of the Trials 9-13 (Table 3-25 above) show that there is a definite relationship between the temperature and the time the solution spends in air on the β- lactose content of the product. The β-lactose content reduced when the solution spent less time in air. At the higher temperature (145°C) and 10 seconds in air, the 1:1 β/α mixed lactose crystal was produced. The crystals produced also had high crystallinity. To confirm the importance of the time in air, the solution was directly injected in the superheated steam (Trial 13). The crystals produced were a mixture of the 1:1 β/α mixed lactose crystal and β-lactose crystal. This was not as expected because during all the previous studies done using the hot pot, the 1:1 β/α mixed lactose crystal was produced when the solution was directly injected into a superheated environment.

Thus it seems that in this process, the solution has to have specific low moisture content (m_c) (unknown at the moment) before it goes into the superheated steam environment.

Observations

When the solution was injected on the drum it started boiling rapidly. During the time the solution was in air, it became medium thick, but it was still boiling. There was no nucleation observed when the solution was in air. After the solution went inside the superheated steam environment, the bubbles subsided and the solution became amorphous rubber. The slow boiling solution then started nucleating after about 35-40 seconds (primary nucleation). The small bubbles that were still seen in the solution acted as seeds and rapid crystallization was observed. Thus all the crystals were formed inside the superheated steam environment in about 2 minutes. During the remaining time (about 13 minutes) most of the remaining moisture was removed increasing the crystallinity.

The temperature of the surrounding air at the place on the drum where the solution was injected was between 75°C-82°C. The high temperature of the air was due to the radiation heat from the drum and the steam.

This was a batch process and produced very small quantity of crystals. To develop a continuous process the drum had to be continuously moving. On the basis of these results a continuous trial was planned.

3.3.5.3 Continuous process using the syringe

To develop a continuous process on the lines of Trial 12, the drum had to be rotating at 15 min/rev. The solution had to be in air for 10 seconds or less. For that to be possible the solution had to be injected very close to the edge of the steel box. Because the drum was moving very slowly, the shortest time the whole drop (drop spreads out when it falls on the drum surface) could remain in air before going into the superheated steam environment was 15-17 sec. It also meant that the solution was in superheated steam environment for about 3-4 minutes. From the above trials it was seen that the crystals were formed in less than 2 minutes, so this time (3-4 min) was sufficient for the crystals to be formed in the superheated steam environment.

Trial 14: Continuous run on the lines of Trial 12

145°C, 15-17 sec in air, drum speed- 15 min/rev and conc.- 120gm/100ml.

Because it was a continuous process, about 10 gm product was collected, which was enough to do a polarimeter analysis and an X-ray diffraction.

Results:

Figure A-9 in Appendix A shows three peaks- one dark peak (8.49) characterising β-lactose and two faint peaks (19.7, 9.75) characterising the 1:1 β/α mixed lactose crystal. This clearly showed that the crystal produced was made up of a majority of the β-lactose crystal and less of the 1:1 β/α mixed lactose crystal.

The X-ray diffraction pattern looks clear and spotty, which meant that the crystals were highly crystalline.

Polarimeter results show that the crystals had 71.6% β-lactose content.

Trial 14: Continuous trial using the syringe	
Polarimeter	71.6% β-lactose
X-ray diffraction	1:1 β/α mixed lactose crystal + β-lactose

Table 3-26: Results of Trial 14.

The polarimeter and X-ray diffraction results both agree with each other in regards to the high β-lactose content.

Observations and Discussion

The solution was still boiling vigorously as it went into the superheated steam. In the superheated steam environment it started crystallizing after about 30 seconds. The possible explanations for high β-lactose content were-

I) The solution did not look as thick as it was during Trial 12. Thus the moisture content (m_c) of the solution might not be as low at it was during Trial 12.

II) Another possible explanation for high β-lactose content was that the temperature at the point where the solution was injected (close to edge of the box) was 123-125°C and the temperature at the edge of the box was 128°C-130°C, may have affected the result as the temperature in Trial 12 was 85-90°C (below 93.5°C, above which β-lactose starts to crystallize).

Thus it was similar to Trial 13 where the solution was directly injected in superheated steam environment (which also had high β-lactose) except that in this case there was less steam around.

It was decided to reduce the surrounding air temperature over the drum where the solution was injected.

Trial 15

To reduce the surrounding air temperature, fresh air was blown from the side, so that the temperature was about 85°C instead of 125°C. This was close to the temperature at which the solution was injected in Trial 12.

Result:

Figure A-10 in Appendix A shows a peak at (8.49) characterising β-lactose along with the two faint peaks -19.72, 9.75. Thus these crystals were made up of the β-lactose crystal and small amount of the 1:1 β/α mixed lactose crystal.

Observations and Discussion

The solution was boiling as it entered the superheated steam environment. After it went into the superheated steam environment the boiling subsided and the solution became thick. After about 40-50 seconds nucleation started and crystallization occurred.

There was a temperature gradient at the edge of the box due to the cold air. The temperature where the solution was injected was 85-90°C. The temperature at the edge of the box was about 110°C, and further away from it was 135°C and then the point where the crystals were formed was 142-145°C.

So the speculation made above in Trial 14 (II) is probably incorrect. The solution also spent about the same time in air as Trial 12. These results all point to the moisture content (m_c) as being an important factor in producing the 1:1 β/α mixed lactose crystal.

Trial 16

Repeat of the Trial 12, to check whether the process is repeatable.

145°C, 10 sec in air, 15 min in superheated steam and conc.-120gm/100ml.

Result

Figure A-11 in Appendix A shows the two distinct peaks (19.72, 9.75), representing the 1:1 β/α mixed lactose crystal and a third peak (8.49) representing β- lactose. This was not expected, as the third peak should have disappeared. The crystals are crystalline in nature as shown by the spotty pattern. This result clearly shows that the process is not always reproducible and there are some unknown factors involved. The process is quite sensitive and some minor changes to the process were changing the composition of the crystal. Some extra trials with shorter times in air and also looking at the increased temperature were completed.

Trial 17

145°C, 5 sec in air, 15 min in superheated steam and conc.-120gm/100ml

The solution was kept in air for 5 seconds and then passed into superheated steam environment. This was done to check the effect of still shorter time in air on the β-lactose content.

Result:

Figure A-12 in Appendix A shows that the peak (8.49) is lighter than in Figure A-11, and the two peaks (19.72, 9.75) are slightly darker. This meant that β- lactose content had dropped down, but was not zero as hoped.

Observations & Discussion

It was hoped that the β- lactose crystal content (the peak 8.49) would disappear. The less time spent in air also had little effect on the β- lactose crystal content. The very first drop injected started crystallising after 1 min and 30sec in the superheated steam environment. All other drops started crystallising after just 38 seconds. This shows that the crystallisation inside the superheated steam environment was not uniform. The change in the time for crystallization is probably due to the different moisture contents. It was unclear whether this had any effect on the β- lactose contents and further studies have to be done to verify this.

Trial 18

155°C, 10 sec in air, 15 min in superheated steam environment and conc.-120gm/100ml.

The drop was kept in air for 10 seconds and then the drum was rotated till the drop was in the superheated steam. The effect of temperature was studied in this trial.

It was expected that because of the higher temperature, the rate of drying would be higher and the solution would get to the amorphous form even quicker and would be drier (less moisture content) when entering the superheated steam environment.

Results:

Figure A-13 in Appendix A shows that the third peak (8.49) still exists and so it can be said that the crystal is a mixture of β- lactose and the 1:1 β/α mixed lactose crystal. The crystal is highly crystalline as seen from the spotty and clear crystal pattern.

Observations and Discussion

There was excessive bubbling observed inside the superheated steam environment, and crystallization commenced after 30-35 sec in the superheated steam environment. Again polarimetric analysis was not possible because not enough product was made due to the drop injection method. Thus higher temperature did not have any effect on the formation of a pure 1:1 β/α mixed lactose crystal.

Inference

All the trials done up till now clearly show that the formation of the pure 1:1 β/α mixed lactose crystal (without any β- lactose) by this process definitely depends on some unknown factors in addition to temperature and formation of amorphous lactose.

These factors could be the moisture content (m_c), fluctuations in temperature, or even time taken by the solution to crystallize in the superheated steam environment. Further studies have to be done to confirm this.

The 1:1 β/α mixed lactose crystal was produced once in Trial 12 but was not repeatable. So it can be said that the process to produce the 1:1 β/α mixed lactose crystal is very sensitive due some unknown factors.

Polarimetric analysis was not possible for Trial 12 as not enough product was made. The actual β-lactose content in the 1:1 β/α mixed lactose crystal was not known and it would be useful information if this relation was known.

To determine this relation some 1:1 β/α mixed lactose crystal could be made in the hot pot and then X-ray diffractions and polarimetric analysis could be completed on those crystals.

This will also confirm the studies by (Lerk *et al.*, 1984 (a)), (Lerk *et al.*, 1984(b)), (Willart *et al.*, 2004) and (Paterson & O'Donnell, 1997) that the 1:1 β/α mixed lactose crystal typically contains about 51-52% β-lactose.

3.3.6 Hot Pot Trials

New heating tape was wound around the hot pot previously used and thermocouples were put on the base, side and the lid of the pot. Steam was introduced in the hot pot through the lid (Figure 3-25).

The temperature of the superheated steam was also logged. Trials were done at 125°C and 135°C. 10 ml of 54.5-wt % concentration lactose solution at 90°C was injected on the drum and kept in superheated steam for 16 minutes, enough time for the solution to completely crystallize.

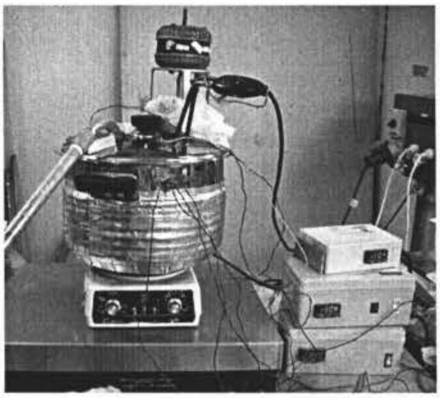


Figure 3-25: Hot pot trials for X-ray diffraction.

Results:

The results of the runs are given in the Table 3-27 below.

Hot Pot trial	
Temperature (°C)	β-lactose content (%)
125°C	50.2%
135°C	53.0%

Table 3-27: β- lactose contents of the samples from Hot pot for X-ray diffraction.

The two products produced by the trials were thought to contain only the 1:1 β/α mixed lactose crystal (without any β- lactose crystals) due to the 50%-53 % β- lactose content. X-ray diffractions were done to determine the actual composition of the crystals.

3.3.7 X-ray diffraction of lactose samples with different β-lactose contents

Six lactose samples all having different β-lactose contents were tested by X-ray diffraction for the type of crystal present in them.

β-lactose produced at Fonterra, Kapuni was acquired and analysed by polarimeter for its β- lactose content, which had 76.9% β-lactose content. The lactose samples analysed by X-ray diffraction are given below in Table 3-28.

β- lactose contents of samples analysed by X-ray diffraction

Sample	β- lactose content (%)
Hot pot sample at 125°C	50.2 %
Hot pot sample at 135°C	53.0 %
β- lactose form Kapuni	76.9 %
Nozzle TPU650017 with tray set up	57 %
Nozzle TPU650017 with needle valve	65.4 %
Trial 7, Part 1, Sample1	74.2 %

Table 3-28: β- lactose contents of samples analysed by X-ray diffraction.

Results and Discussion

Figures A-14 and A-15 in Appendix A show the X-ray diffraction patterns for the hot pot sample at 125°C and 135°C respectively. It was expected that these samples would produce an entirely pure 1:1 β/α mixed lactose crystal, but surprisingly the X-ray diffraction pattern shows a third peak (8.49) characterising the β-lactose crystal. Thus these products were made up of the 1:1 β/α mixed lactose crystal and β-lactose crystal. This result does not support any of the previous work done in which the product having 50-52 % β-lactose content was entirely made of the 1:1 β/α mixed lactose crystal.

Figure A-16 in Appendix A shows the X-ray diffraction pattern of the pure β-lactose obtained from Fonterra, Kapuni in which only one dark peak at 8.49 can be seen. Thus as expected this product consists entirely of β- lactose crystals.

Figure A-17 in Appendix A shows the X-ray diffraction of the product obtained by the Nozzle TPU650017 with tray set up. The pattern shows all the three peaks, which means that the product contained the 1:1 β/α mixed lactose crystal along with β- lactose crystal. This was expected due to the β- lactose content being higher than 52%.

Figure A-18 in Appendix A shows the X-ray diffraction pattern of the product obtained from the Nozzle TPU650017 with needle valve set up. A spotty peak at 8.49 can be clearly seen along with a weak peak at 7.57, which means that the product contained a lot of β-lactose crystals, and α-lactose crystals with no evidence of the 1:1 β/α mixed lactose crystal. This indicates that small amount of α-lactose must have crystallised in the lines due to the drop in temperature before it was sprayed onto the drum.

Figure A-19 in Appendix A shows the X-ray diffraction for Trial 7, Part 1, Sample1. A very dark peak at 8.49 shows the presence of majority of the β-lactose crystal and small amount of the 1:1 β/α mixed lactose crystal. This was expected due to 74.2 % β- lactose content.

Inference

The results show that a noticeable amount of the 1:1 β/α mixed lactose crystal was formed when the β-lactose content in the product was below about 60%. Because pure β-lactose from Fonterra, Kapuni and product of Trial 7, Part 1, Sample1 had similar β-lactose contents (76.9% and 74.2%), meant that the crystallization rates were similar and their X-ray diffraction patterns were also similar. But there is a very small quantity of the 1:1 β/α mixed lactose crystal in the product produced by Trial 7, Part 1, Sample1, and this could be due to the crystallization in the superheated steam environment.

3.4 *CHAPTER OVERVIEW*

The main objective of this work was to develop a continuous process to produce the 1:1 β/α mixed lactose crystal. Because there was no work done before on the development of a continuous process, the right conditions and the controlling variables were not known, and a lot of trials were completed looking at various conditions. From this, an understanding of the possible mechanism for the formation of the 1:1 β/α mixed lactose crystal was formulated.

From previous work it was understood that fast drying rates were required in order for the 1:1 β/α mixed lactose crystal to be formed. Using this understanding it was decided to create a superheated steam environment over a roller drier in an effort to create conditions on a continuous plant similar to those that were successful on the batch process.

Lactose solution was continuously sprayed on the roller drum using spray nozzle TP730023 at temperatures between 125°C to 155°C at flow rates between 110 ml/min to 40ml/min and drum speed 1min/revolution. This produced products having 80-85% β-lactose content. Thus it was clear that the flow rate had to be lower in order to get higher rates of evaporation. Spray nozzle TPU650017 with a needle valve produced flow rates as low as 26.66 ml/min. At the same temperatures, drum speeds and concentration, but at 26.66 ml/min flow rate, there was a trend of changing β-lactose contents, with the lowest being 65.4% β-lactose. This showed that still lower flow rates were needed in order to achieve higher rates of evaporation to produce products having β-lactose contents less than 60%. It was observed that amorphous lactose was being formed which was sometimes left on the drum surface even after the first revolution. This showed that the rate of evaporation was high enough to produce amorphous lactose but it was not getting enough time to crystallise in the superheated steam environment. Thus still lower flow rates and slower drum speeds were indicated. Lactose solution that was sprayed over a tray which was designed to allow only small amount of the solution to pass through produced a product with about 58% β-lactose. X-ray diffraction showed that the crystal was a mixture of 1:1 β/α mixed lactose crystal and β-lactose crystal. This confirmed that to produce the 1:1 β/α mixed lactose crystal very low flow rates in the range of 1.5ml to 3ml/min flow rate were required and drum speeds slower than 9 minutes/revolution.

To produce a continuous spray at flow rates about 2ml/min, two fluid nozzles were used. Repeat trials with this set up and similar conditions that produced 58% β-lactose content product failed to produce the same product. More trials were completed to understand the relation between the speed of the drum, concentration of the solution and flow rate. It was observed that at very slow drum speeds, above 30min/rev, the crystallised product was re-wetted by new solution getting sprayed on the drum surface. Samples collected after the first revolution showed different β-lactose content than the samples collected after second revolution confirming the effect of nucleation due to the seeds left over on the drum surface after the first revolution. Trial 7, Sample 1 produced 59% β-lactose which was a mixture of 1:1 β/α mixed lactose crystal and β-lactose crystal. The results were not repeatable. It was observed that the 1:1 β/α mixed lactose crystal was formed when the lactose solution formed a rubbery amorphous solution which quickly crystallized in the superheated steam environment.

At this stage the mechanism proposed was that, 1:1 β/α mixed lactose crystal is formed when amorphous lactose solution is quickly crystallised in a superheated steam environment. X-ray diffraction of the products from the Hot Pot trials clearly showed that a noticeable amount of the 1:1 β/α mixed lactose crystal was formed in products having β-lactose contents less than 60%. These products were a mixture of the 1:1 β/α mixed lactose crystal and β-lactose.

Spray dried amorphous lactose was then crystallised over the roller drier inside the superheated steam environment at temperatures 125°C, 135°C and 155°C. Spray dried amorphous lactose had about 58% β-lactose content while the crystallised amorphous lactose had 57-58% β-lactose content. This showed that amorphous lactose crystallised into a product having anomeric ratio similar to the amorphous form. This meant that the rate of crystallisation was faster than the rate of mutarotaion and thus did not allow the molecules to mutarotate or re-orient themselves into a different form other than that existed in the amorphous lactose. The X-ray diffraction pattern on the product showed that the conditioned products were a mix of the 1:1 β/α mixed lactose crystal and β-lactose crystal and not pure1:1 β/α mixed lactose crystal. This confirmed the hypothesis that rapid crystallisation of amorphous lactose in the superheated steam environment produced the 1:1 β/α mixed lactose crystal.

To produce the amorphous state on the roller drier from the solution, it was decided to inject the solution onto the roller drier in air for a few seconds and then introduce the boiling liquid on the roller drier into the superheated steam environment. The solution was injected by a syringe onto the drum surface at 135°C and 145°C and kept in air for 10 and 15 seconds, before introducing it into the superheated steam environment for 15 minutes. In Trial 12 the lactose solution that was injected at 145°C for 10 sec in air and 15 minutes in superheated steam produced crystals having a structure that was different to that of a β-lactose crystal or a α-lactose crystal and had similar X-ray diffraction pattern as the 1:1 β/α mixed lactose crystal documented in the literature and the crystal formed at Massey in 1997. It was found that the β-lactose content was less when the solution spent less time in air. The possible explanation is that because the solution was in air for less time, the moisture content might have been slightly higher, with higher molecular mobility which allowed the molecules to re-orient themselves into the new form that quickly crystallised due to the higher temperature at 145°C.

To develop a continuous process, the solution was injected on a rotating roller drier at speeds such that the solution was in air for about 10-12 seconds and in superheated steam for about 15 minutes in superheated steam (Trial 14 and 15). The resulting products were again a mixture of a small amount of 1:1 β/α mixed lactose crystal and β-lactose crystal and not pure1:1 β/α mixed lactose crystal as obtained in Trial 12.

CHAPTER 4

CONCLUSION AND RECOMMENDATIONS

The crystal formed by Paterson & O'Donnell (1997) appears to be the same as the 1:1 β/α mixed lactose crystal form reported by Lerk *et al.* (1984 (a)) and Willart *et al.* (2004). Willart *et al.* (2004) gives conditions under which the 1:1 β/α mixed lactose crystal can be produced. Lerk *et al.* (1984(b)) and Willart *et al.* (2004) produced the 1:1 β/α mixed lactose crystal by heating spray dried amorphous lactose at different temperatures and (Lerk *et al.*, 1984 (a)) produced it by thermal treatment to solid state α-lactose monohydrate. The present work was an attempt to develop a continuous process to produce the 1:1 β/α mixed lactose crystal from a lactose solution under superheated steam environment.

The attempts to develop a continuous process to produce the 1:1 β/α mixed lactose crystal were unsuccessful, but the 1:1 β/α mixed lactose crystal was produced once in Trial 12 in a small quantity. The 1:1 β/α mixed lactose crystal was produced by this process at a lower temperature of 145°C as compared to the temperature 170°C-180°C as reported by Lerk *et al.* (1984 (a)). The X-ray diffraction pattern of the 1:1 β/α mixed lactose crystal produced in this work was different from that of pure β-lactose and pure α-lactose monohydrate and was found to be similar to the 1:1 β/α mixed lactose crystal reported by Lerk *et al.* (1984 (a)) and Paterson & O'Donnell (1997).

A noticeable amount of the 1:1 β/α mixed lactose crystals starts forming in the product when the β-lactose content of the product goes below about 59% β-lactose content. Ideally the β-lactose content of the 1:1 β/α mixed lactose crystals should be about 50%.

It was also demonstrated in the current work that the 1:1 β/α mixed lactose crystal was formed when the lactose solution forms a rubbery amorphous solution with certain moisture content (m_c) and then quickly crystallizes in the superheated steam environment. Without the superheated steam environment the β-lactose content of the product was found to be high and the X-ray diffraction also showed the crystals to be made up of β-lactose crystal.

It can be concluded that the process partly worked, but the formation of the 1:1 β/α mixed lactose crystal from a solution seems to be very sensitive to some unknown factors and further studies have to be carried out to find out the right parameters. From this work the moisture content (m_c) of the amorphous lactose solution seems to be an important factor and further investigation is recommended. Due to the high temperature (90°C) and high concentration of the solution (120gm/100ml water), the concentration of the solution quickly changes with time and even starts to crystallize in the vessel holding the solution. So for the development of a continuous process, lower concentrations should be investigated.

To continue studying the effects of moisture content (m_c) using the drop method by syringe, the effect of different drop sizes should be studied along with the effect of solutions having different concentrations.

Crystallization of amorphous lactose in superheated steam environment should be investigated further as there was evidence of formation of the 1:1 β/α mixed lactose crystal. Crystallization at temperatures of superheated steam higher than 145°C should be investigated because Lerk *et al.* (1984(b)) had produced the 1:1 β/α mixed lactose crystal by heating amorphous lactose to 200°C.

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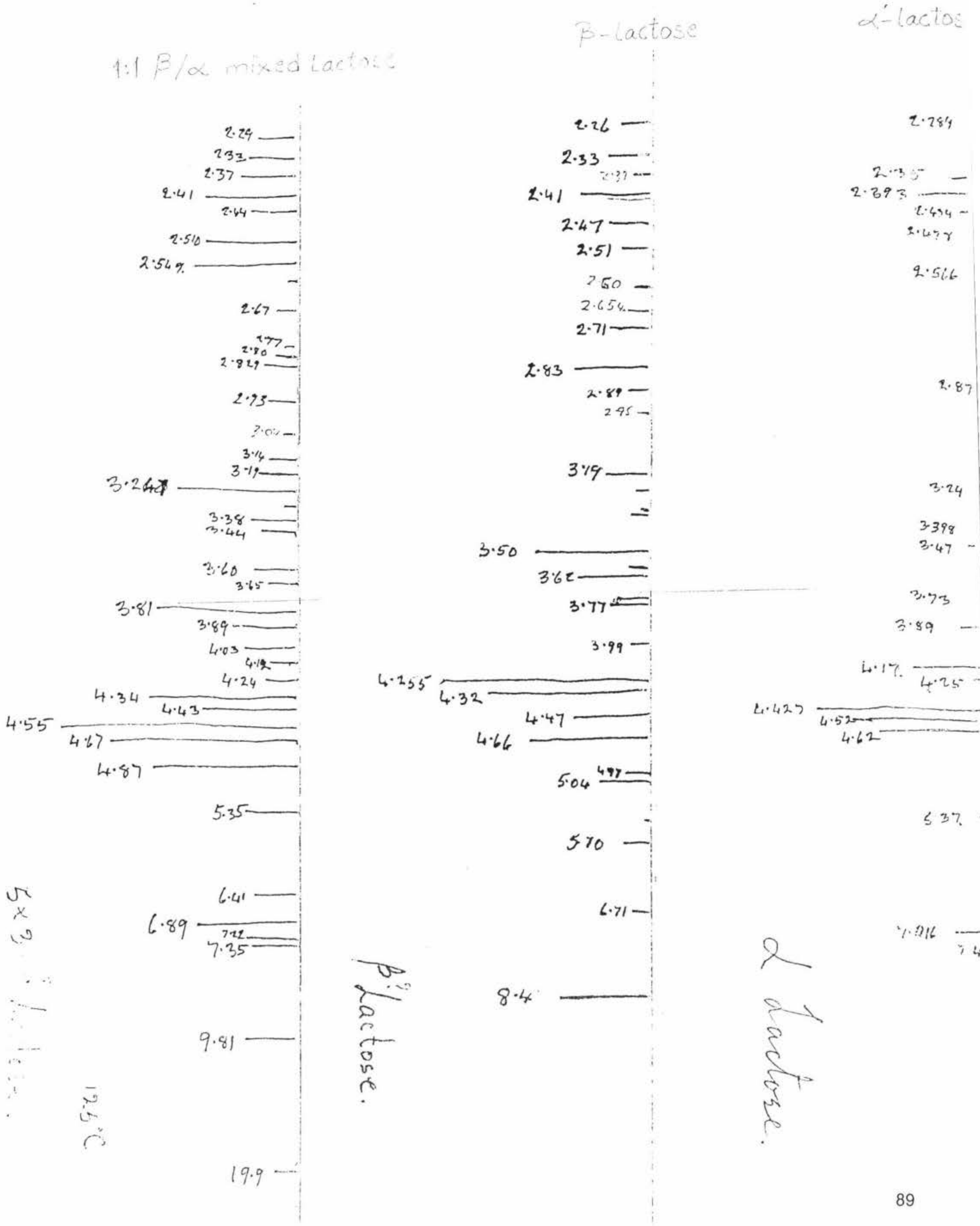
NOMENCLATURE

$R\infty$	Polarimeter reading at equilibrium	
$[R\infty]$	Specific optical rotation	(°)
R_x	Polarimeter reading at any time t	
R_0	Specific optical rotation at time =0	(°)
L	Length of polarimeter sample cell in decimetres	(dm)
c	Concentration of the anhydrous lactose solution	(gm/100ml)
$[\beta]$	Specific optical rotation of beta lactose	(°)
$[\alpha]$	Specific optical rotation of alpha lactose	(°)
α	Alpha lactose content in the product	(%)
m_c	Moisture content	(%)
T_g	Glass transition temperature	(°C)

APPENDIX A

Reference Card



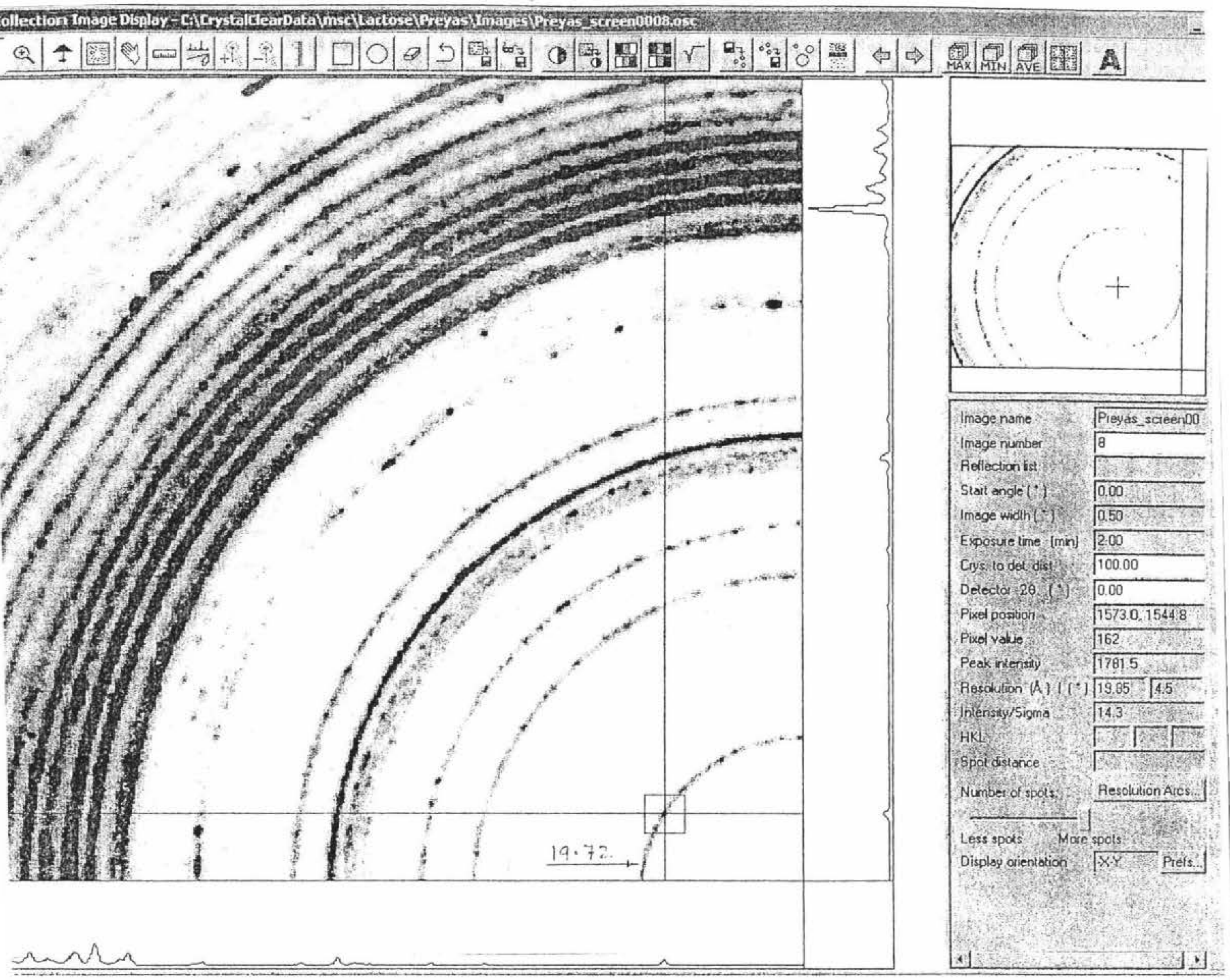


Image name: Preyas_screen00
Image number: 8
Reflection list:
Start angle (°): 0.00
Image width (°): 0.50
Exposure time (min): 2.00
Crys. to det. dist: 100.00
Detector 2θ (°): 0.00
Pixel position: 1573.0, 1544.8
Pixel value: 162
Peak intensity: 1781.5
Resolution (Å) | (°): 19.85 | 4.5
Intensity/Sigma: 14.3
HKL:
Spot distance:
Number of spots:
Display orientation: -X-Y

Figure I (a) showing the value of the 1st major peak (19.72) for the 1:1β/α mixed lactose crystal

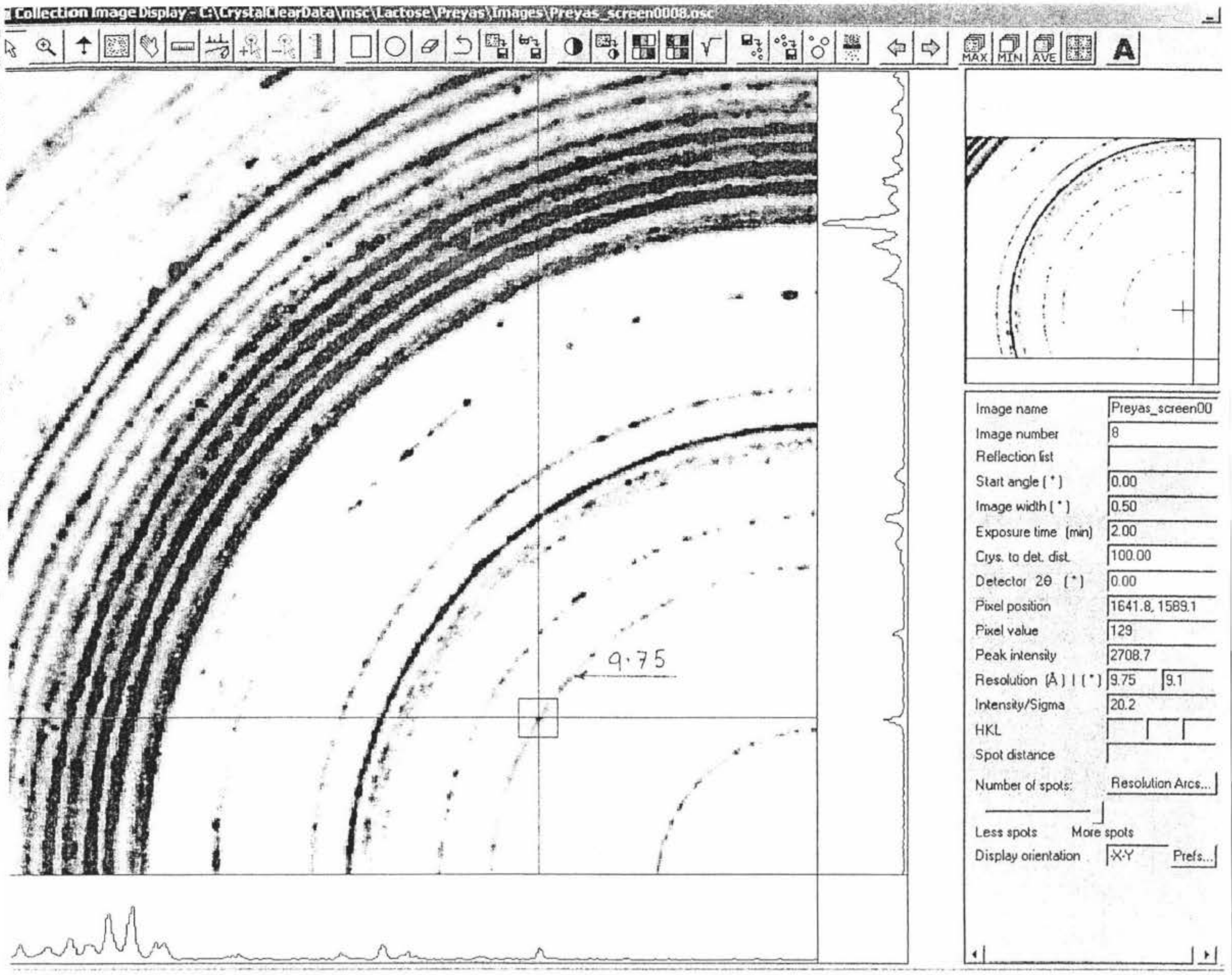


Image name	Preyas_screen00
Image number	8
Reflection list	
Start angle (°)	0.00
Image width (°)	0.50
Exposure time (min)	2.00
Crys. to det. dist.	100.00
Detector 2θ (°)	0.00
Pixel position	1641.8, 1589.1
Pixel value	129
Peak intensity	2708.7
Resolution (Å) | (°)	9.75 9.1
Intensity/Sigma	20.2
HKL	
Spot distance	
Display orientation	-X-Y

Figure I (b) showing the value of the 2nd major peak (9.75) for the 1:1β/α mixed lactose crystal

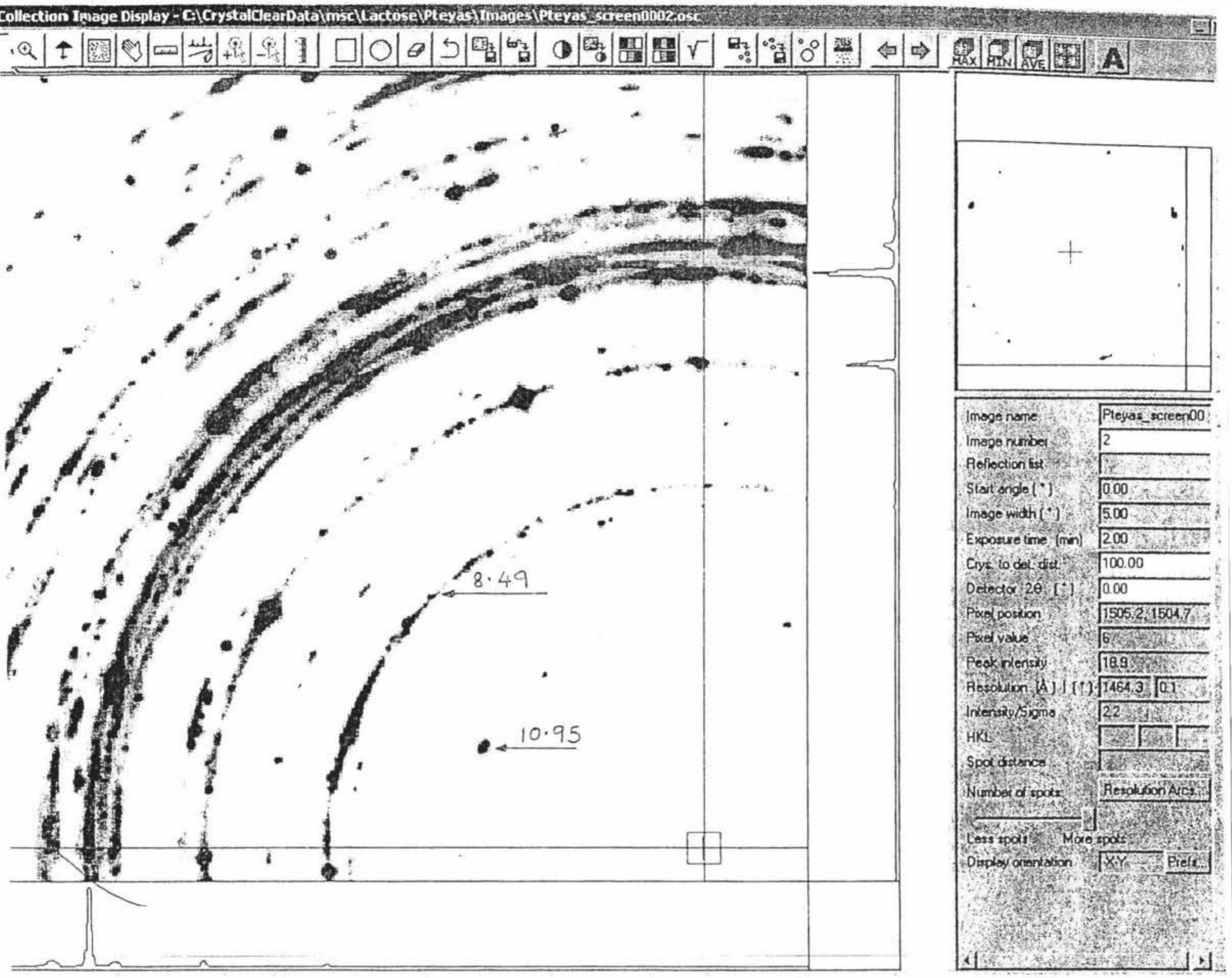


Image name	Pteyas_screen00
Image number	2
Reflection list	
Start angle (°)	0.00
Image width (°)	5.00
Exposure time (min)	2.00
Crys. to det. dist.	100.00
Detector 2θ (°)	0.00
Pixel position	1505.2, 1504.7
Pixel value	6
Peak intensity	18.9
Resolution (Å) | (°)	1464.3 | 0.1
Intensity/Sigma	2.2
HKL	
Spot distance	
Number of spots	
Display orientation	X-Y

Figure II: X-ray diffraction pattern of β- lactose

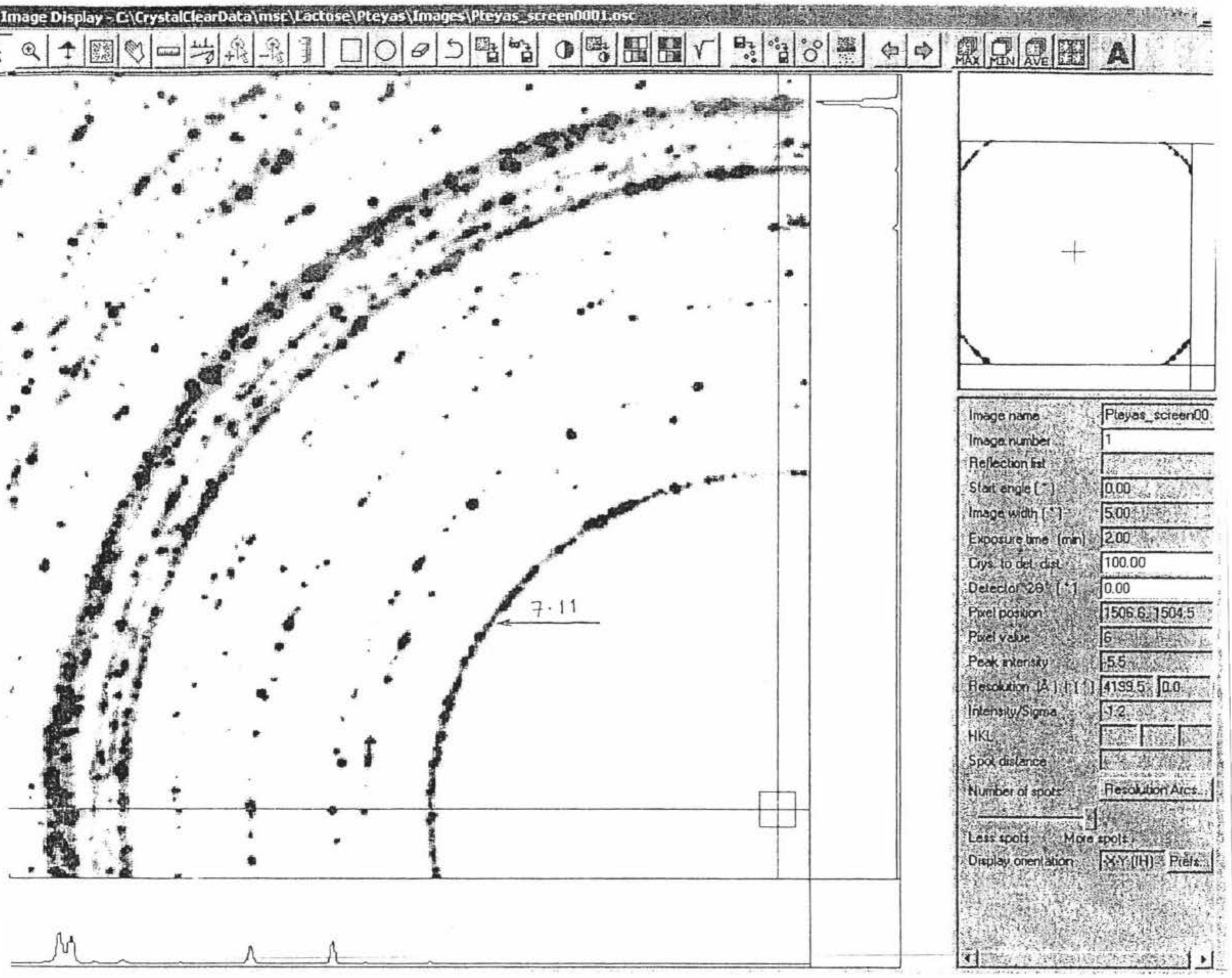
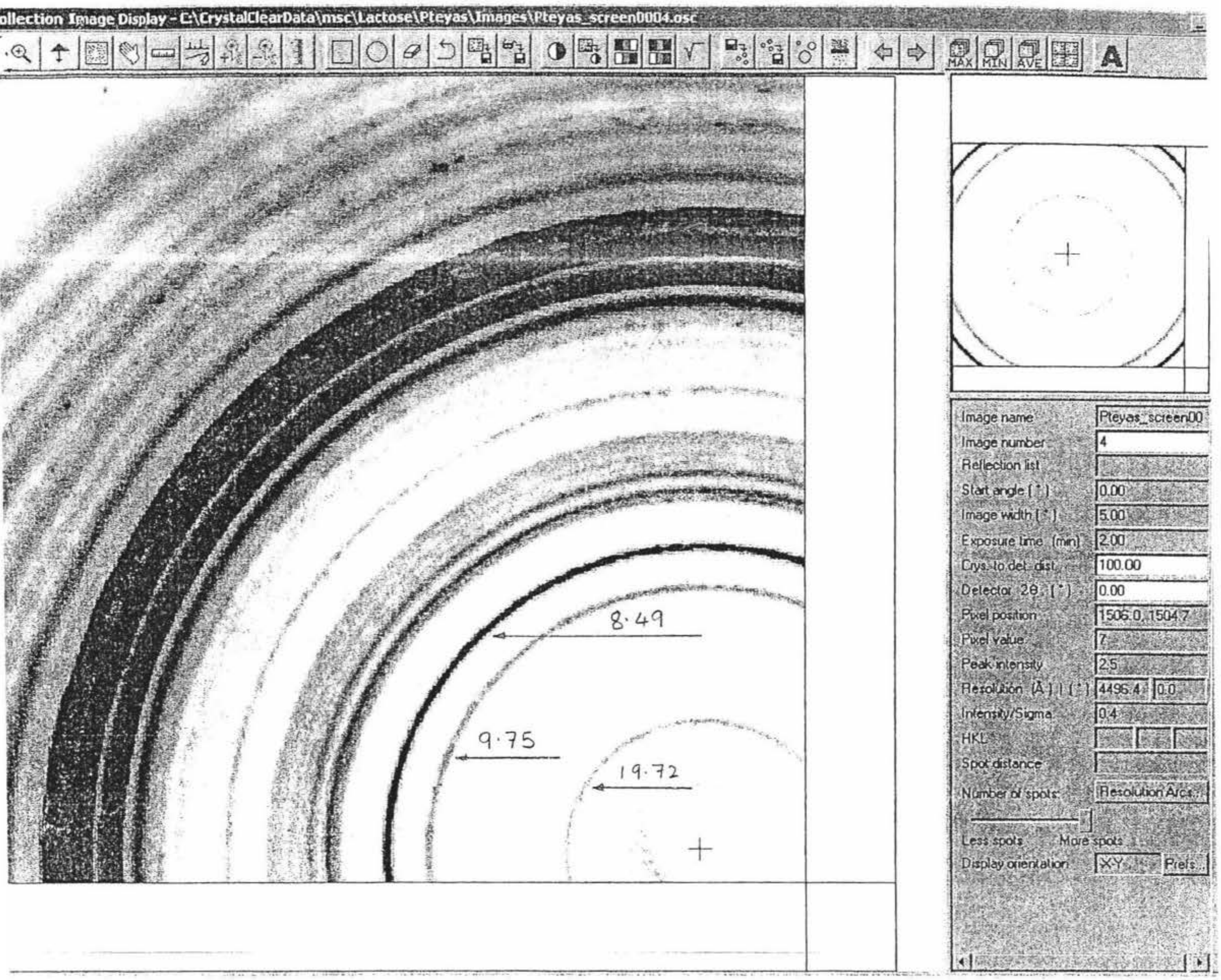


Image name: Pteyas_screen00
Image number: 1
Reflection list:
Start angle (°): 0.00
Image width (°): 5.00
Exposure time (min): 2.00
Crys. to det. dist.: 100.00
Detector 2θ (°): 0.00
Pixel position: 1506.6, 1504.5
Pixel value: 6
Peak intensity: -5.5
Resolution (Å) / θ (°): 4199.5 0.0
Intensity/Sigma: -1.2
HKL:
Spot distance:
Number of spots:
Display orientation: X-Y (IH)

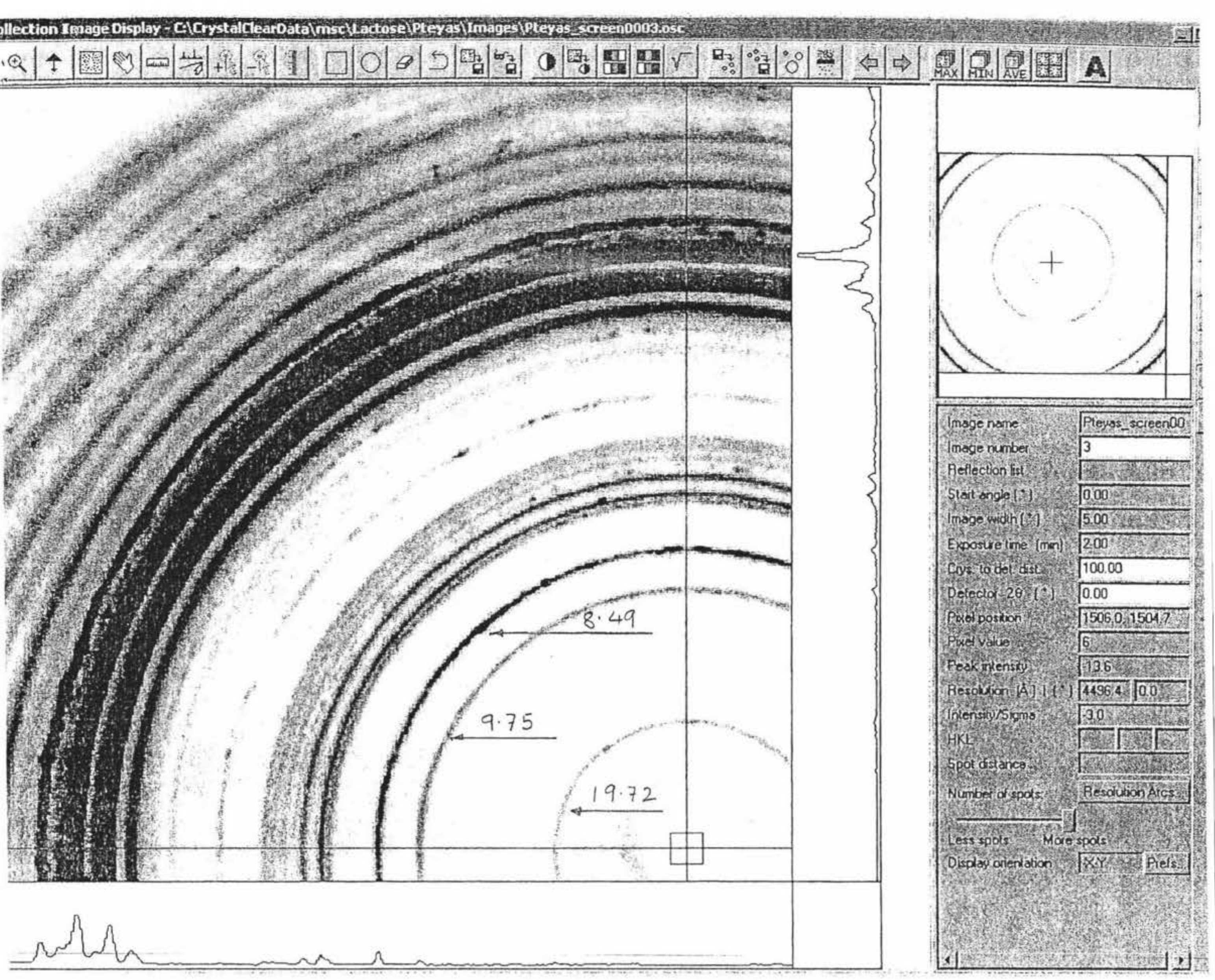
Figure III: X-ray diffraction pattern of α-lactose



ollection Image Display - C:\CrystalClearData\msc\Lactose\Pteyas\Images\Pteyas_screen0004.osc

Image name	Pteyas_screen00
Image number	4
Reflection list	
Start angle [°]	0.00
Image width [°]	5.00
Exposure time (min)	2.00
Crys. to det. dist.	100.00
Detector 2θ [°]	0.00
Pixel position	1506.0, 1504.7
Pixel value	7
Peak intensity	2.5
Resolution (Å) | (°)	4496.4 0.0
Intensity/Sigma	0.4
HKL	
Spot distance	
Number of spots:	
Display orientation	X-Y

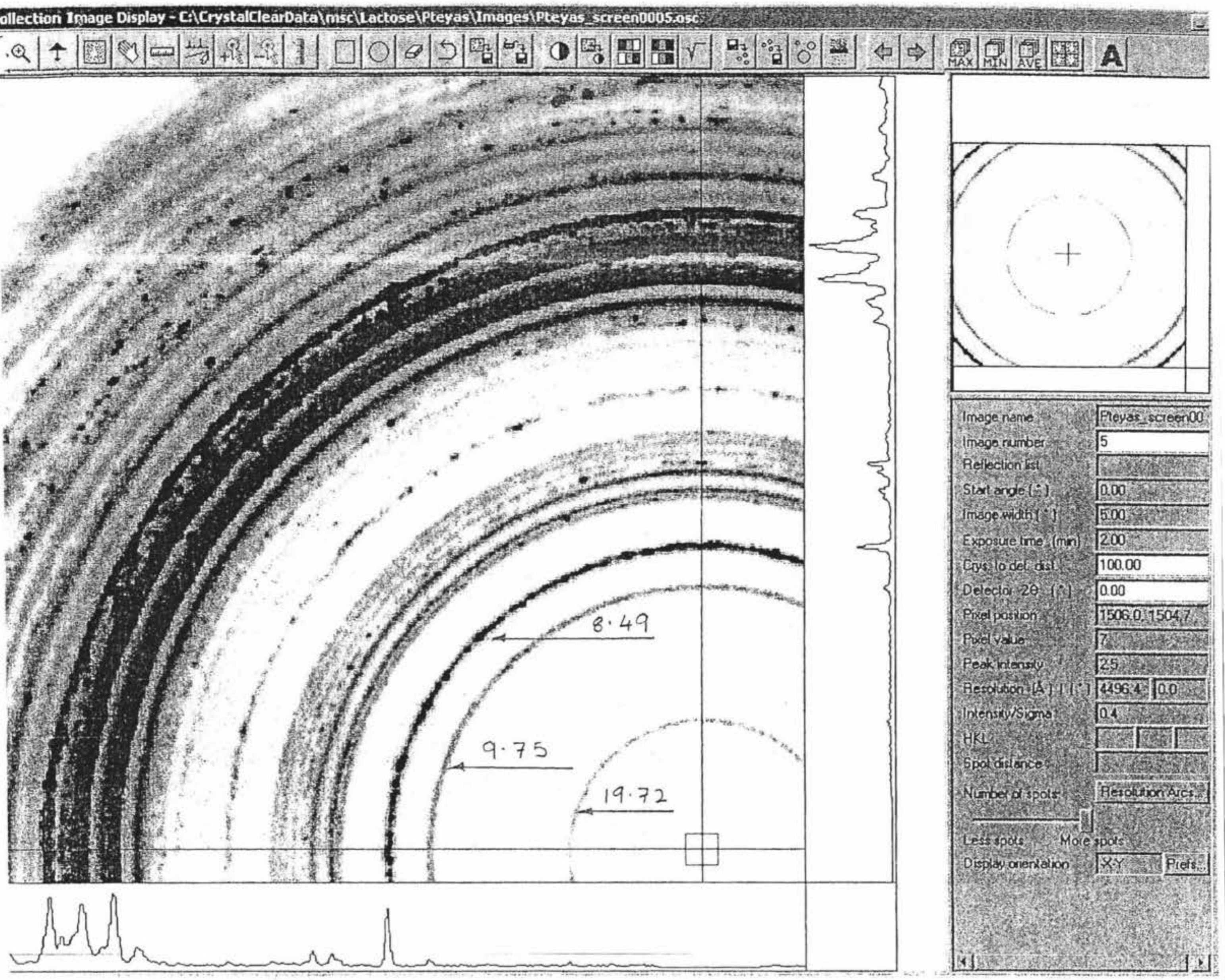
Figure A-1: Amorphous lactose conditioned at 125°C



ollection Image Display - C:\CrystalClearData\msc\Lactose\Pteyas\Images\Pteyas_screen0003.osc

Image name: Pteyas_screen00
Image number: 3
Reflection list:
Start angle [°]: 0.00
Image width [°]: 5.00
Exposure time (min): 2.00
Crys. to det. dist.: 100.00
Detector 2θ [°]: 0.00
Pixel position: 1506.0, 1504.7
Pixel value: 6
Peak intensity: -13.6
Resolution [Å] | [°]: 4496.4 | 0.0
Intensity/Sigma: -3.0
HKL:
Spot distance:
Number of spots:
Display orientation: X-Y

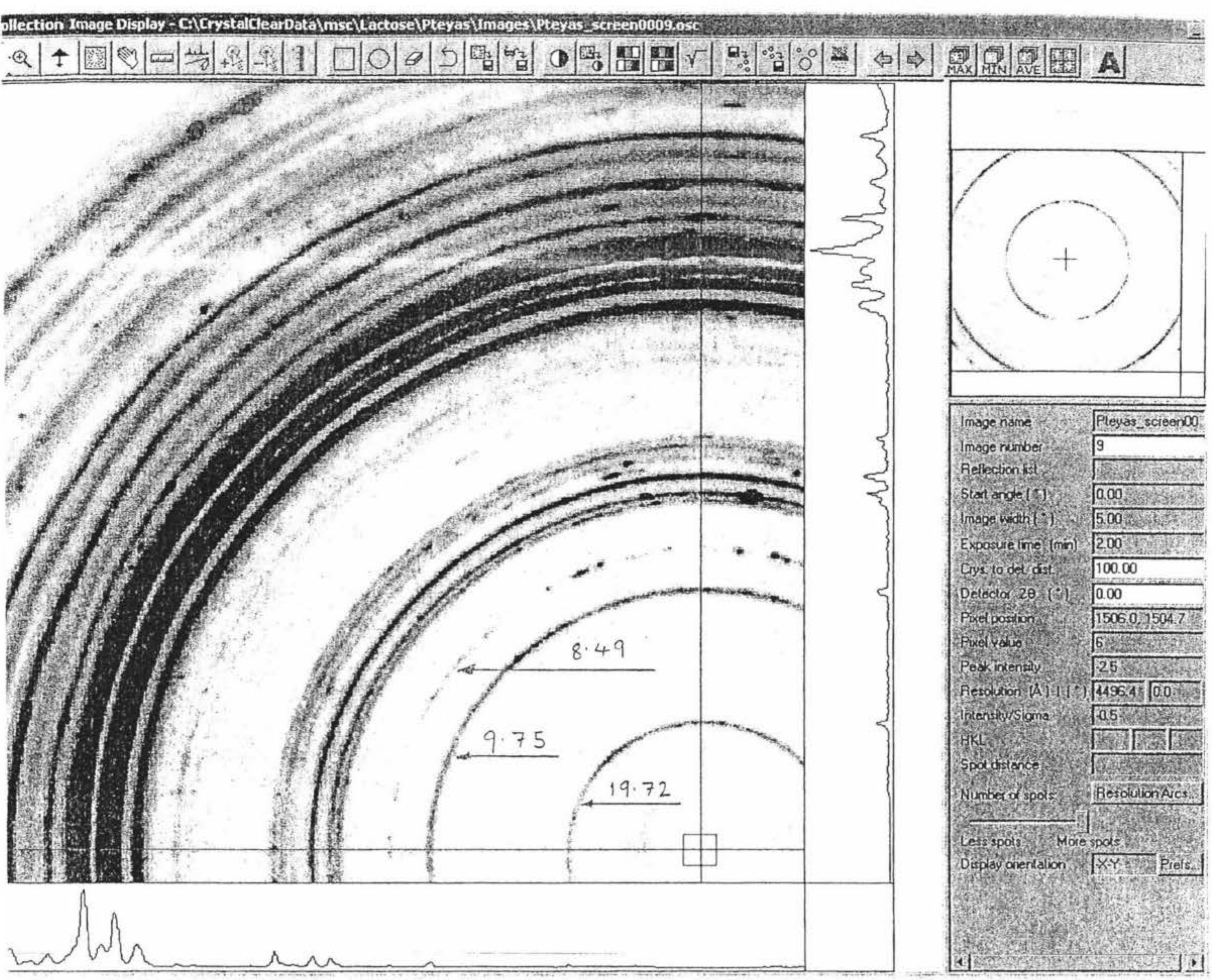
Figure A-2: Amorphous lactose conditioned at 135°C



ollection Image Display - C:\CrystalClearData\msc\Lactose\Pteyas\Images\Pteyas_screen0005.osc

Image name	Pteyas_screen00
Image number	5
Reflection list	
Start angle (°)	0.00
Image width (°)	5.00
Exposure time (min)	2.00
Crys. to det. dist.	100.00
Detector 2θ (°)	0.00
Pixel position	1506.0, 1504.7
Pixel value	7
Peak intensity	2.5
Resolution (Å) | (°)	4496.4 | 0.0
Intensity/Sigma	0.4
HKL	
Spot distance	
Number of spots	Resolution Arcs...
Less spots More spots	
Display orientation	X-Y Prefs...

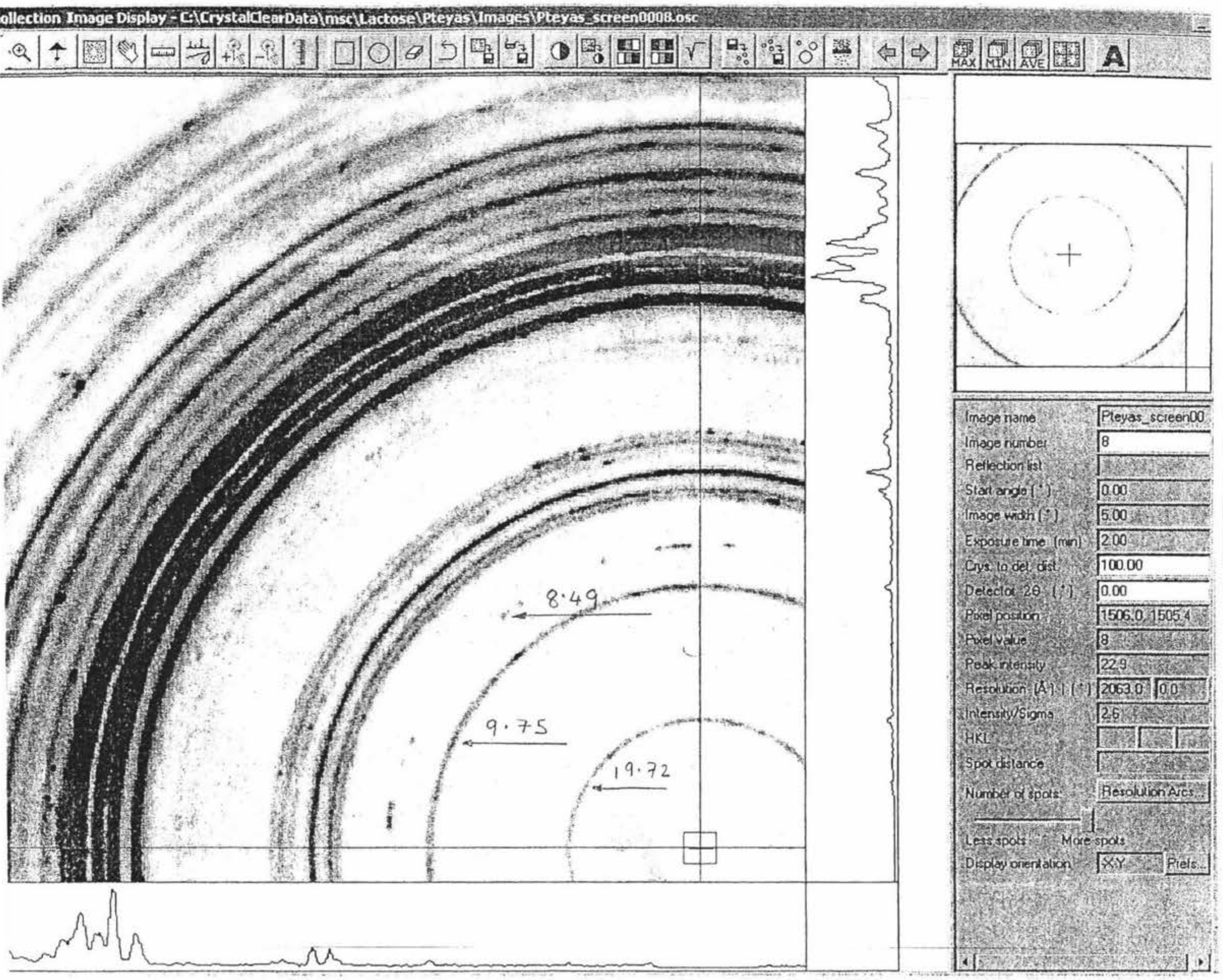
Figure A-3: Amorphous lactose conditioned at 145°C



ollection Image Display - C:\CrystalClearData\msc\Lactose\Pteyas\Images\Pteyas_screen0009.osc

Image name: Pteyas_screen00
Image number: 9
Reflection list:
Start angle (°): 0.00
Image width (°): 5.00
Exposure time (min): 2.00
Crys. to det. dist.: 100.00
Detector 2θ (°): 0.00
Pixel position: 1506.0, 1504.7
Pixel value: 6
Peak intensity: -2.5
Resolution (Å) | I (°): 4496.4 0.0
Intensity/Sigma: -0.5
HKL:
Spot distance:
Number of spots: Resolution Arcs...
Less spots More spots
Display orientation: X-Y Prefs...

Figure A-4: 135°C, 20 sec in air and 15 min in sup. Steam (Trial 9)



ollection Image Display - C:\CrystalClearData\msc\Lactose\Pteyas\Images\Pteyas_screen0008.osc

Image name	Pteyas_screen00
Image number	8
Reflection list	
Start angle (°)	0.00
Image width (°)	5.00
Exposure time (min)	2.00
Crys. to det. dist.	100.00
Detector 2θ (°)	0.00
Pixel position	1506.0, 1505.4
Pixel value	8
Peak intensity	22.9
Resolution (Å) | (°)	2063.0 0.0
Intensity/Sigma	2.6
HKL	
Spot distance	
Number of spots:	
Display orientation	X-Y

Figure A-5: 135°C, 10 sec in air and 15 min in sup. Steam (Trial 10)

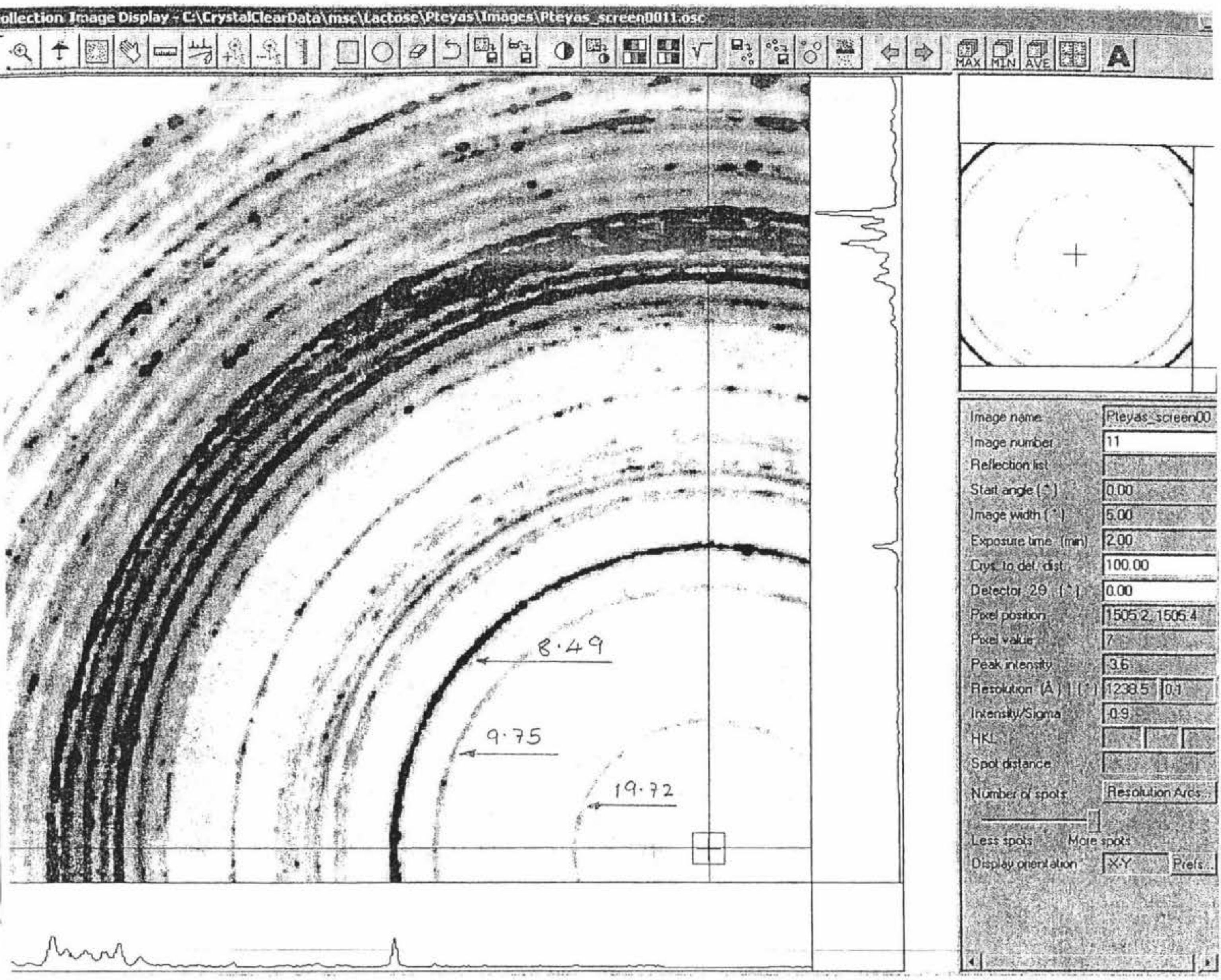
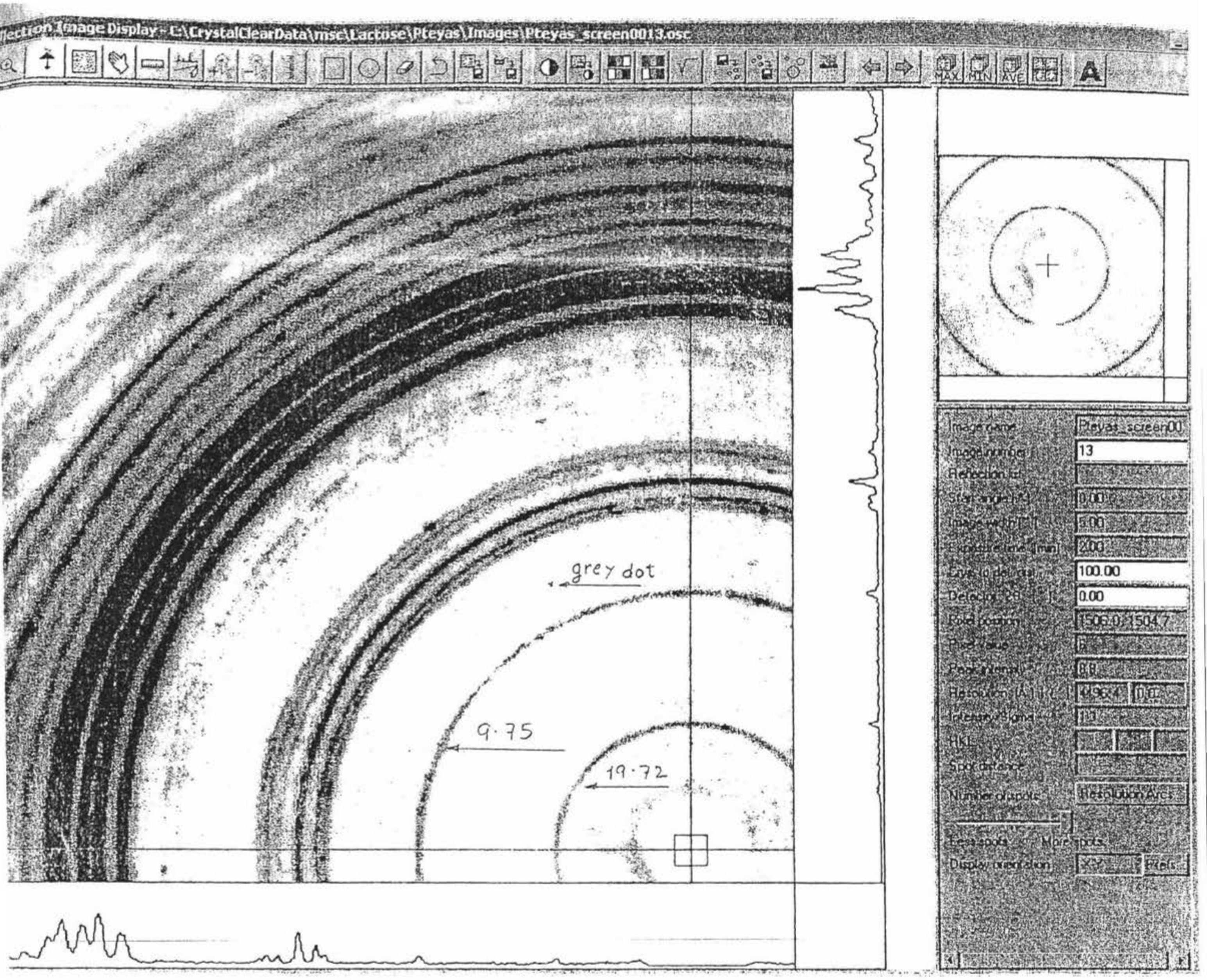


Image name	Pteyas_screen00
Image number	11
Reflection list	
Start angle (°)	0.00
Image width (°)	5.00
Exposure time (min)	2.00
Crys. to det. dist	100.00
Detector 2θ (°)	0.00
Pixel position	1505.2, 1505.4
Pixel value	7
Peak intensity	3.6
Resolution (Å) | (°)	1238.5 | 0.1
Intensity/Sigma	-0.9
HKL	
Spot distance	
Number of spots	Resolution Arcs...

Display orientation	X-Y

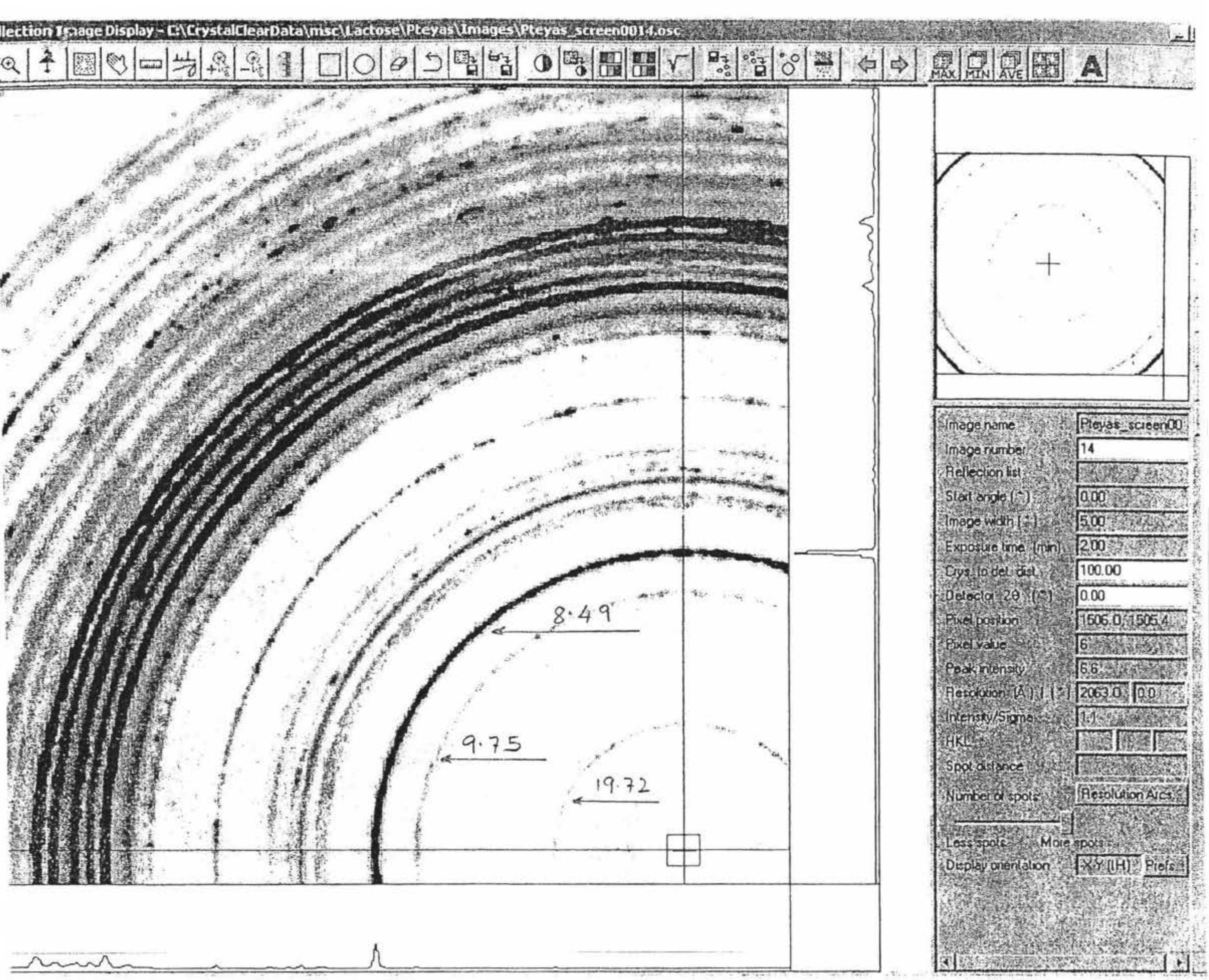
Figure A-6: 145°C, 20 sec in air and 15 min in sup. Steam (Trial 11)



flection Image Display - C:\CrystalClearData\msc\Lactose\Pteyas\Images\Pteyas_screen0013.osc

Image name: Pteyas_screen00
Image number: 13
Start angle [°]: 0.00
Image width [°]: 5.00
Exposure time [min]: 2.00
Crys to det dist: 100.00
Detector 2θ [°]: 0.00
Pixel position: 1506.0, 1504.7
Pixel value: 6
Peak intensity: 8.8
Number of spots: Resolution Arcs
Less spots — More spots
Display orientation: X-Y Prefs

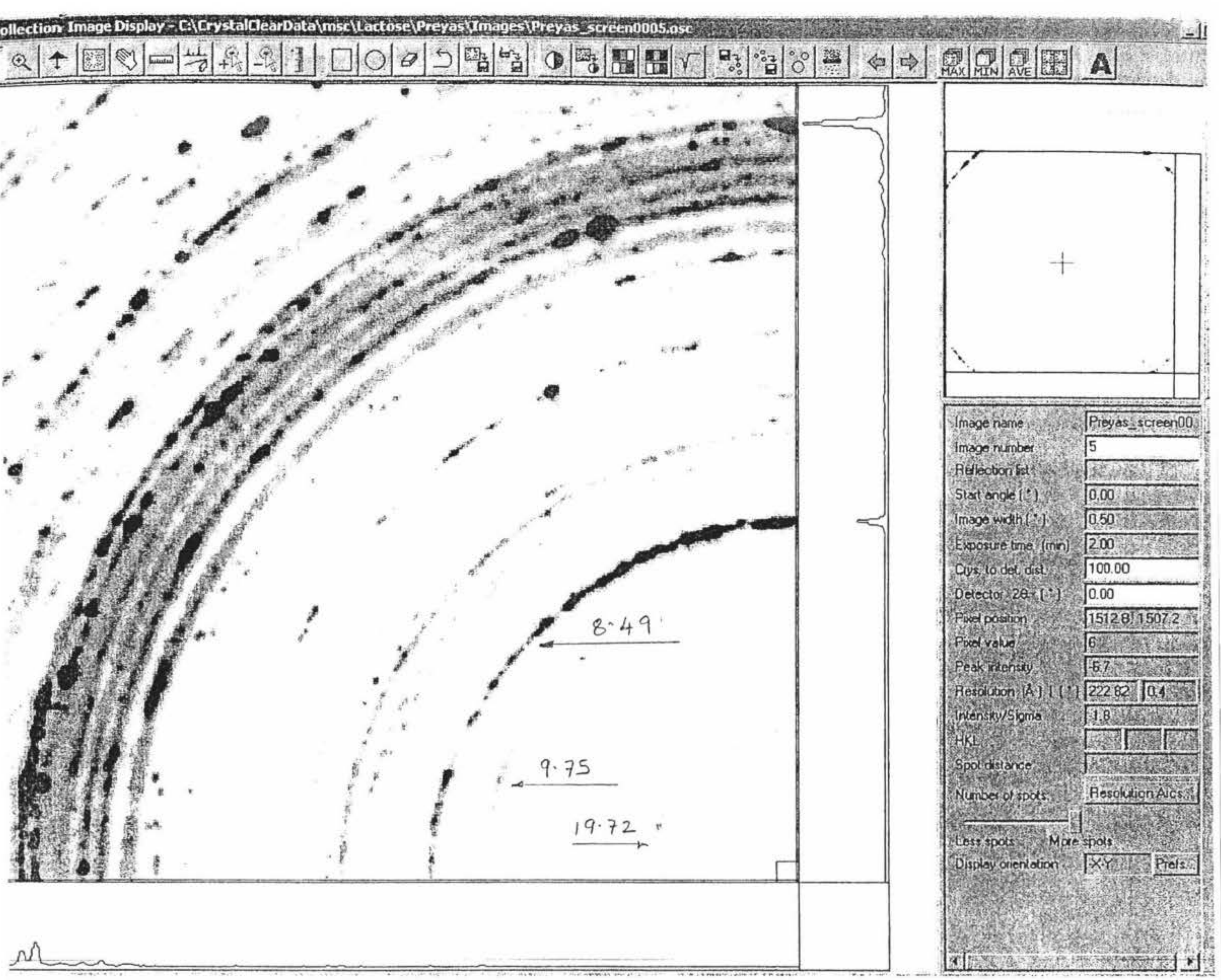
Figure A-7: 145°C, 10 sec in air and 15 min in sup. Steam (Trial12)



llection Image Display - C:\CrystalClearData\msc\Lactose\Pteyas\Images\Pteyas_screen0014.osc

Image name	Pteyas_screen00
Image number	14
Reflection list	
Start angle (°)	0.00
Image width (°)	5.00
Exposure time (min)	2.00
Crys. to det. dist.	100.00
Detector 2θ (°)	0.00
Pixel position	1506.0, 1505.4
Pixel value	6
Peak intensity	6.6
Resolution (Å) / (°)	2063.0 0.0
Intensity/Sigma	1.1
HKL	
Spot distance	
Number of spots	Resolution Arcs
Less spots More spots	
Display orientation	-X-Y (IH) Prefs

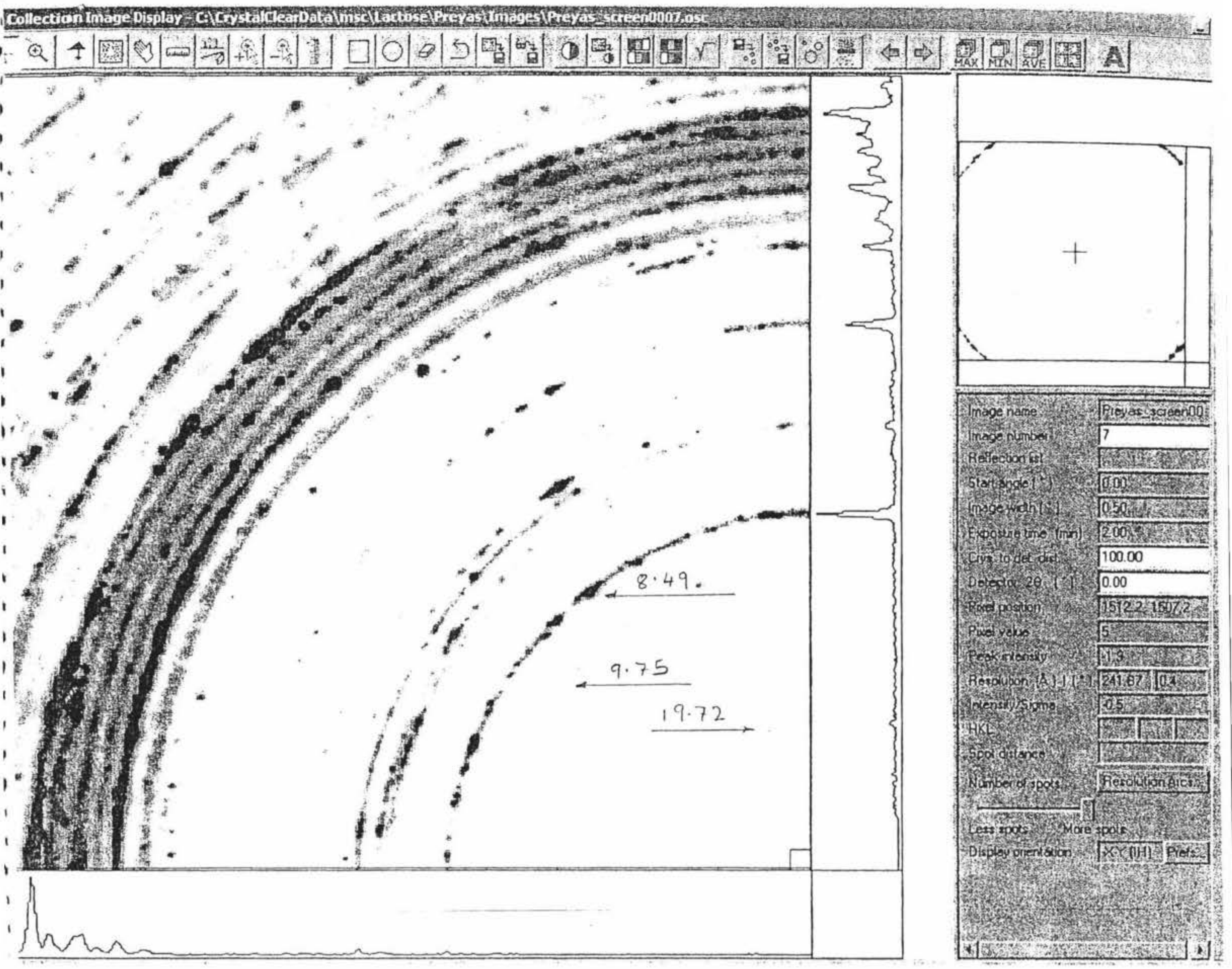
Figure A-8: Injected directly into sup. Steam environment (Trial 13)



ollection Image Display - C:\CrystalClearData\msc\Lactose\Preyas\Images\Preyas_screen0005.osc

Image name: Preyas_screen00
Image number: 5
Reflection list:
Start angle (°): 0.00
Image width (°): 0.50
Exposure time (min): 2.00
Crys. to det. dist.: 100.00
Detector 2θ (°): 0.00
Pixel position: 1512.8 1507.2
Pixel value: 6
Peak intensity: -6.7
Resolution (Å) | (°): 222.82 0.4
Intensity/Sigma: -1.8
HKL:
Spot distance:
Number of spots:
Less spots More spots
Display orientation: -X-Y

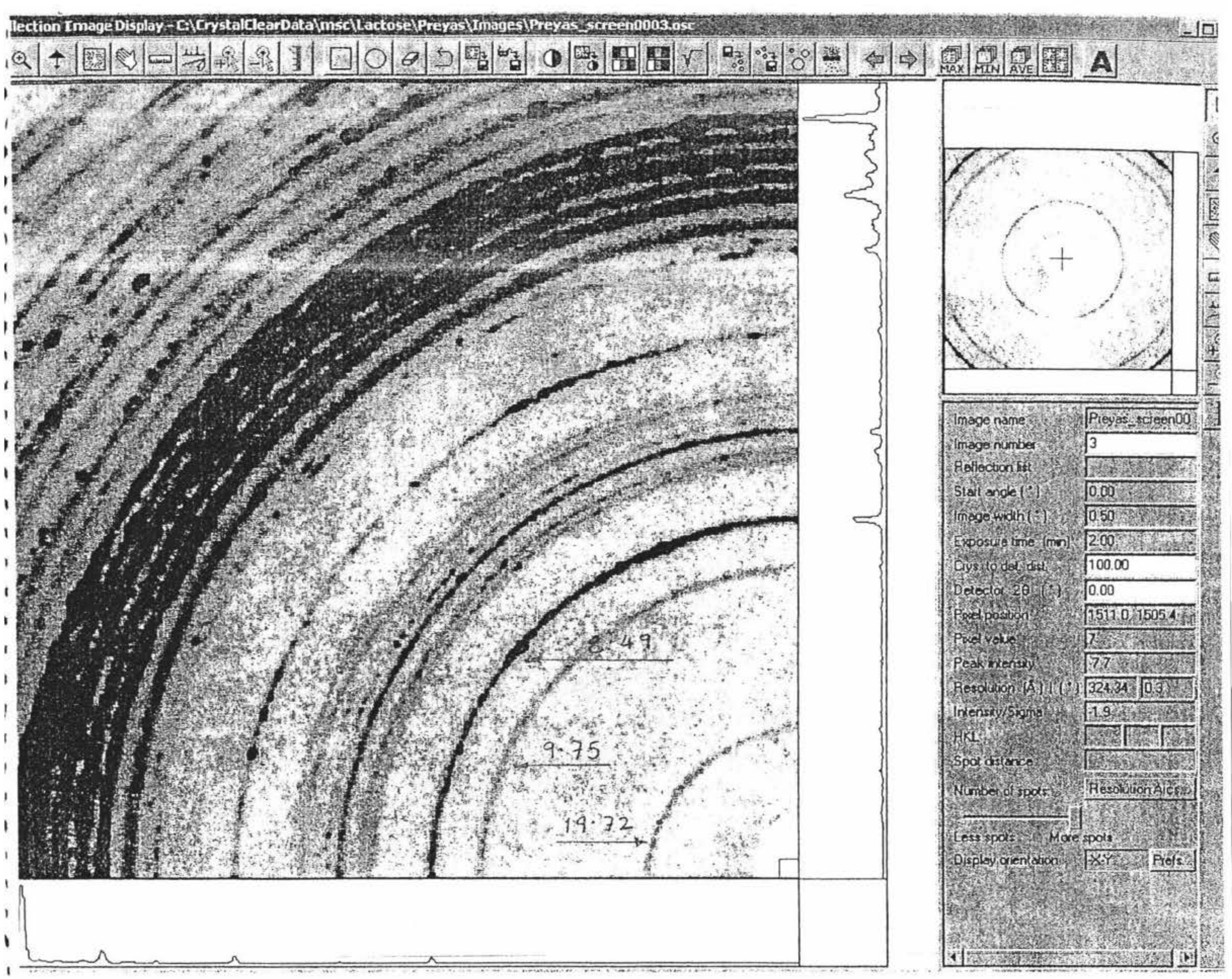
Figure A-9: Continuous run on the lines of Trial 12 (Trial 14)



Collection Image Display - C:\CrystalClearData\msc\Lactose\Preyas\Images\Preyas_screen0007.osc

Image name: Preyas_screen00
Image number: 7
Reflection list:
Start angle (°): 0.00
Image width (°): 0.50
Exposure time (min): 2.00
Crys. to det. dist.: 100.00
Detector 2θ (°): 0.00
Pixel position: 1512.2, 1507.2
Pixel value: 5
Peak intensity: -1.3
Resolution (Å) | (°): 241.87 | 0.4
Intensity/Sigma: -0.5
HKL:
Spot distance:
Number of spots
Display orientation: X-Y (IH)

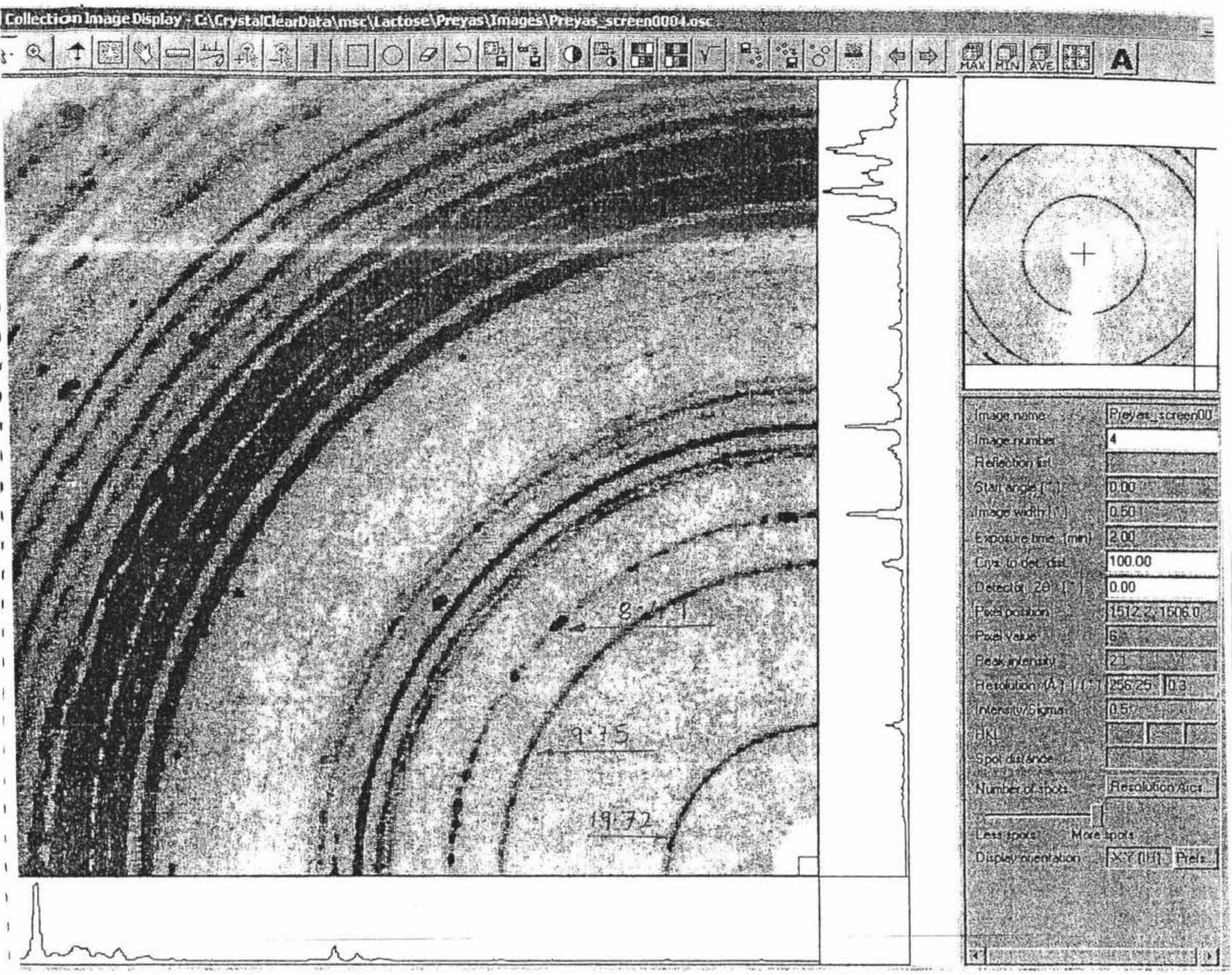
Figure A-10: Trial 15



lection Image Display - C:\CrystalClearData\msc\Lactose\Preyas\Images\Preyas_screen0003.osc

Image name	Preyas_screen00
Image number	3
Reflection list	
Start angle (°)	0.00
Image width (°)	0.50
Exposure time (min)	2.00
Crys. to det. dist.	100.00
Detector 2θ (°)	0.00
Pixel position	1511.0 1505.4
Pixel value	7
Peak intensity	7.7
Resolution (Å) | (°)	324.34 0.3
Intensity/Sigma	1.9
HKL	
Spot distance	
Display orientation	-X-Y

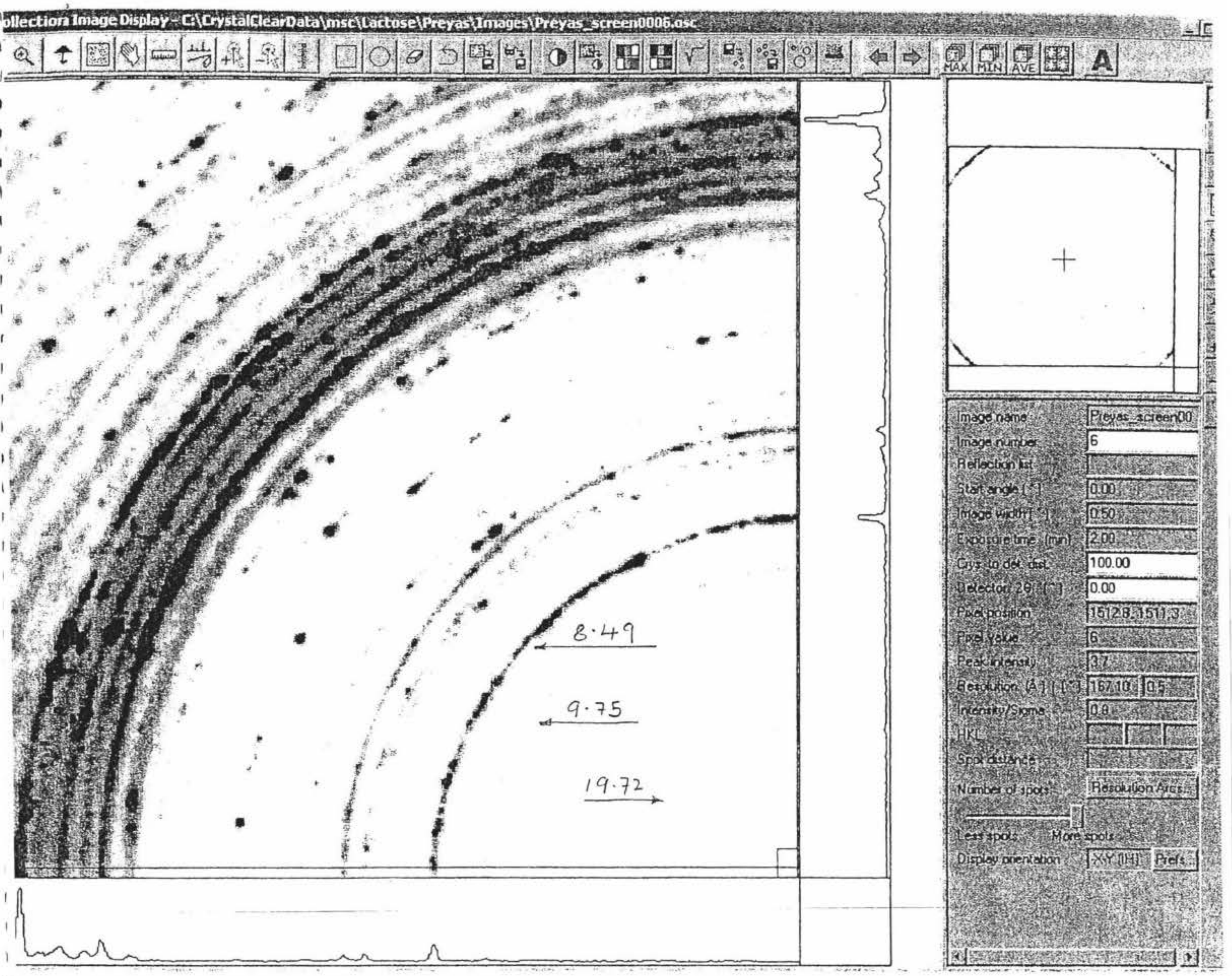
Figure A-11: Repeat trial of Trial 12 (Trial 16)



Collection Image Display - C:\CrystalClearData\msc\Lactose\Preyas\Images\Preyas_screen0004.osc

Image name: Preyas_screen00
Image number: 4
Start angle [°]: 0.00
Image width [°]: 0.50
Exposure time (min): 2.00
Crys. to det. dist.: 100.00
Detector 2θ [°]: 0.00
Pixel position: 1512.2, 1506.0
Pixel value: 6
Peak intensity: 21
Resolution (Å) / (°): 256.25 0.3
Intensity/Sigma: 0.5
Display orientation: X-Y (IH)

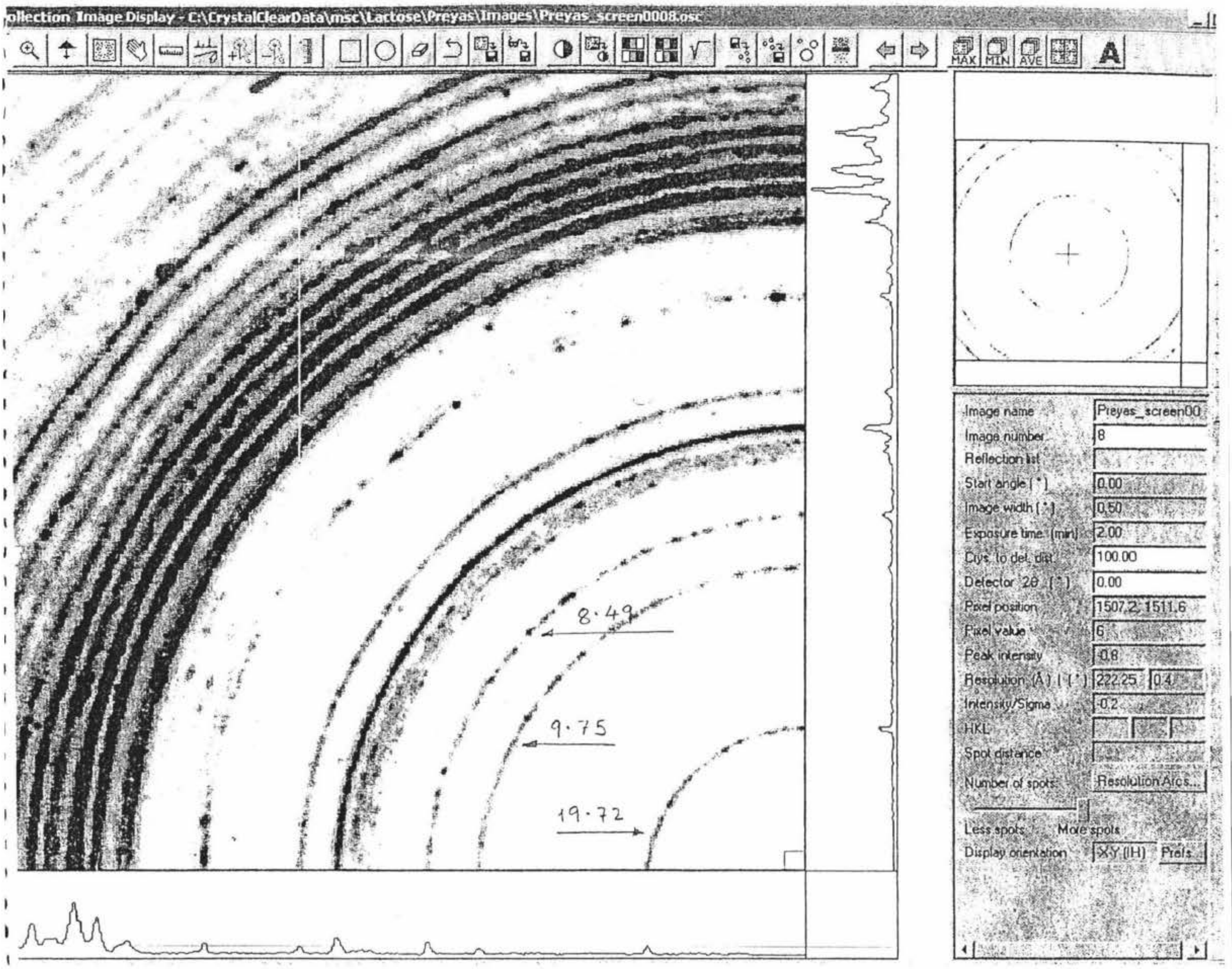
Figure A-12: 145°C, 5sec in air and 15 min in sup. Steam (Trial 17)



ollection Image Display - C:\CrystalClearData\msc\Lactose\Preyas\Images\Preyas_screen0006.osc

Image name: Preyas_screen00
Image number: 6
Reflection list:
Start angle (°): 0.00
Image width (°): 0.50
Exposure time (min): 2.00
Crys. to det. dist.: 100.00
Detector 2θ (°): 0.00
Pixel position: 1512.8, 1511.3
Pixel value: 6
Peak intensity: 3.7
Resolution (Å) | (°): 167.10 | 0.5
Intensity/Sigma: 0.8
HKL:
Spot distance:
Number of spots:
Display orientation: X-Y (IH)

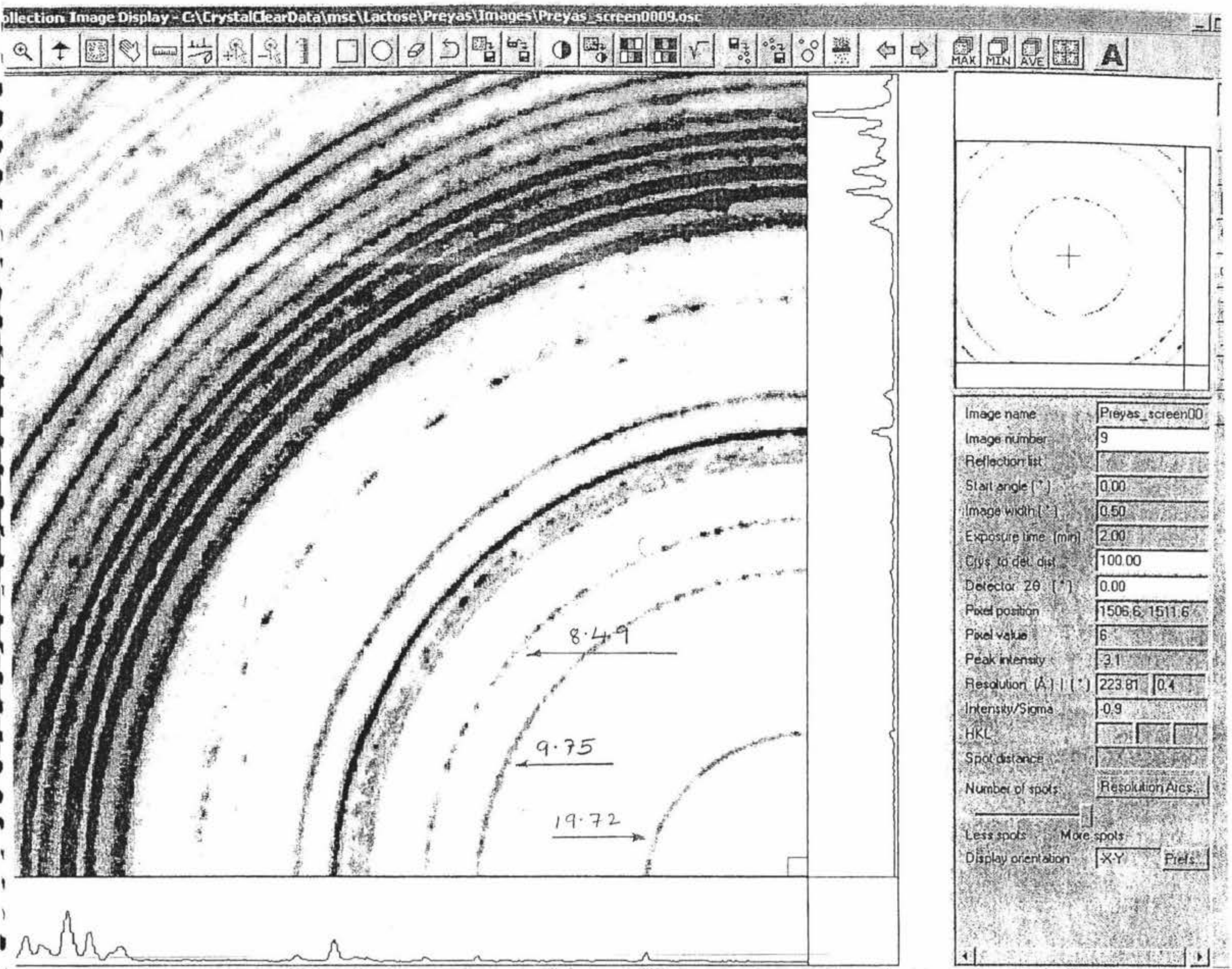
Figure A-13: 155°C, 10sec in air, 15 min in sup. Steam (Trial 18)



ollection Image Display - C:\CrystalClearData\msc\Lactose\Preyas\Images\Preyas_screen0008.osc

Image name	Preyas_screen00
Image number	8
Reflection list	
Start angle (°)	0.00
Image width (°)	0.50
Exposure time (min)	2.00
Crys. to det. dist.	100.00
Detector 2θ (°)	0.00
Pixel position	1507.2, 1511.6
Pixel value	6
Peak intensity	-0.8
Resolution (Å) | (°)	222.25 0.4
Intensity/Sigma	-0.2
HKL	
Spot distance	
Number of spots	
Display orientation	-X-Y (IH)

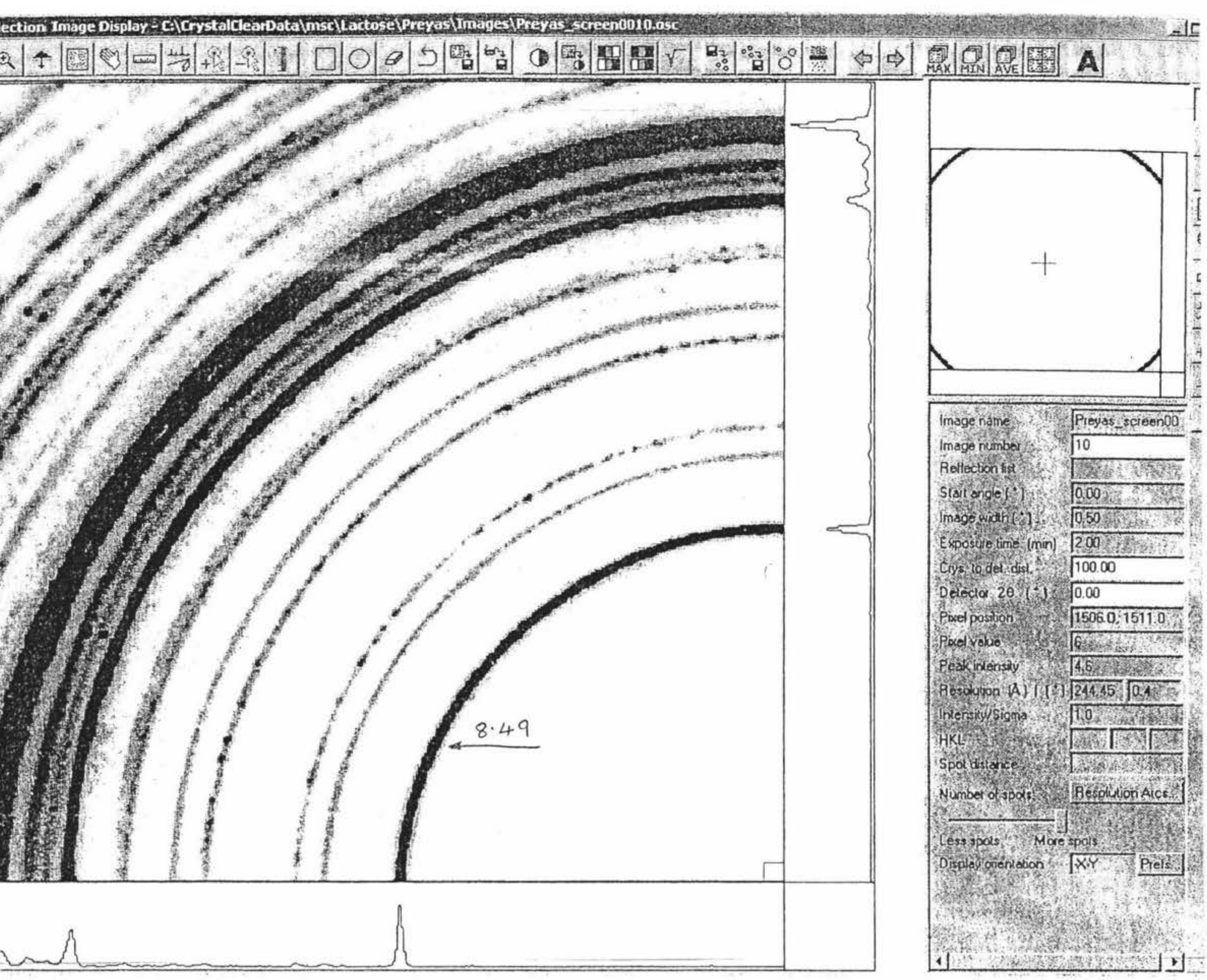
Figure A-14: Hot pot at 125°C



ollection Image Display - C:\CrystalClearData\msc\Lactose\Preyas\Images\Preyas_screen0009.osc

Image name: Preyas_screen00
Image number: 9
Reflection list:
Start angle (°): 0.00
Image width (°): 0.50
Exposure time (min): 2.00
Crys. to det. dist.: 100.00
Detector 2θ (°): 0.00
Pixel position: 1506.6, 1511.6
Pixel value: 6
Peak intensity: -3.1
Resolution (Å) | (°): 223.81 | 0.4
Intensity/Sigma: -0.9
HKL:
Spot distance:
Number of spots: Resolution Arcs...
Less spots More spots
Display orientation: -X-Y Prefs...

Figure A-15: Hot pot at 135°C



ection Image Display - C:\CrystalClearData\msc\Lactose\Preyas\Images\Preyas_screen0010.osc

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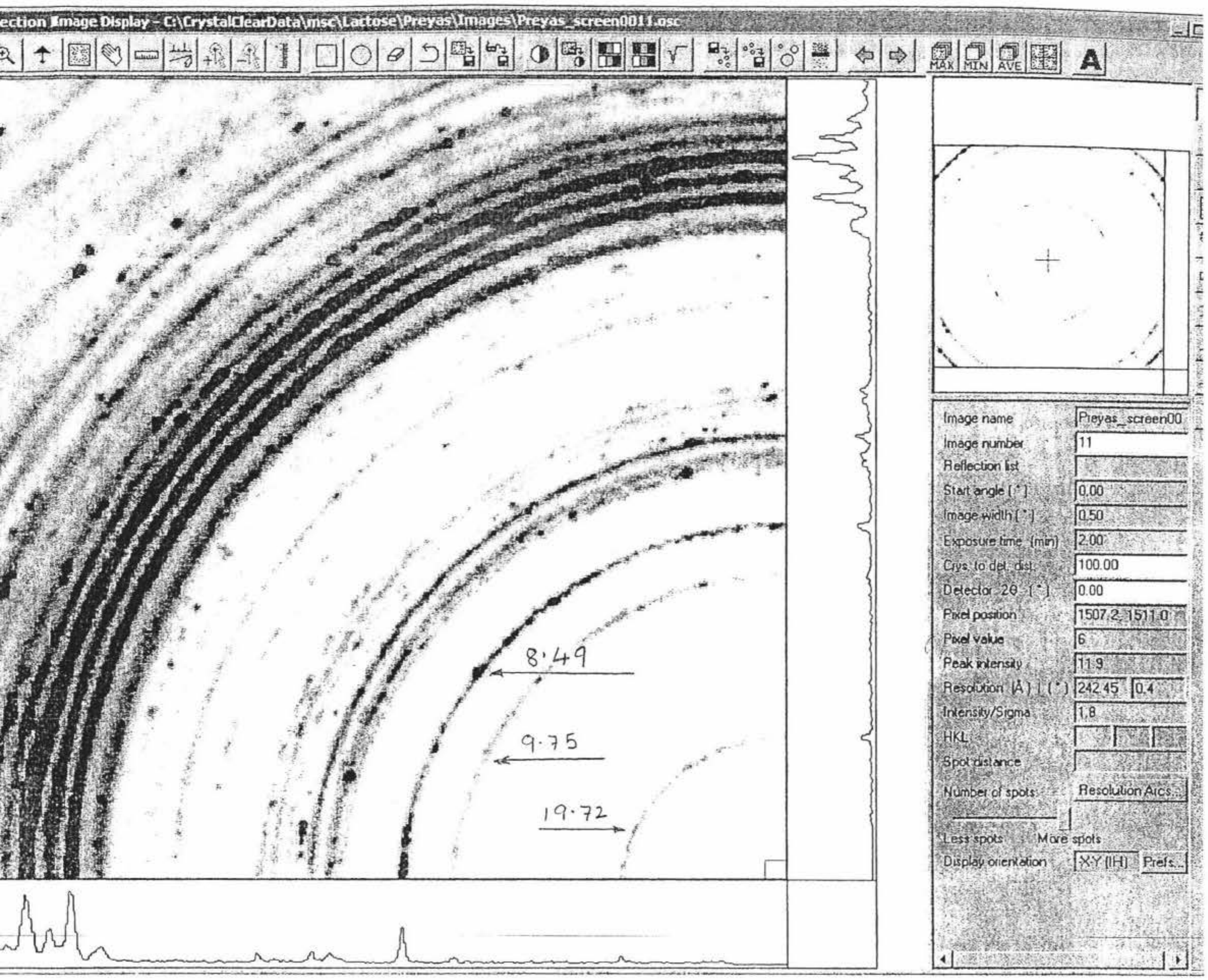
Image name	Preyas_screen00
Image number	10
Reflection list	
Start angle (°)	0.00
Image width (°)	0.50
Exposure time (min)	2.00
Crys. to det. dist.	100.00
Detector 2θ (°)	0.00
Pixel position	1506.0, 1511.0
Pixel value	6
Peak intensity	4.6
Resolution (Å) / (°)	244.45 0.4
Intensity/Sigma	1.0
HKL	
Spot distance	
Number of spots:	
Display orientation	X-Y

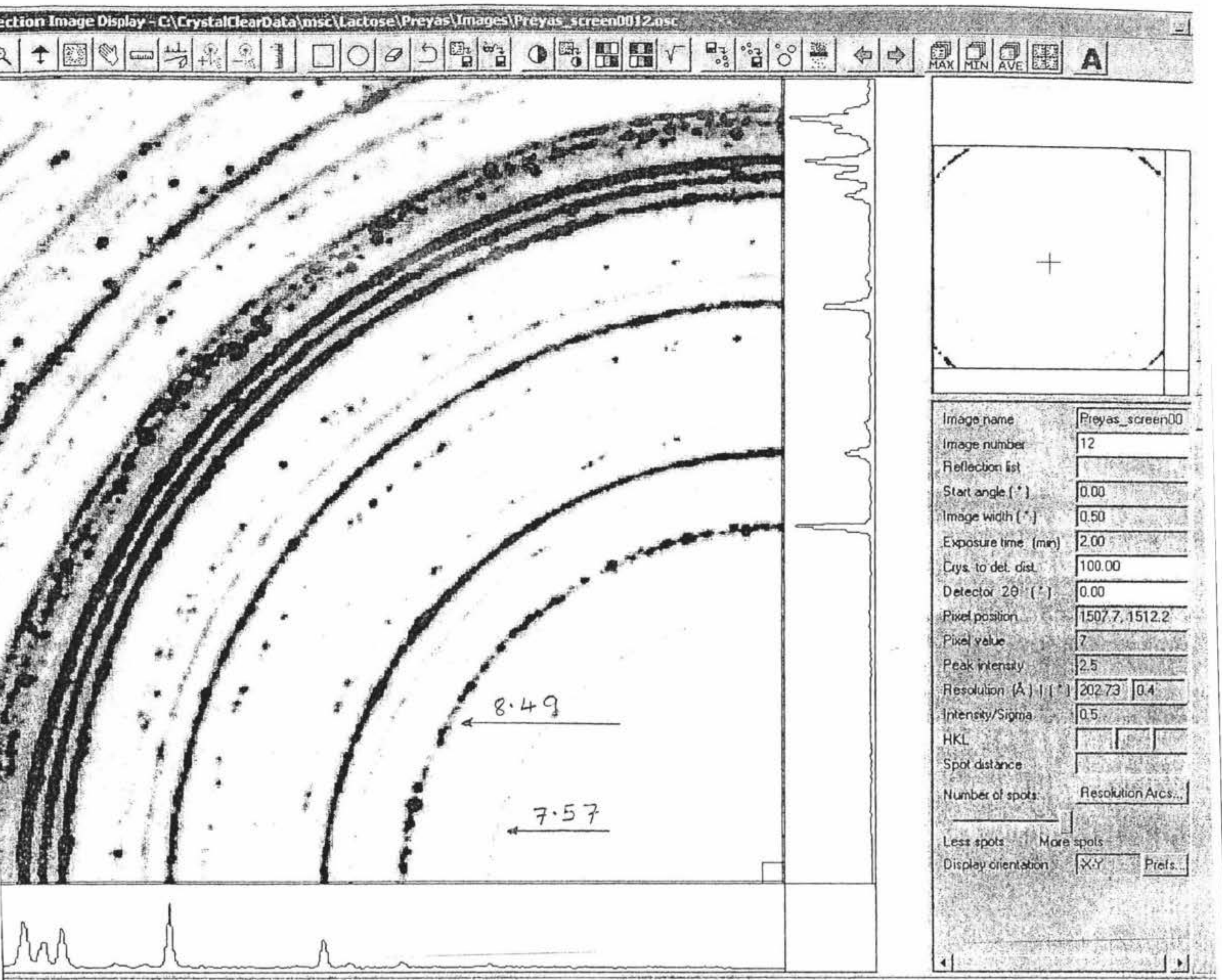
Figure A-16: β-lactose from Fonterra, Kapuni



ection Image Display - C:\CrystalClearData\msc\Lactose\Preyas\Images\Preyas_screen0011.osc

Image name: Preyas_screen00
Image number: 11
Reflection list:
Start angle [°]: 0.00
Image width [°]: 0.50
Exposure time (min): 2.00
Crys. to det. dist.: 100.00
Detector 2θ [°]: 0.00
Pixel position: 1507.2, 1511.0
Pixel value: 6
Peak intensity: 11.9
Resolution (Å) | (°): 242.45 0.4
Intensity/Sigma: 1.8
HKL:
Spot distance:
Number of spots:
Less spots More spots
Display orientation: X-Y (IH)

Figure A-17: Nozzle TPU650017 with tray set up



ection Image Display - C:\CrystalClearData\msc\Lactose\Preyas\Images\Preyas_screen0012.osc

Image name	Preyas_screen00
Image number	12
Reflection list	
Start angle (°)	0.00
Image width (°)	0.50
Exposure time (min)	2.00
Crys. to det. dist.	100.00
Detector 2θ (°)	0.00
Pixel position	1507.7, 1512.2
Pixel value	7
Peak intensity	2.5
Resolution (Å) | (°)	202.73 0.4
Intensity/Sigma	0.5
HKL	
Spot distance	
Number of spots:	Resolution Arcs...
Less spots More spots	
Display orientation	X-Y Prefs...

Figure A-18: Nozzle TPU650017 with needle valve

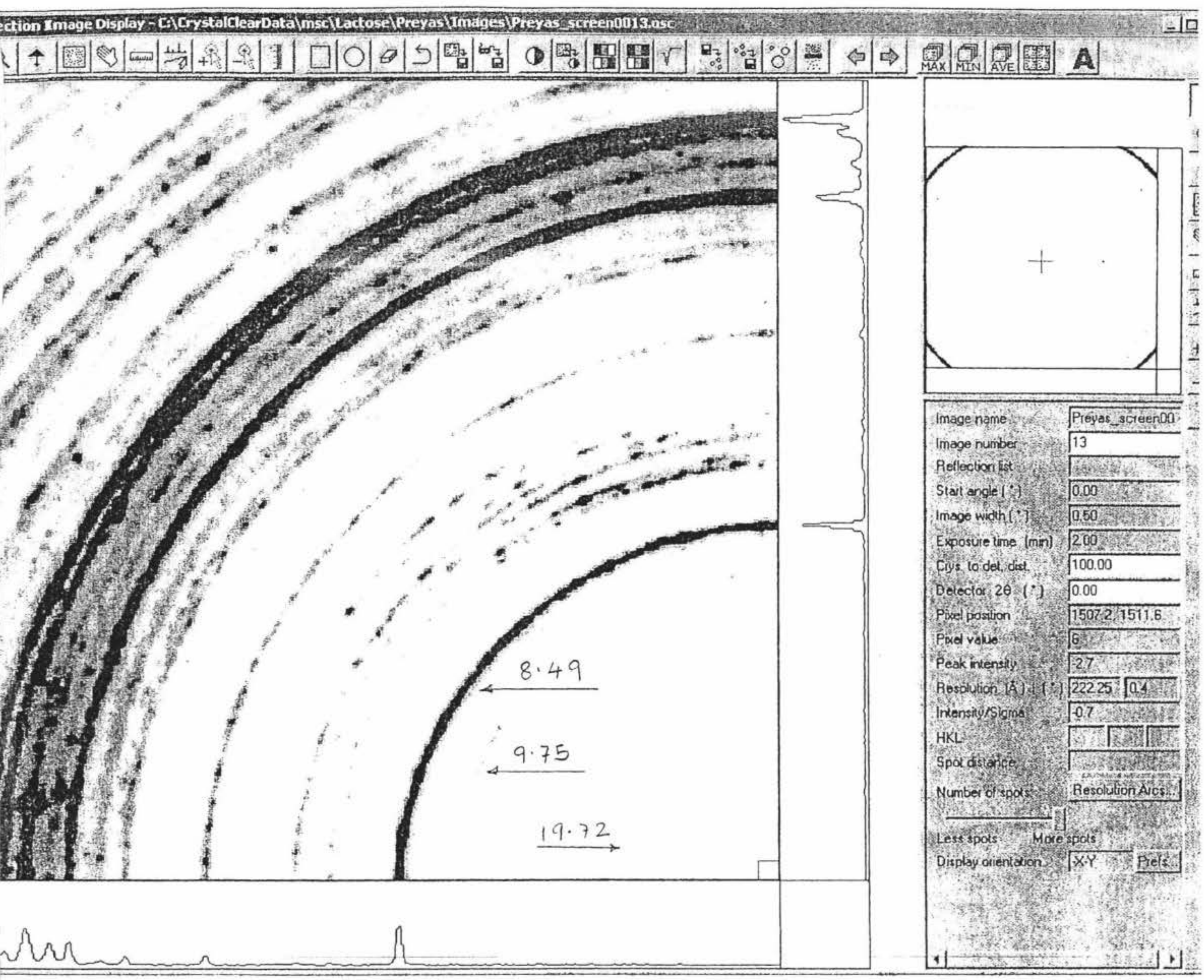

ection Image Display - C:\CrystalClearData\msc\Lactose\Preyas\Images\Preyas_screen0013.osc

Image name: Preyas_screen00
Image number: 13
Reflection list:
Start angle (°): 0.00
Image width (°): 0.50
Exposure time (min): 2.00
Crys. to det. dist.: 100.00
Detector 2θ (°): 0.00
Pixel position: 1507.2, 1511.6
Pixel value: 6
Peak intensity: -2.7
Resolution (Å) / (°): 222.25 | 0.4
Intensity/Sigma: -0.7
HKL:
Spot distance:
Number of spots:
Less spots | More spots
Display orientation: -X-Y

Figure A-19: Trial 7, Part 1 sample1