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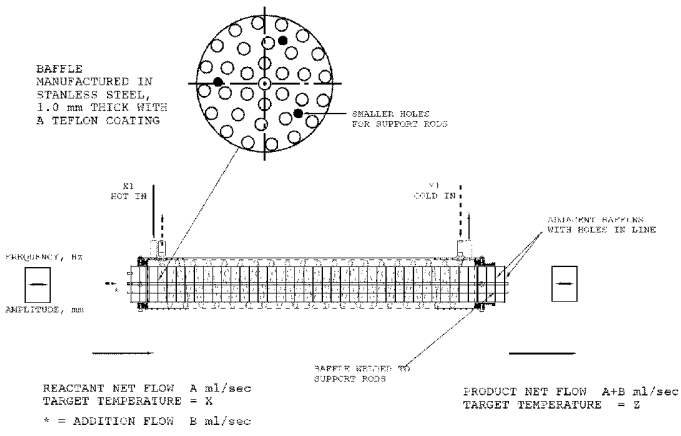
(54) **Title**: CRYSTALLISATION PROCESS AND APPARATUS

Figure 2




(57) **Abstract**: A process is provided for the crystallisation of a solute from a solution, said process comprising: (i) passing the solution through an oscillatory mixed vessel comprising one or more obstacles having a plurality of openings and having means for controlling the solubility of a solute in a solution within said vessel; and (ii) controlling the solubility of the solute within the solution such that crystallisation occurs. Also provided is apparatus for use in said process.

WO 2011/051728 A1

# Crystallisation Process and Apparatus

The present invention relates to novel processes for the manufacture of crystalline material, in particular to oscillatory mixed crystallisation processes, apparatus suitable for use in said processes and crystalline material produced by said processes.

Three of the most important downstream separation processes are extraction, adsorption and crystallisation. Of these, crystallisation often presents the greatest challenge because it is the most difficult process to scale up successfully.

It is well recognised that the precise crystalline nature of an active pharmaceutical agent can have a significant impact on the properties of a formulation containing it, e.g. formulation stability, dissolution rate of the active agent and ultimately the bioavailability (see, for example, Peterson ML et al, *J Pharm Pharmaceut Sci* 2006 9(3):317-326). Therefore, from a production perspective, the crystalline quality must be carefully controlled (including the degree of crystallinity, specific polymorphic form, consistency of crystal size, shape and surface smoothness).

The basic principles behind crystal formation are well understood, though challenges remain in crystal production mainly due the practical impediments with scale-up and the deviation of real apparatus from theoretical ideal systems.

Crystallisation is governed by complex interacting variables - a simultaneous mass and heat transfer process with a strong dependence on fluid and particle mechanics. It takes place in a multiphase, multicomponent system. It is concerned with particulate solids whose size and size distribution, both incapable of unique definition, vary with time. The solids are suspended in solution that can fluctuate between a so-called metastable equilibrium and a labile state and the solution composition can also vary with time.

Continuous, steady state is often regarded as the ideal procedure for many types of process plant equipment, but this is not always true for crystallisation. Batch operation, usually in a conventional stirred tank reactor, offers many advantages such as simplicity of equipment and minimisation of encrustation on surfaces but the operating costs are high. Cleaning between batches is labour intensive and wasteful of energy and solvents.

Constant mixing, normally provided by mechanical stirring, is essential during the crystallisation of a solute from solution so as to avoid the formation of aggregates. However, mechanical stirring can result in heterogeneous distributions of local concentrations and, since the crystal growth is largely dependent upon the degree of supersaturation in the surrounding solution, to heterogeneous crystal growth. The high shear forces required for effective mixing in larger

vessels and the induced collisions of crystals with the vessel wall, the stirring mechanism and other crystals can lead to fragmentation and imperfections in shape. Additionally, persistent agitation will promote further nucleation, as opposed to the simple growth of existing crystals, thereby reducing the consistency of crystal size.

The person skilled in the art is therefore aware of the need to ensure a highly controlled, uniform, yet simultaneously protected and unperturbed, environment for crystallisation. An approach which enables the direct production of crystalline material of a required quality could avoid the need for the downstream processing which is sometimes necessary with the product of conventional crystallisation methods.

Oscillatory flow technology has been known for around thirty years. In the last few years, researchers have considered its use in process intensification because it offers efficient and controlled mixing. As a reactor technology, a baffled tube approach offers scope for processes that meet the necessary performance criteria - these cases being where the flow rate of feed into the reactor and the intensity of the mixing are tailored to minimise the impact of axial dispersion. Unfortunately, such defined conditions are not normally suitable for crystallisation experiments. A low residence time, a consequence of the current approach, means the cooling rate, saturation and nucleation for crystallisation are all negatively affected. Vessels with sufficient residence time for effective crystallisation would be impractically large.

US4832500 describes the use of an imposed oscillating motion upon fluent material contained within a vessel so that the material is caused to cross and re-cross stationary obstacles in the form of rings with sharp innermost extremities or a thin strip formed into a helix coaxial with the vessel, to provide vigorous mixing.

US6114415 describes a batch or continuous process for producing coagulated particles of latex in a receptacle equipped with baffles containing at least one orifice and wherein an oscillatory flow or impulsive flow is applied to form eddies or vortices.

US6429268 describes an apparatus and method for the continuous phase separated synthesis of particulates, using a reactor vessel having stationary annular baffles and means to oscillate the liquid within the reactor vessel.

Smith KB and Mackley MR, *Chem Eng Res Des* 2006 84(A11):1001-1011 describes an investigation into the scale-up of oscillatory flow mixing in baffled tubes.

Ristic RI, *Chem Eng Res Des* 2007 85(A7):937-944 discusses the use of *in-situ* atomic force microscopy and laser optical microscopy to monitor crystal growth in a small scale oscillatory

baffled batch crystalliser wherein the baffles were annular in nature and the temperature within the vessel was maintained at a constant level.

International patent application WO2009/122143 describes the use of a pulse-flow reactor to age precipitated slurry of metal catalyst material. Precipitation is stated to be a very rapid process. The aging process involves a change in the chemical nature of the precipitated material and may result in the evolution of gas. The pulse-flow apparatus comprises two or more temperature control zones which are operated at different temperatures, though adjacent zones may be heating or cooling.

Consequently, there remains a need in the art for a process that enables the convenient production of high quality crystalline material on a commercial scale. The present invention seeks to address this need and others.

According to the present invention there is provided a process for the crystallisation of a solute from a solution, said process comprising:

(i) passing the solution through an oscillatory mixed vessel comprising one or more obstacles having a plurality of openings and having means for controlling the solubility of a solute in a solution within said vessel; and

(ii) controlling the solubility of the solute within the solution such that crystallisation occurs.

The process of the invention it is a controlled crystallisation, it therefore involves a change of physical form of a solute to a solid crystal and will not normally involve changes in the chemical nature of the material (i.e. suitably the chemical composition of the feedstock and the product of the crystallisation is the same).

Suitably, the solute will be substantially pure (i.e. consisting mainly of a single chemical entity which is to be crystallised), such as at least 95% pure, for example at least 98% pure, in particular at least 99% pure.

Suitably the process of the present invention is a biphasic system, only involving a liquid and a solid phase.

Also provided is an apparatus for the crystallisation of a solute from a solution thereof, said apparatus comprising:

(i) a vessel for the containment of a solution of solute;

(ii) means for the oscillatory mixing of a solution of solute contained within said vessel, the means for the oscillatory mixing comprising one or more obstacles each having a plurality of openings; and

(iii) means for controlling the solubility of a solute within a solution contained within said vessel.

Additionally provided is the use of an oscillatory mixed vessel comprising one or more obstacles having a plurality of openings and having means for controlling the solubility of a solution of solute within said vessel for the crystallisation of a solute from a solution thereof.

The invention is illustrated by way of the figures, in which:

Figure 1 provides a schematic representation of an apparatus according to the invention as described in Example 1.

Figure 2 shows a detailed cross-section view of one module as described in Example 1.

Figure 3 shows the temperature measurements obtained during Example 2.

Figure 4 shows the particle analysis for the product of Example 2 (batch process of the present invention).

Figure 5 shows the particle analysis for a control sample of lactose monohydrate.

Figure 6 shows a schematic representation of an apparatus according to the invention as described in Example 1, which further comprises a product collection vessel.

Figure 7 summary of operating conditions for the continuous crystallisation described in Example 3.

Figure 8 shows the particle analysis for the product of Example 3 (continuous process of the present invention).

Figure 9 shows the particle analysis for the product of the Comparative Example (batch process with natural cooling).

The skilled person will recognise that the concept of crystallising a solute from solution does not preclude the presence of solid material within the process liquor as a whole (such solid, for example, being the product of the crystallisation process or optionally seeding material added to promote crystallisation). Consequently, the 'solution' may simply refer to the liquid portion of a suspension.

The vessel of use in the present invention will typically be elongate in nature, with a typical length of 25 m or less, such as 20 m or less, in particular 15 m or less and especially 10 m or less. The vessel length will typically be 0.25 m or greater, such as 1 m or greater and in particular 2 m or greater. Often the vessel will be in the range of 0.25 m to 15 m in length.

The vessel will generally be cylindrical, usually having a diameter of 1 m or less, such as 0.75 m or less, in particular 0.5 m or less and especially 0.25 m or less. A cylindrical vessel will typically have a diameter of at least 1 cm, such as at least 2 cm, in particular at least 3 cm and especially at least 5 cm. Often the vessel will have a diameter in the range of 1 cm to 20 cm.

The vessel volume will usually be in the range of 500 ml to 2000 L. Often the vessel will have a volume in the range of 0.5 L to 1000 L. Other vessel volumes of interest are those in the range of 100 ml to 2000 L, such as 0.1 L to 1000 L.

An elongate vessel may be configured as a single unit, or for convenience may comprise a plurality of shorter modules which are connected in series, thereby enabling a compact arrangement such as when the individual modules are arranged in a substantially parallel manner. An elongate vessel will typically comprise 1 to 50 individual modules.

The vessel may be manufactured from a range of materials, though will typically be made of glass or stainless steel, optionally lined with a low surface energy material to minimise encrustation during use. Suitable low surface energy materials include polytetrafluoroethane (PTFE) and or fluorinated ethylene propylene (FEP).

The obstacles will generally be substantially planar in form (e.g. 0.2-10 mm in thickness, such as 0.5-10 mm in thickness, depending upon the materials of construction and required strength, and substantially corresponding in shape to the cross-section of the vessel). A vessel will normally contain 5 to 5000 obstacles, such as 5 to 500 obstacles. Each obstacle will contain a plurality of openings/orifices, such as 2-1000 orifices, for example 2-200 orifices and especially 3-100 orifices or 10-100 orifices. Each orifice, which will usually be substantially circular in cross-section, will typically be in the region of 0.1 cm to 30 cm in diameter, such as 0.5 cm to 10 cm and especially 0.5 cm to 5 cm. The proportion of free space provided by the orifices will normally be in the range of 10-80%, such as 10-50%, in particular 15-30%. Often the proportion of free space provided by the orifices will be about 25% of the cross-sectional area.

Suitably, the orifices are distributed in a regular arrangement over the surface of the obstacle, to ensure fluid flow conditions are as consistent as possible over the entire cross-section of the vessel. The orifices will normally be uniform (i.e. their size, number and arrangement) for all obstacles in a vessel. The orifices on neighbouring obstacles may be aligned (i.e. such that a

line connecting the centre of corresponding orifices would be parallel to the principal axis of fluid flow), although will suitably be offset.

During operation, the obstacles will usually be located in a stationary arrangement relative to the vessel. However, in some embodiments the oscillatory motion may be introduced through movement of the obstacles rather than the process liquor. The skilled person will realise that an obstacle which is stationary during use need not be permanently fixed in position and may be removably positioned for ease of access (e.g. cleaning or replacement).

Embodiments wherein the relative oscillatory movement of the process liquor relative to the obstacles is induced by a combination of movement of the obstacles and movement of process liquor could also be envisaged.

Obstacles may be constructed from a range of materials, though will typically be constructed from similar materials to the vessel itself, such as stainless steel. Obstacles may be coated with a low surface energy material such as polytetrafluoroethane (PTFE) and or fluorinated ethylene propylene (FEP).

Obstacles will usually be positioned at a separation of about 0.5 to 5 times the orifice diameter, more typically about 1 to 2 times the orifice diameter and especially about 1.5 times the orifice diameter.

The process liquor entering the vessel may be entirely liquid or may be a suspension (e.g. seeded with material to promote crystallisation). In certain embodiments the process liquor entering the vessel will be entirely liquid, and may optionally be seeded during its residence within the vessel (i.e. the vessel comprises means for allowing the addition of seeding material). In the interest of forming pure, high quality crystals of the solute, seeding material will typically be the same chemical entity.

Seeding of a process liquor can aid the reliability of the crystallisation process and is therefore often desirable. However, alternative means exist for the initiation of crystallisation, for example, ultrasonic means may also be utilised to promote nucleation. Ultrasonic means are of particular interest since they may be applied without the introduction of material into the process stream, thereby reducing the risk of accidental contamination.

The process may be performed on a batch basis, wherein the apparatus will be filled with the process liquor, crystallisation occurs, and the product liquor then removed from the apparatus for recovery of the solid crystalline material.

The concept of time in a large batch crystalliser is often underestimated - the crystallisation slurry can wait hours in a large batch vessel to complete filtration, during which time the quality

and consistency of the crystalline material may be detrimentally impacted. Furthermore, cleaning of batch vessels between runs is labour intensive and wasteful of solvents. For these reasons, the process will suitably be performed on a continuous basis. In such circumstances process liquor will normally enter at a first end of the vessel, crystallisation will occur during transit through the vessel, before the product liquor exits the vessel at the second end before recovery of the solid crystalline material.

An apparatus tailored for use in a continuous process will be designed and operated such that the level of axial mixing is minimised while radial mixing is maximised without unnecessary detriment to the crystallisation (e.g. crystal attrition).

An apparatus tailored for use in a batch process may have greater axial mixing, and in fact axial mixing may be desirable to ensure homogeneous conditions throughout the batch vessel.

By the term 'means for the oscillatory mixing' is meant the features necessary for the imposition of an oscillatory motion upon the process liquor which, in conjunction with the one or more obstacles each having a plurality of openings, results in the effective radial mixing of the process liquor with limited axial mixing. In practical terms, a continuous flow vessel may be subjected to an impulsive flow profile which is superimposed on the primary flow though the vessel, the result being essentially the same as the imposition of a true oscillatory flow.

A range of means are suitable for inducing the oscillatory mixing, such as pistons, diaphragms, bellows or electromagnetic systems. The optimal amplitude of oscillation will vary depending upon other conditions within the vessel (vessel design, obstacle design, properties of the process liquor etc.), although will typically be in the range of 0.1-100 mm peak to peak, such as 1-20 mm. The optimal frequency will also vary dependent upon other conditions, though will typically be in the range of 0.01-50 Hz, such as 0.1-20 Hz.

Oscillatory mixing should be of sufficient intensity to ensure that crystallised material remains in suspension (thereby avoiding deposition and clogging of the apparatus). The mixing intensity (including the frequency and amplitude) may therefore be tailored to the formation crystals of a particular size. Larger crystals will typically require more intense mixing to remain in suspension.

Low shear/gentle mixing facilitates crystal growth while aggressive mixing can result in particle attrition and therefore produce smaller crystals (which may be desirable in some circumstances).

Suitably, the crystalline product of the process will have a median particle size of less than 1 mm, such as between 1 and 500 um, especially between 1 and 200 um.

The oscillatory means may be provided through means capable of oscillating the obstacles themselves, rather than the process liquor.

Typical residence times for the process will be in the region of 0.5-20 hours.

During operation the Reynolds number (Re) for the process liquor will typically be less than 10000, to avoid undesirable attrition of developing crystals. Suitably the Reynolds number will be in the region of 10-2000 (such as 100-2000).

In certain embodiments, the crystallisation apparatus will be configured with the elongate vessels arranged substantially horizontally.

Crystallisation of a solute depends on three key factors: firstly, the solubility with temperature and solvent composition; secondly, crystal growth rate; and thirdly, the optimal "cooling curve". See, for example, Mullin JW, *Crystallisation*, Fourth Edition, 2001, Butterworth-Heinemann.

Usually, solubility increases with temperature. Crystallisation can then be initiated either by reducing the temperature or by changing the solvent composition to one where the solubility is reduced (i.e. the addition of an anti-solvent). The pitfall with this oversimplification is that solutions can often contain more solute than that present at saturation. Such supersaturated solutions are termed metastable or labile. Known methods to overcome this thermodynamic barrier include adding seed crystals, adding a co-solvent or more usually an anti-solvent and subjecting the saturated liquor to ultrasound.

Crystallisation also depends on the crystal growth rate, which is controlled by diffusion and is therefore dependent on the degree of supersaturation. This is described by the equation:

$$dM/dt = kA(c - c^*)$$

where M is the crystal mass, A is the total crystal area, k is a mass transfer coefficient and c and c* are the solute concentration actually in the solution and at saturation respectively.

For spherical crystals – an ideal case, the equation can be revised by replacing the mass with a crystal radius:

$$dr/dt = (k_D/\rho)(c - c^*) = G$$

where G is the crystal growth rate, usually in units of m/s

In order to achieve a uniform growth rate, it is necessary to control the mass transfer coefficient, i.e. the mixing. While oscillatory flow offers controlled hydrodynamics, conventional performance conditions are not suitable for crystallisation experiments. It is therefore

necessary to change the reactor geometry for the purposes of improving the working envelope. A controlled growth rate allows crystals either with better particle size distribution or large enough to filter.

The third factor is the cooling rate. In general, the greatest chance of a successful crystallisation occurs under a constant crystal growth rate. From experimental studies, it is possible to determine the degree of supersaturation and also the growth rate. An attempt to establish an optimum cooling curve for batch cooling crystallisation is provided by Mullin and Nyvlt *Chem Eng Sci* 1971 26:369-377. A saturation balance on a batch cooling crystallisation gives the following equation:

$$-\frac{d\Delta c}{dt} = \frac{dc^*}{dt} + k_g A \Delta c^g + k_b A \Delta c^b$$

$c = concentration$
$c = equilibriium\ concentration$
$\Delta c = supersaturation(c - c^*)$
$t = time$
$A = total\ crystal\ area$
$k_g = growth\ constant$
$k_b = nucleation\ constant$
$g\ and\ b\ are\ 'orders'\ of\ growth\ and\ nucleation\ respectively$

The first term on the right hand side of the equation corresponds to the creation of supersaturation by cooling. The second and third terms describe the de-supersaturation rate caused by crystal growth and nucleation, respectively.

For a seeded system, making a number of simplifying assumptions (such as constant supersaturation, negligible nucleation and growth only on the added seeds), a general expression of the optimum cooling curve becomes:

$$-\frac{d\theta}{dt} = \frac{3W_{s0}G(t)L^2(t)}{\left[\frac{d\Delta c}{d\theta} - \frac{dc^*}{d\theta}\right]L_{s0}^3}$$

$W_{s0} = mass\ of\ added\ seeds$
$L_{s0} = seed\ size$
$\theta_0, \theta_f = batch\ temperature\ range$
$G = crystal\ growth\ rate$
$L = final\ crystal\ size$

The batch time and corresponding cooling curve can be determined by numerically integrating this expression. Further simplifying assumptions, e.g. if G≠G(L,θ), $dc^*/d\theta = 0$ and $d\Delta c/d\theta = 0$, allows a very simple expression for predicting an approximate cooing curve to be obtained:

$$\theta_t = \theta_0 - (\theta_0 - \theta_f)(t/\tau)^3$$

$$\theta_0, \theta_f, \theta_t = \textit{temperature at the beginning, end and at any time t during the process}$$
$$\tau = \textit{overall batch time}$$

This equation enables the conclusion that at the start when time is small, cooling should be undertaken slowly, linearly. As time gets larger, cooling should be progressing faster and faster to get large pure crystals.

A similar strategy can be applied to additions of anti-solvent as an alternative (or even additional means) to controlling supersaturation during the process.

For unseeded solutions, a modification of the equation is:

$$\theta_t = \theta_0 - (\theta_0 - \theta_f)(t/\tau)^4$$

which leads to even more gentle decrease in temperature in the initial stages of the cooling process.

The extension to a continuous system is a straightforward procedure. The batch temperature range can be related to the temperature at the beginning and at the end of the continuous tube, and the cooling rate is a function of the residence time. Low cooling rates and high residence times are usual crystallisation conditions.

The apparatus according to the present invention will contain means for controlling the solubility of a solute within a solution. Such means may be (i) means for controlling the temperature of the solution, for example by way of a liquid filled jacket (e.g. water filled) or an electrical jacket; (ii) means for altering the composition of the solvent, e.g. means for the addition of an anti-solvent or (iii) a combination of these.

In order to allow precise control of the temperature at a given point along the length of the vessel, in the case of a liquid filled jacket it may be desirable to utilise a ‘double jacket’ approach.

As discussed above, the optimal cooling (or alternatively solvent composition curve) can readily be determined for any given solute. Ideally, this cooling curve will be precisely followed during the crystallisation process, thereby ensuring ideal conditions are achieved.

In batch processes it is possible to pursue the optimal cooling curve, the key hurdle being ensuring that heat transfer occurs effectively within the vessel such that the process liquor is homogenous in temperature both radially and axially.

In a continuous process, since residence time is a function of distance travelled along the vessel, it is more challenging to follow the optimal cooling curve, for example where the means for controlling the temperature is provided through a liquid filled jacket. In continuous process systems it is therefore desirable that the means for controlling the solubility comprises a plurality of sections over each of which the optimal cooling curve is approximated based on the residence of the process liquor transiting through said section. Desirably a continuous process apparatus will have 2, 3, 4, 5, 6, or more sections, each with its own liquid filled jacket (in some cases desirably with its own double liquid jacket). In some circumstances an electrical jacket may allow a better approximation of the optimal cooling curve, being more readily divisable into sections.

In order to follow the optimal cooling curve a given section of a continuous process apparatus will be operated at a lower temperature than those preceding it. Such operation can conveniently be achieved, for example, in a double jacketed apparatus where the hot jacket liquid runs co-current to the process liquor and the end of the hot jacket for the first section is connected to the beginning of the hot jacket for the second section. The cold jacket liquid temperature and flow rates for each section are then controlled independently as necessary to ensure that the optimum cooling curve is followed by the process.

If the means for controlling the solubility of a solute within a solution comprises means for the addition of an anti-solvent, the skilled person will realise that in a continuous process apparatus, these means will be distributed along the vessel length (in a uniform or non-uniform manner) and in operation will be used in such a way that the optimal solvent composition curve for crystallisation is followed as closely as possible.

Thermal means for controlling the solubility of a solute within a solution will generally be preferred.

In one embodiment of the invention the process is performed in batch mode. In a second embodiment of the invention the process is performed in continuous mode.

## EXAMPLES

The invention is illustrated by reference to the following non-limiting examples:

**EXAMPLE 1 – An apparatus according to the present invention**

An elongate vessel was constructed based on four modules each of which had its own temperature control jacket. The construction of the apparatus was such that it could be operated as a single unit (4 modules) or using only some of the modules (e.g. 1, 2 or 3 modules), in either batch or continuous modes. The vessel is illustrated diagrammatically in Figure 1.

Each module is cylindrical, constructed from polished stainless steel, having a length of 740 mm and in internal diameter of 69 mm. A module contains 42 obstacles, also constructed from stainless steel, which are positioned 18 mm from one another with the openings in neighbouring obstacles aligned. Each obstacle has 33 circular openings of 6 mm in diameter. Each obstacle has a FEP non-stick coating.

Temperature control within a module is provided through a double water filled jacket – a primary jacket arranged with liquid flow in a co-current configuration, within which a secondary coil is positioned with liquid flow in a counter-current configuration.

Temperature monitoring is possible at the junctions at the end of the modules and at the middle of the module through temperature measuring devices positioned approximately centrally within the cross-section. Based on temperature readouts, the operation of the water filled jacket on each module could be adapted as necessary to mimic a desired cooling profile (either over time or over the length of the module dependent upon use in batch or continuous mode).

The crystallisation vessel also includes ultrasonic means for initiating crystallisation (Sonicator 4000, Misonix). The ultrasonic device can be located at any position at the ends of the module and can be operated in pulsed or continuous mode.

Oscillatory mixing means were provided by pistons operated using a hydraulic actuator. Both the frequency and stroke of the piston can be varied on demand to achieve optimum mixing conditions and solids suspension with the selected baffle configuration.

The crystallisation vessel also includes pH measurement and adjustment means for initiating crystallisation (Polyclave VP325, Hamilton, GB). The pH device can be located at any position at the ends of the module and can be operated in batch or continuous mode.

The crystallisation vessel also includes measurement and adjustment of dissolved gases means for initiating or measuring crystallisation processes (VisiFerm 3834, Hamilton, GB). The

device can be located at any position at the ends of the module and can be operated in batch or continuous mode.

**EXAMPLE 2 – An apparatus according to the present invention and its use in a batch process**

**Apparatus**

An elongate vessel was constructed based on a single module which had one temperature control jacket.

The module is cylindrical, constructed from glass, having a length of 400 mm and in internal diameter of 69 mm. The module contained 22 obstacles, constructed from stainless steel, which were positioned 18 mm from one another with the openings in neighbouring obstacles aligned. Each obstacle has 33 circular openings of 6 mm in diameter. Each obstacle has a FEP non-stick coating.

Temperature control within the module is provided through a single water filled jacket.

Temperature monitoring is possible at the ends of the module and at the middle of the module through temperature measuring devices positioned approximately centrally within the cross-section. Based on temperature readouts, the operation of the water filled jacket on the module could be adapted as necessary to mimic a desired cooling profile (either over time or over the length of the module dependent upon use in batch or continuous mode).

The crystallisation vessel also includes ultrasonic means for initiating crystallisation. The ultrasonic device can be located at any position at the ends of the module and can be operated in pulsed or continuous mode. However, the ultrasonic device was not used in the present example.

Oscillatory mixing means were provided by pistons operated using a hydraulic actuator. Both the frequency and stroke of the piston can be varied on demand to achieve optimum mixing conditions and solids suspension with the selected baffle configuration.

**Method**

The apparatus was run in batch mode using the single module.

The module was filled with a suspension of lactose monohydrate (Sigma Aldrich Company), 102g/100g of water, the solubility of lactose monohydrate at 80 °C. The suspension was warmed to 85 °C and the temperature maintained until all of the solid material had dissolved. The temperature was then reduced to 80 °C and allowed to reach steady state. The

characteristics of the oscillatory mixing were adjusted to a frequency of 8 Hz and an amplitude of 11-12 mm peak to peak.

The solution was then cooled (to 10 °C) according to the optimal cooling profile illustrated in Figure 3.

At the end of the 14 hour test, samples of crystallised material were removed, filtered, washed in ethanol and dried in a vacuum oven at 40 °C.

The particle size grading of the crystalline product was determined using a particle size analyser (Malvern Mastersizer 2000). Notably, the particle size distribution obtained through the use of the inventive apparatus (see Figure 4) is narrow compared with the standard material i.e. the lactose monohydrate before processing (see Figure 5). The commonest size is approximately 50 microns.

**Conclusions**

The process according to the invention has the advantage of resulting in a narrow distribution of the sizes of the particles obtained which means in particular the absence of large clumps of materials. by controlling the oscillatory conditions and cooling curve.

The presence of fine particles could be addressed through either optimisation of the process parameters or post-processing (e.g. re-dissolving the fine particles in a subsequent operation).

## EXAMPLE 3 – An apparatus according to the present invention and its use in a continuous process

**Apparatus**

An elongate vessel was constructed consisting of four modules arranged in series, each of which had its own temperature control jacket, as described in Example 1 and illustrated in Figures 1 and 6.

**Method**

The apparatus was operated in a continuous flow mode.

The four modules were filled with a solution of lactose monohydrate (Sigma Aldrich Company), 80g/100g of water, the solubility of lactose monohydrate at 70 °C. All four modules were warmed to 75 °C, the resulting solution was clear and all of the solid material had dissolved. The characteristics of the oscillatory mixing were adjusted to a frequency of 8 Hz and amplitude of 2 mm peak to peak.

In order to initiate the continuous cycle, lactose feed was introduced into the first module using a peristaltic pump (Watson Marlow) at a rate of 50±1 ml/min (equating to a residence time of 3.5 hours). The feed temperature was 75±2 °C. Product was collect in a 5L glass vessel,

The temperature control in each module was set according to the optimal cooling profile calculated from the expression

$$\theta_t = \theta_0 - (\theta_0 - \theta_f)(t/\tau)^4$$

and a residence time of 3.5 hours. Assuming a crystal overall growth rate G of 8.3E-09 m/s (Walstra, Dairy Science and Technology, 2006), this residence time should produce lactose crystals of median size 105 um. The calculated and experimental temperature profiles are illustrated graphically in Figure 7. The experimental time required to achieve this cooling profile was approximately 2 hours

The continuous crystallisation was operated for 21 hours, corresponding to about 6 residence time cycles, to ensure that the system had approached steady state conditions. Samples of crystalline material were removed, filtered, washed in ethanol and dried in an oven at 40 °C. The particle size grading of the crystalline product (after coning and quartering for representative samples) was determined using a particle size analyser (Malvern Mastersizer 2000). Figure 8 shows the results for a sample taken after 21 hours.

The profile illustrates a consistent volume distribution with a span value of 2.318. The medium of the volume distribution D(0.5) is 98 um (a value at which 50% of the sample is smaller and 50% is larger), close to the calculated target value of 105 um.

**Conclusions**

In continuous conditions, an extended run time without encrustation and a consistent product volume distribution have been achieved with particle size characteristics close to a calculated target value. The commercial value of a controllable continuous crystallisation process of the nature described herein is clear.

The presence of fine particles could be addressed through either optimisation of the process parameters or post-processing (e.g. re-dissolving the fine particles in a subsequent operation) or completing the final stages of the crystallisation in a batch vessel as indicated in Figure 6.

**Comparative Example - Preparation of lactose monohydrate crystals in a batch vessel with constant stirring**

A 4 L lactose monohydrate solution (Sigma Aldrich Company, 80g in 100g of deionised water, solubility at 70 °C) was made up in a 5 L jacketed glass vessel and heated to 80 °C. The solution was stirred at 350 rpm (IKA overhead stirrer, KA® Werke GmbH & Co. KG, Germany) with a 2 blade glass anchor stirrer (10 cm across) which was situated 5 cm above the bottom of the container. The solution was allowed to cool down naturally to 22 °C. The resulting crystals were filtered using in a 70 ml filter tube, 5 um PTFE sinter (International Sorbent Technology Ltd, UK) and washed with pure ethanol. The crystals were allowed to dry at 40 °C in an oven for 48 hours. The particle size grading of the crystalline product (after coning and quartering samples) was determined using a particle size analyser (Malvern Mastersizer 2000).

The results illustrated in Figure 9 show a volume distribution span of 2.471 and a medium value D(0.5) of 126 um, a higher volume distribution span of product than observed using the continuous process according to the present invention.

Throughout the specification and the claims which follow, unless the context requires otherwise, the word ‘comprise’, and variations such as ‘comprises’ and ‘comprising’, will be understood to imply the inclusion of a stated integer, step, group of integers or group of steps but not to the exclusion of any other integer, step, group of integers or group of steps.

All documents referred to herein, including patents and patent applications, are incorporated by reference in their entirety.

## Claims

1. A process for the crystallisation of a solute from a solution, said process comprising:

(i) passing the solution through an oscillatory mixed vessel comprising one or more obstacles having a plurality of openings and having means for controlling the solubility of a solute in a solution within said vessel; and

(ii) controlling the solubility of the solute within the solution such that crystallisation occurs.

2. The process according to claim 1, wherein the solute and crystalline solid are chemically unchanged.

3. The process according to either claim 1 or 2, wherein the oscillatory mixed vessel is elongate.

4. The process according to claim 3, wherein the length of the vessel is 25 m or less.

5. The process according to either claim 3 or 4, wherein the length of the vessel is 0.25 m or greater.

6. The process according to any one of claims 3 to 5, wherein the vessel is cylindrical.

7. The process according to claim 6, wherein the diameter of the vessel is 1 m or less.

8. The process according to claim either claim 6 or 7, wherein the diameter of the vessel is 1 cm or more.

9. The process according to any one of claims 1 to 8, wherein the one or more obstacles are stationary relative to the vessel.

10. The process according to any one of claims 1 to 8, wherein the one or more obstacles are movable relative to the vessel.

11. The process according to any one of claims 1 to 10, wherein the one or more obstacles are substantially planar.

12. The process according to any one of claims 1 to 11, wherein the means for controlling the solubility of a solute comprises means for controlling the temperature of the solution.

13. The process according to claim 12, wherein the means for controlling the temperature of the solution comprises a liquid filled jacket.

14. The process according to claim 12, wherein the means for controlling the temperature of the solution comprises an electrical jacket.

15. The process according to any one of claims 1 to 14, wherein the means for controlling the solubility of a solute comprises means for the addition of an anti-solvent.

16. The process according to any one of claims 1 to 15, wherein the vessel is adapted for continuous crystallisation.

17. The process according to claim 16, wherein the vessel comprises at least two sections in which the solubility is independently controlled.

18. The process according to claim 17, wherein the vessel comprises at least three sections in which the solubility is independently controlled.

19. The process according to claim 18, wherein the vessel comprises at least four sections in which the solubility is independently controlled.

20. The process according to any one of claims 17 to 19, wherein the temperature of each section of the vessel is at a lower level than those preceding it.

21. The process according to any one of claims 1 to 14, wherein the vessel is adapted for batch crystallisation.

22. The process according to any one of claims 1 to 21, which comprises the use of ultrasonic means for initiating crystallisation.

23. The process according to any one of claims 1 to 21, which comprises the use of seeding material for initiating crystallisation.

24. Apparatus for the crystallisation of a solute from a solution thereof, said apparatus comprising:

(i) a vessel for the containment of a solution of solute;

(ii) means for the oscillatory mixing of a solution of solute contained within said vessel, the means for the oscillatory mixing comprising one or more obstacles each having a plurality of openings; and

(iii) means for controlling the solubility of a solute within a solution contained within said vessel.

25. The apparatus according to claim 24, wherein the vessel is elongate.

26. The apparatus according to claim 25, wherein the length of the vessel is 25 m or less.

27. The apparatus according to either claim 25 or 26, wherein the length of the vessel is 0.25 m or greater.

28. The apparatus according to any one of claims 25 to 27 wherein the vessel is cylindrical.

29. The apparatus according to claim 28, wherein the diameter of the vessel is 1 m or less.

30. The apparatus according to either claim 28 or 29, wherein the diameter of the vessel is 1 cm or more.

31. The apparatus according to any one of claims 24 to 30, wherein the one or more obstacles are stationary relative to the vessel.

32. The apparatus according to any one of claims 24 to 30, wherein the one or more obstacles are movable relative to the vessel.

33. The apparatus according to any one of claims 24 to 32, wherein the one or more obstacles are substantially planer.

34. The apparatus according to any one of claims 24 to 33, wherein the means for controlling the solubility of a solute comprises means for controlling the temperature of the solution.

35. The apparatus according to claim 34, wherein the means for controlling the temperature of the solution comprises a liquid filled jacket.

36. The apparatus according to claim 34, wherein the means for controlling the temperature of the solution comprises an electrical jacket.

37. The apparatus according to any one of claims 24 to 36, wherein the means for controlling the solubility of a solute comprises means for the addition of an anti-solvent.

38. The apparatus according to any one of claims 24 to 37, which is adapted for a continuous crystallisation process.

39. The apparatus according to claim 38, wherein the apparatus comprises at least two sections in which the solubility is independently controlled.

40. The apparatus according to claim 39, wherein the apparatus comprises at least three sections in which the solubility is independently controlled.

41. The apparatus according to claim 40, wherein the apparatus comprises at least four sections in which the solubility is independently controlled.

42. The apparatus according to any one of claims 24 to 37, which is adapted for a batch crystallisation process.

43. The apparatus according to any one of claims 24 to 42, which comprises ultrasonic means for initiating crystallisation.

44. Use of an apparatus according to any one of claims 24 to 43 for the crystallisation a solute from a solution thereof.

Figure 1

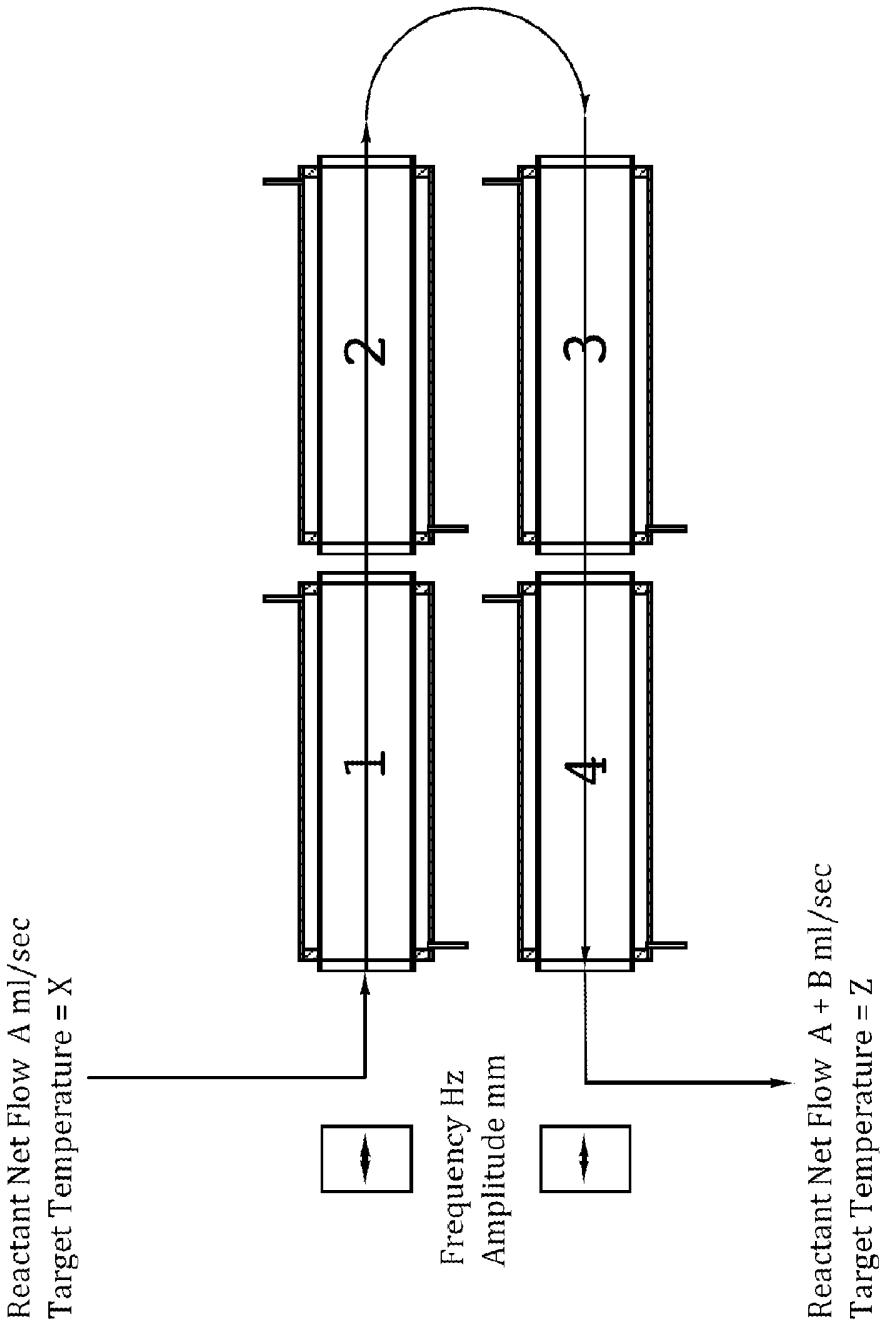
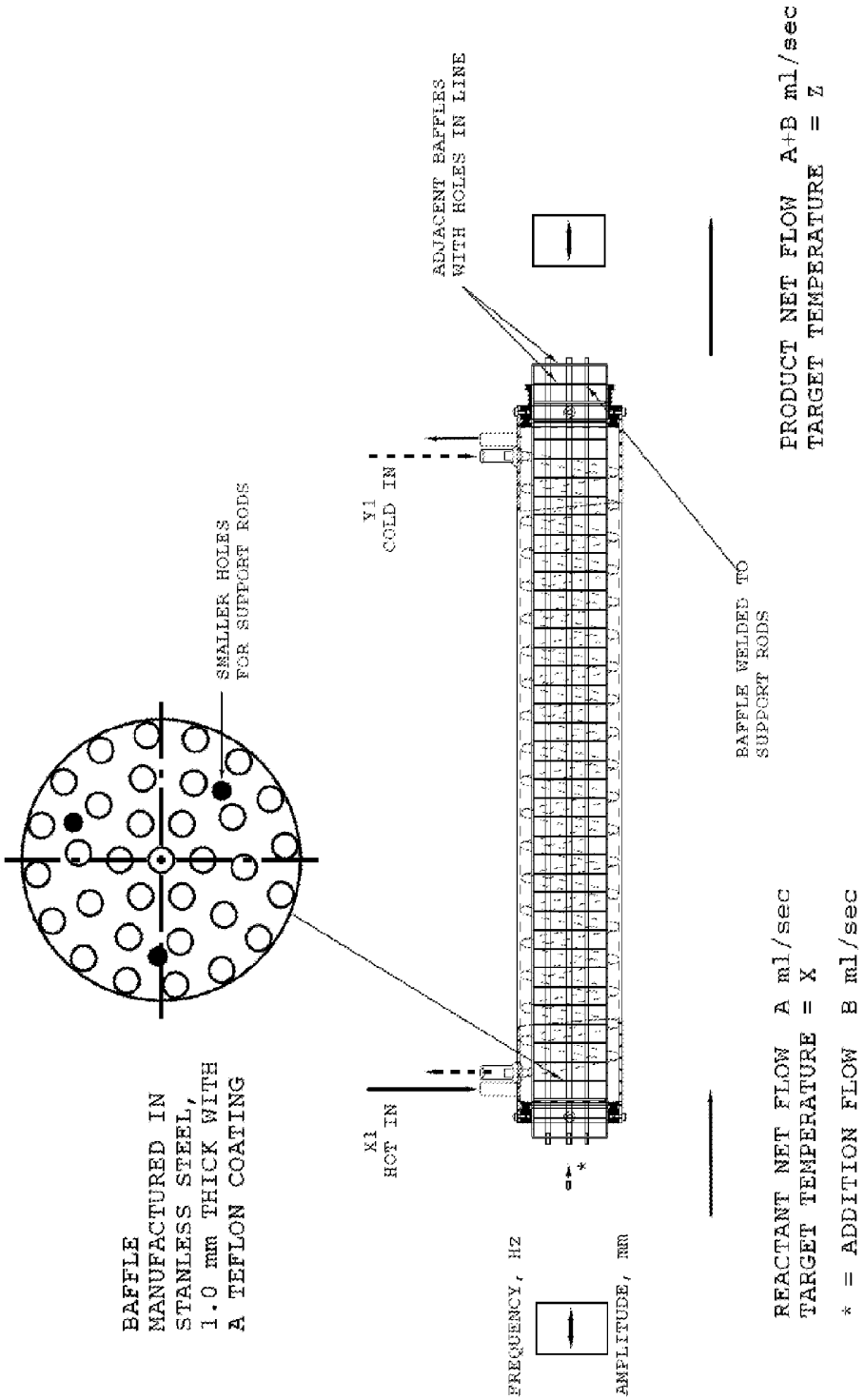

Reactant Net Flow A ml/sec
Target Temperature = X
1
2
3
4
Frequency Hz
Amplitude mm
Reactant Net Flow A + B ml/sec
Target Temperature = Z

Figure 2


BAFFLE
MANUFACTURED IN
STANLESS STEEL,
1.0 mm THICK WITH
A TEFLON COATING
SMALLER HOLES
FOR SUPPORT RODS
X1
HOT IN
Y1
COLD IN
ADJACENT BAFFLES
WITH HOLES IN LINE
BAFFLE WELDED TO
SUPPORT RODS
PRODUCT NET FLOW A+B ml/sec
TARGET TEMPERATURE = Z
REACTANT NET FLOW A ml/sec
TARGET TEMPERATURE = X
* = ADDITION FLOW B ml/sec
FREQUENCY, HZ
AMPLITUDE, MM

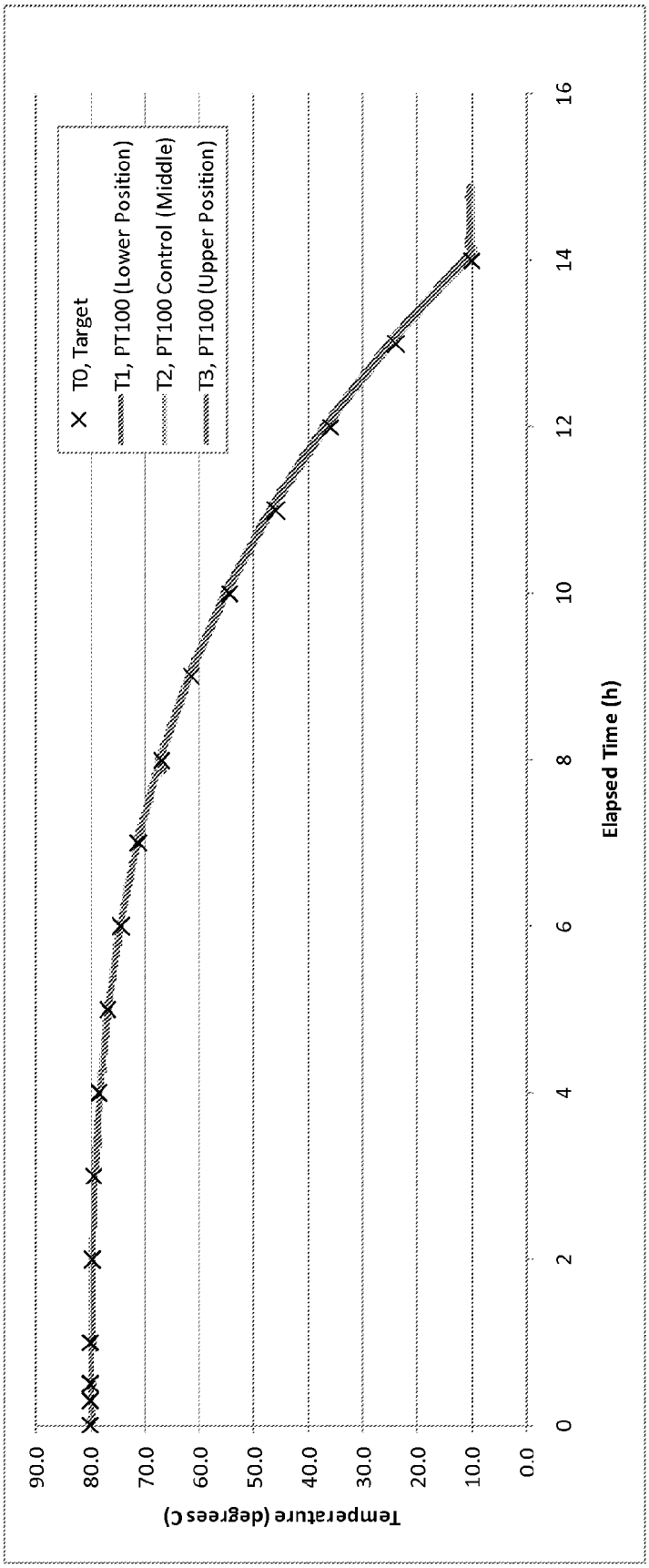
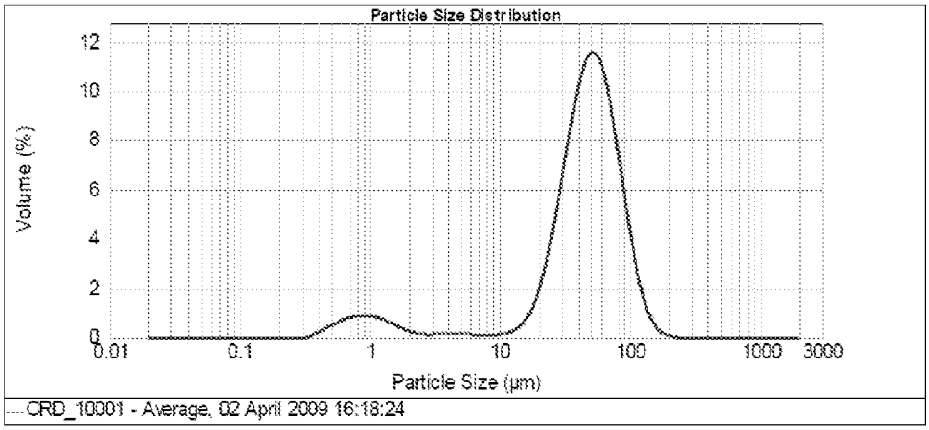

T0, Target
T1, PT100 (Lower Position)
T2, PT100 Control (Middle)
T3, PT100 (Upper Position)
Temperature (degrees C)
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0
2
4
6
8
10
12
14
16
Elapsed Time (h)

Figure 3

## Figure 4

| | | | |
|---|---|---|---|
| **Particle Name:** Lactose | **Accessory Name:** Hydro 2000MU (A) | **Analysis model:** General purpose | **Sensitivity:** Enhanced |
| **Particle RI:** 1.347 | **Absorption:** 0.1 | **Size range:** 0.020 to 2000.000 um | **Obscuration:** 10.40 % |
| **Dispersant Name:** Ethanol | **Dispersant RI:** 1.360 | **Weighted Residual:** 2.703 % | **Result Emulation:** Off |
| **Concentration:** 0.0272 %Vol | **Span :** 1.483 | **Uniformity:** 0.468 | **Result units:** Volume |
| **Specific Surface Area:** 0.645 m²/g | **Surface Weighted Mean D[3,2]:** 9.298 um | **Vol. Weighted Mean D[4,3]:** 50.781 um | |

d(0.1): 17.895 um d(0.5): 47.461 um d(0.9): 88.304 um




| Size (µm) | Volume In % |
|---|---|
| 0.012 | 0.00 |
| 0.011 | 0.00 |
| 0.012 | 0.00 |
| 0.015 | 0.00 |
| 0.017 | 0.00 |
| 0.020 | 0.00 |
| 0.023 | 0.00 |
| 0.026 | 0.00 |
| 0.030 | 0.00 |
| 0.035 | 0.00 |
| 0.040 | 0.00 |
| 0.046 | 0.00 |
| 0.052 | 0.00 |
| 0.060 | 0.00 |
| 0.069 | 0.00 |
| 0.079 | 0.00 |
| 0.091 | 0.00 |
| 0.105 | 0.00 |

| Size (µm) | Volume In % |
|---|---|
| 0.105 | 0.00 |
| 0.120 | 0.00 |
| 0.138 | 0.00 |
| 0.158 | 0.00 |
| 0.182 | 0.00 |
| 0.209 | 0.00 |
| 0.240 | 0.00 |
| 0.275 | 0.00 |
| 0.316 | 0.01 |
| 0.363 | 0.16 |
| 0.417 | 0.31 |
| 0.479 | 0.46 |
| 0.550 | 0.59 |
| 0.631 | 0.70 |
| 0.724 | 0.77 |
| 0.832 | 0.80 |
| 0.955 | 0.79 |
| 1.096 | 0.76 |

| Size (µm) | Volume In % |
|---|---|
| 1.096 | 0.71 |
| 1.258 | 0.61 |
| 1.445 | 0.47 |
| 1.660 | 0.34 |
| 1.905 | 0.22 |
| 2.188 | 0.14 |
| 2.512 | 0.11 |
| 2.884 | 0.12 |
| 3.311 | 0.14 |
| 3.802 | 0.15 |
| 4.365 | 0.15 |
| 5.012 | 0.13 |
| 5.754 | 0.11 |
| 6.607 | 0.09 |
| 7.586 | 0.09 |
| 8.710 | 0.10 |
| 10.000 | 0.11 |
| 11.482 | 0.14 |

| Size (µm) | Volume In % |
|---|---|
| 11.482 | 0.22 |
| 13.183 | 0.39 |
| 15.136 | 0.74 |
| 17.378 | 1.35 |
| 19.953 | 2.28 |
| 22.909 | 3.57 |
| 26.303 | 5.13 |
| 30.200 | 6.85 |
| 34.674 | 8.47 |
| 39.811 | 9.74 |
| 45.709 | 10.41 |
| 52.481 | 10.30 |
| 60.256 | 9.42 |
| 69.183 | 7.91 |
| 79.433 | 6.02 |
| 91.201 | 4.12 |
| 104.713 | 2.47 |
| 120.226 | |

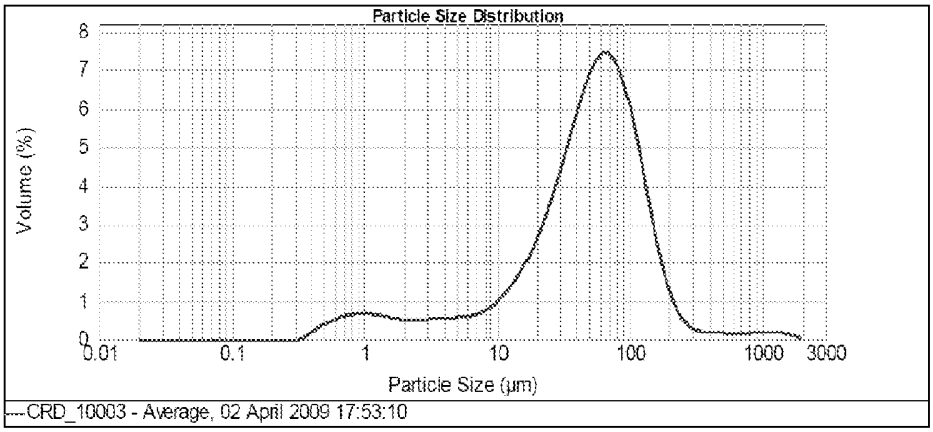
| Size (µm) | Volume In % |
|---|---|
| 120.226 | 1.29 |
| 138.038 | 0.57 |
| 158.489 | 0.22 |
| 181.970 | 0.09 |
| 208.930 | 0.03 |
| 239.883 | 0.03 |
| 275.423 | 0.03 |
| 316.228 | 0.03 |
| 363.078 | 0.03 |
| 416.869 | 0.03 |
| 478.630 | 0.03 |
| 549.541 | 0.03 |
| 630.957 | 0.03 |
| 724.436 | 0.03 |
| 831.764 | 0.03 |
| 954.993 | 0.03 |
| 1096.478 | 0.03 |
| 1258.925 | |

| Size (µm) | Volume In % |
|---|---|
| 1258.925 | 0.00 |
| 1445.440 | 0.00 |
| 1659.587 | 0.00 |
| 1905.461 | 0.00 |
| 2187.762 | 0.00 |
| 2511.886 | 0.00 |
| 2884.032 | 0.00 |
| 3311.311 | 0.00 |
| 3801.894 | 0.00 |
| 4365.158 | 0.00 |
| 5011.872 | 0.00 |
| 5754.399 | 0.00 |
| 6606.934 | 0.00 |
| 7585.776 | 0.00 |
| 8709.636 | 0.00 |
| 10000.000 | 0.00 |

## Figure 5

| | | | |
|---|---|---|---|
| **Particle Name:** Lactose | **Accessory Name:** Hydro 2000MU (A) | **Analysis model:** General purpose | **Sensitivity:** Enhanced |
| **Particle RI:** 1.347 | **Absorption:** 0.1 | **Size range:** 0.020 to 2000.000 um | **Obscuration:** 9.14 % |
| **Dispersant Name:** Ethanol | **Dispersant RI:** 1.360 | **Weighted Residual:** 0.929 % | **Result Emulation:** Off |
| **Concentration:** 0.0223 %Vol | **Span :** 2.460 | **Uniformity:** 0.993 | **Result units:** Volume |
| **Specific Surface Area:** 0.622 m²/g | **Surface Weighted Mean D[3,2]:** 9.640 um | **Vol. Weighted Mean D[4,3]:** 76.787 um | |

d(0.1): 6.271 um d(0.5): 52.271 um d(0.9): 134.833 um




| Size (µm) | Volume In % |
|---|---|
| 0.010 | 0.00 |
| 0.011 | 0.00 |
| 0.013 | 0.00 |
| 0.015 | 0.00 |
| 0.017 | 0.00 |
| 0.020 | 0.00 |
| 0.023 | 0.00 |
| 0.026 | 0.00 |
| 0.030 | 0.00 |
| 0.035 | 0.00 |
| 0.040 | 0.00 |
| 0.046 | 0.00 |
| 0.052 | 0.00 |
| 0.060 | 0.00 |
| 0.069 | 0.00 |
| 0.079 | 0.00 |
| 0.091 | 0.00 |
| 0.105 | 0.00 |

| Size (µm) | Volume In % |
|---|---|
| 0.105 | 0.00 |
| 0.120 | 0.00 |
| 0.138 | 0.00 |
| 0.158 | 0.00 |
| 0.182 | 0.00 |
| 0.209 | 0.00 |
| 0.240 | 0.00 |
| 0.276 | 0.00 |
| 0.318 | 0.01 |
| 0.365 | 0.14 |
| 0.417 | 0.28 |
| 0.479 | 0.37 |
| 0.550 | 0.46 |
| 0.631 | 0.53 |
| 0.724 | 0.58 |
| 0.832 | 0.62 |
| 0.955 | 0.65 |
| 1.096 | 0.69 |

| Size (µm) | Volume In % |
|---|---|
| 1.259 | 0.58 |
| 1.256 | 0.56 |
| 1.445 | 0.52 |
| 1.660 | 0.49 |
| 1.905 | 0.47 |
| 2.188 | 0.46 |
| 2.512 | 0.47 |
| 2.884 | 0.48 |
| 3.311 | 0.50 |
| 3.802 | 0.51 |
| 4.365 | 0.52 |
| 5.012 | 0.53 |
| 5.754 | 0.54 |
| 6.607 | 0.56 |
| 7.586 | 0.66 |
| 8.710 | 0.78 |
| 10.000 | 0.96 |
| 11.482 | 1.17 |

| Size (µm) | Volume In % |
|---|---|
| 11.482 | 1.17 |
| 13.183 | 1.44 |
| 15.136 | 1.77 |
| 17.378 | 2.15 |
| 19.953 | 2.60 |
| 22.909 | 3.11 |
| 26.303 | 3.69 |
| 30.200 | 4.32 |
| 34.674 | 4.97 |
| 39.811 | 5.60 |
| 45.709 | 6.15 |
| 52.481 | 6.56 |
| 60.256 | 6.73 |
| 69.183 | 6.66 |
| 79.433 | 6.27 |
| 91.201 | 5.63 |
| 104.713 | 4.77 |
| 120.226 | 3.79 |

| Size (µm) | Volume In % |
|---|---|
| 120.226 | 3.79 |
| 138.038 | 2.81 |
| 158.489 | 1.94 |
| 181.970 | 1.24 |
| 208.930 | 0.75 |
| 239.883 | 0.43 |
| 275.423 | 0.27 |
| 316.228 | 0.20 |
| 363.078 | 0.17 |
| 416.869 | 0.16 |
| 478.630 | 0.15 |
| 549.541 | 0.14 |
| 630.957 | 0.13 |
| 724.436 | 0.14 |
| 831.764 | 0.17 |
| 954.993 | 0.18 |
| 1096.478 | 0.16 |
| 1258.925 | |

| Size (µm) | Volume In % |
|---|---|
| 1259.925 | 0.16 |
| 1445.440 | 0.12 |
| 1659.587 | 0.07 |
| 1905.461 | 0.02 |
| 2187.762 | 0.00 |
| 2511.886 | 0.00 |
| 2884.032 | 0.00 |
| 3311.311 | 0.00 |
| 3801.894 | 0.00 |
| 4365.158 | 0.00 |
| 5011.872 | 0.00 |
| 5754.399 | 0.00 |
| 6606.934 | 0.00 |
| 7585.776 | 0.00 |
| 8709.636 | 0.00 |
| 10000.000 | |

**Figure 6**

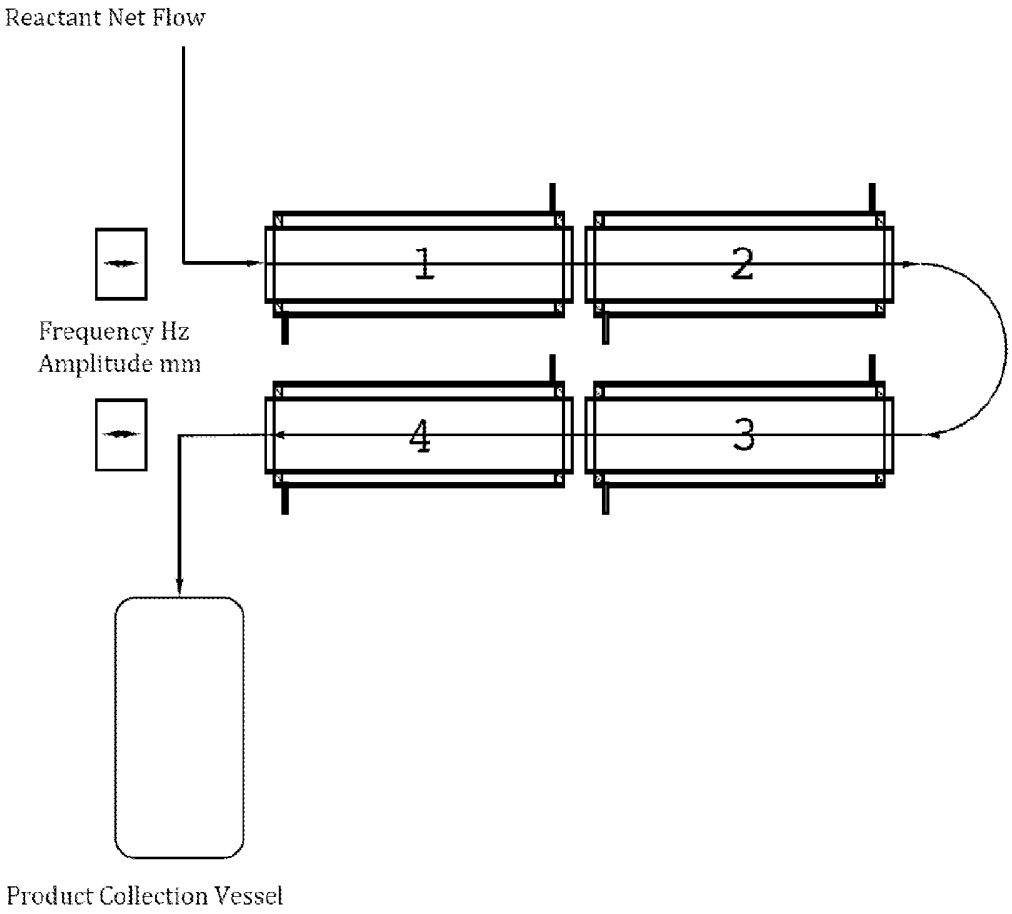
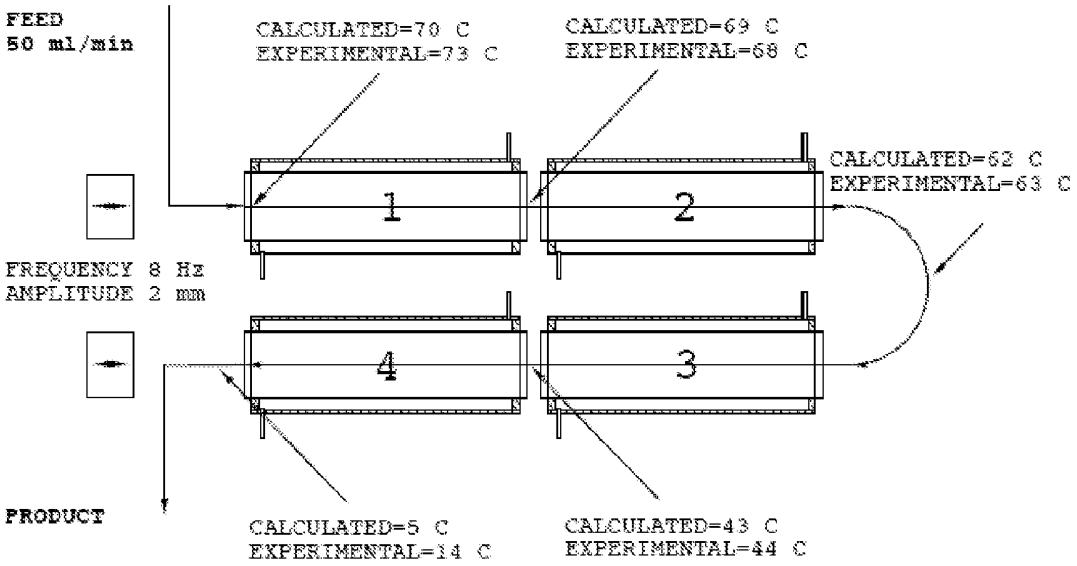
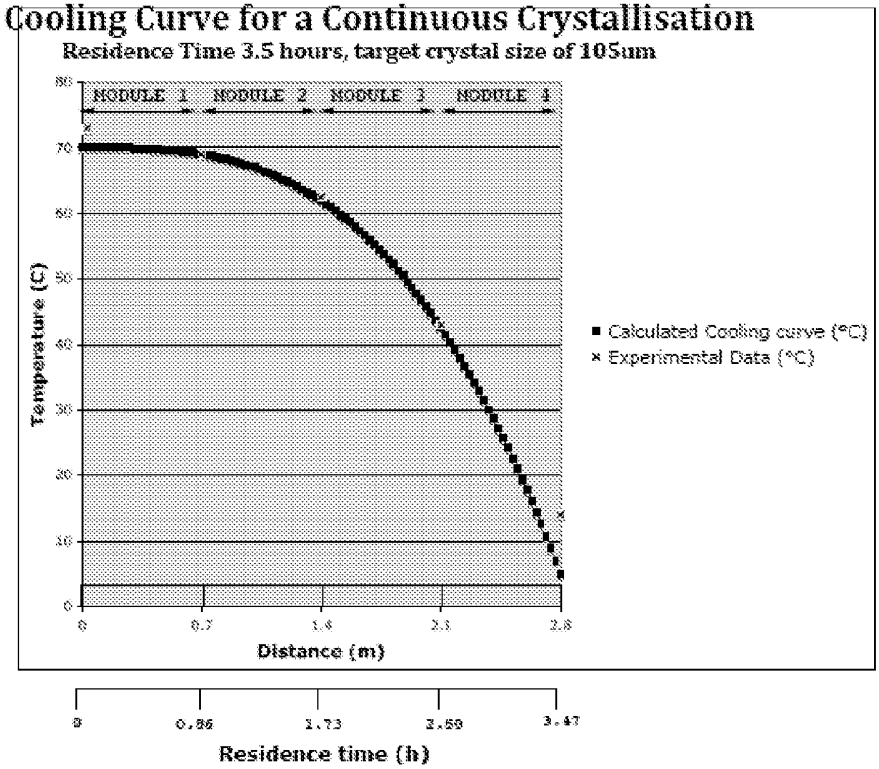

Reactant Net Flow
1
2
Frequency Hz
Amplitude mm
4
3
Product Collection Vessel

Figure 7

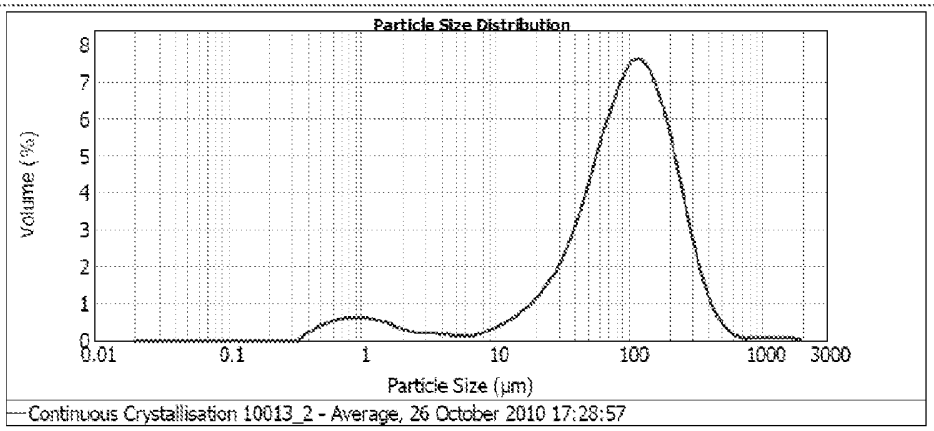

FEED
50 ml/min
CALCULATED=70 C
EXPERIMENTAL=73 C
CALCULATED=69 C
EXPERIMENTAL=68 C
CALCULATED=62 C
EXPERIMENTAL=63 C
1
2
FREQUENCY 8 Hz
AMPLITUDE 2 mm
4
3
PRODUCT
CALCULATED=5 C
EXPERIMENTAL=14 C
CALCULATED=43 C
EXPERIMENTAL=44 C


Cooling Curve for a Continuous Crystallisation
Residence Time 3.5 hours, target crystal size of 105um
MODULE 1
MODULE 2
MODULE 3
MODULE 4
Temperature (C)
Distance (m)
Residence time (h)
Calculated Cooling curve (°C)
Experimental Data (°C)

## Figure 8

| | | | |
|---|---|---|---|
| **Particle Name:** Lactose | **Accessory Name:** Hydro 2000MU (A) | **Analysis model:** General purpose | **Sensitivity:** Enhanced |
| **Particle RI:** 1.347 | **Absorption:** 0.1 | **Size range:** 0.020 to 2000.000 um | **Obscuration:** 12.58 % |
| **Dispersant Name:** Ethanol | **Dispersant RI:** 1.360 | **Weighted Residual:** 0.634 % | **Result Emulation:** Off |
| **Concentration:** 0.0451 %Vol | **Span :** 2.318 | **Uniformity:** 0.753 | **Result units:** Volume |
| **Specific Surface Area:** 0.488 m²/g | **Surface Weighted Mean D[3,2]:** 12.287 um | **Vol. Weighted Mean D[4,3]:** 122.917 um | |

d(0.1): 20.016 um d(0.5): 97.732 um d(0.9): 248.575 um




| Size (um) | Volume In % |
|---|---|
| 0.010 | 0.00 |
| 0.011 | 0.00 |
| 0.013 | 0.00 |
| 0.015 | 0.00 |
| 0.017 | 0.00 |
| 0.020 | 0.00 |
| 0.023 | 0.00 |
| 0.026 | 0.00 |
| 0.030 | 0.00 |
| 0.035 | 0.00 |
| 0.040 | 0.00 |
| 0.046 | 0.00 |
| 0.052 | 0.00 |
| 0.060 | 0.00 |
| 0.069 | 0.00 |
| 0.079 | 0.00 |
| 0.091 | 0.00 |
| 0.105 | 0.00 |

| Size (um) | Volume In % |
|---|---|
| 0.105 | 0.00 |
| 0.120 | 0.00 |
| 0.138 | 0.00 |
| 0.158 | 0.00 |
| 0.182 | 0.00 |
| 0.209 | 0.00 |
| 0.240 | 0.00 |
| 0.275 | 0.00 |
| 0.316 | 0.01 |
| 0.363 | 0.16 |
| 0.417 | 0.27 |
| 0.478 | 0.35 |
| 0.550 | 0.44 |
| 0.631 | 0.50 |
| 0.724 | 0.54 |
| 0.832 | 0.56 |
| 0.955 | 0.56 |
| 1.096 | 0.56 |

| Size (um) | Volume In % |
|---|---|
| 1.096 | 0.52 |
| 1.259 | 0.47 |
| 1.445 | 0.40 |
| 1.660 | 0.33 |
| 1.905 | 0.25 |
| 2.188 | 0.20 |
| 2.512 | 0.17 |
| 2.884 | 0.16 |
| 3.311 | 0.15 |
| 3.802 | 0.14 |
| 4.365 | 0.11 |
| 5.012 | 0.09 |
| 5.754 | 0.09 |
| 6.607 | 0.12 |
| 7.586 | 0.17 |
| 8.710 | 0.25 |
| 10.000 | 0.34 |
| 11.482 | 0.34 |

| Size (um) | Volume In % |
|---|---|
| 11.482 | 0.45 |
| 13.183 | 0.57 |
| 15.136 | 0.71 |
| 17.378 | 0.86 |
| 19.953 | 1.09 |
| 22.909 | 1.35 |
| 26.303 | 1.66 |
| 30.200 | 2.05 |
| 34.674 | 2.52 |
| 39.811 | 3.07 |
| 45.709 | 3.69 |
| 52.481 | 4.35 |
| 60.256 | 5.03 |
| 69.183 | 5.66 |
| 79.433 | 6.24 |
| 91.201 | 6.65 |
| 104.713 | 6.85 |
| 120.226 | 6.85 |

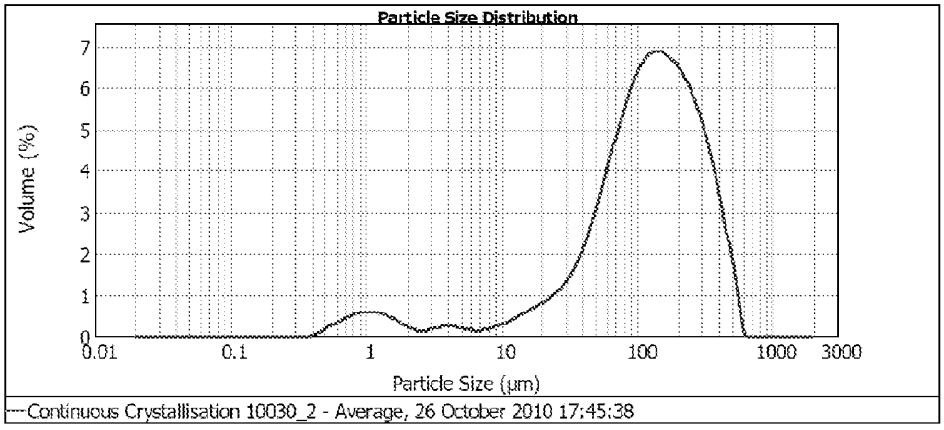
| Size (um) | Volume In % |
|---|---|
| 120.226 | 6.82 |
| 138.038 | 6.53 |
| 158.489 | 6.00 |
| 181.970 | 5.28 |
| 208.930 | 4.41 |
| 239.883 | 3.51 |
| 275.423 | 2.65 |
| 316.228 | 1.93 |
| 363.078 | 1.38 |
| 416.869 | 0.98 |
| 478.630 | 0.70 |
| 549.541 | 0.50 |
| 630.957 | 0.36 |
| 724.436 | 0.26 |
| 831.764 | 0.19 |
| 954.993 | 0.14 |
| 1096.478 | 0.10 |
| 1258.925 | 0.07 |

| Size (um) | Volume In % |
|---|---|
| 1258.925 | 0.05 |
| 1445.440 | 0.05 |
| 1659.587 | 0.03 |
| 1905.461 | 0.01 |
| 2187.762 | 0.00 |
| 2511.886 | 0.00 |
| 2884.032 | 0.00 |
| 3311.311 | 0.00 |
| 3801.894 | 0.00 |
| 4365.158 | 0.00 |
| 5011.872 | 0.00 |
| 5754.399 | 0.00 |
| 6606.934 | 0.00 |
| 7585.776 | 0.00 |
| 8709.636 | 0.00 |
| 10000.000 | 0.00 |

## Figure 9

| | | | |
|---|---|---|---|
| **Particle Name:** Lactose | **Accessory Name:** Hydro 2000MU (A) | **Analysis model:** General purpose | **Sensitivity:** Enhanced |
| **Particle RI:** 1.347 | **Absorption:** 0.1 | **Size range:** 0.020 to 2000.000 um | **Obscuration:** 12.13 % |
| **Dispersant Name:** Ethanol | **Dispersant RI:** 1.360 | **Weighted Residual:** 2.167 % | **Result Emulation:** Off |
| **Concentration:** 0.0528 %Vol | **Span :** 2.471 | **Uniformity:** 0.744 | **Result units:** Volume |
| **Specific Surface Area:** 0.365 m²/g | **Surface Weighted Mean D[3,2]:** 16.459 um | **Vol. Weighted Mean D[4,3]:** 156.725 um | |

d(0.1): 25.279 um d(0.5): 125.871 um d(0.9): 336.258 um




| Size (µm) | Volume In % |
|---|---|
| 0.010 | 0.00 |
| 0.011 | 0.00 |
| 0.013 | 0.00 |
| 0.015 | 0.00 |
| 0.017 | 0.00 |
| 0.020 | 0.00 |
| 0.023 | 0.00 |
| 0.026 | 0.00 |
| 0.030 | 0.00 |
| 0.035 | 0.00 |
| 0.040 | 0.00 |
| 0.046 | 0.00 |
| 0.052 | 0.00 |
| 0.060 | 0.00 |
| 0.069 | 0.00 |
| 0.079 | 0.00 |
| 0.091 | 0.00 |
| 0.105 | 0.00 |

| Size (µm) | Volume In % |
|---|---|
| 0.105 | 0.00 |
| 0.120 | 0.00 |
| 0.138 | 0.00 |
| 0.158 | 0.00 |
| 0.182 | 0.00 |
| 0.209 | 0.00 |
| 0.240 | 0.00 |
| 0.275 | 0.00 |
| 0.316 | 0.00 |
| 0.363 | 0.00 |
| 0.417 | 0.00 |
| 0.479 | 0.18 |
| 0.550 | 0.28 |
| 0.631 | 0.37 |
| 0.726 | 0.45 |
| 0.832 | 0.51 |
| 0.955 | 0.54 |
| 1.096 | |

| Size (µm) | Volume In % |
|---|---|
| 1.096 | 0.53 |
| 1.259 | 0.48 |
| 1.445 | 0.40 |
| 1.660 | 0.30 |
| 1.905 | 0.20 |
| 2.188 | 0.14 |
| 2.512 | 0.13 |
| 2.884 | 0.16 |
| 3.311 | 0.20 |
| 3.802 | 0.22 |
| 4.365 | 0.20 |
| 5.012 | 0.16 |
| 5.754 | 0.13 |
| 6.607 | 0.13 |
| 7.586 | 0.16 |
| 8.710 | 0.22 |
| 10.000 | 0.30 |
| 11.482 | |

| Size (µm) | Volume In % |
|---|---|
| 11.482 | 0.39 |
| 13.183 | 0.48 |
| 15.136 | 0.57 |
| 17.378 | 0.67 |
| 19.953 | 0.77 |
| 22.909 | 0.91 |
| 26.303 | 1.05 |
| 30.200 | 1.35 |
| 34.674 | 1.89 |
| 39.811 | 2.43 |
| 45.709 | 2.87 |
| 52.481 | 3.29 |
| 60.256 | 3.68 |
| 69.183 | 4.61 |
| 79.433 | 5.22 |
| 91.201 | 5.63 |
| 104.713 | 6.00 |
| 120.226 | |

| Size (µm) | Volume In % |
|---|---|
| 120.226 | 6.00 |
| 138.038 | 6.17 |
| 158.489 | 6.20 |
| 181.970 | 6.12 |
| 208.930 | 5.93 |
| 239.883 | 5.65 |
| 275.423 | 5.26 |
| 316.228 | 4.78 |
| 363.078 | 4.18 |
| 416.869 | 3.41 |
| 478.630 | 2.49 |
| 549.541 | 1.55 |
| 630.957 | 0.84 |
| 724.436 | 0.00 |
| 831.764 | 0.00 |
| 954.993 | 0.00 |
| 1096.478 | 0.00 |
| 1258.925 | |

| Size (µm) | Volume In % |
|---|---|
| 1258.925 | 0.00 |
| 1445.440 | 0.00 |
| 1659.587 | 0.00 |
| 1905.461 | 0.00 |
| 2187.762 | 0.00 |
| 2511.886 | 0.00 |
| 2884.032 | 0.00 |
| 3311.311 | 0.00 |
| 3801.894 | 0.00 |
| 4365.158 | 0.00 |
| 5011.872 | 0.00 |
| 5754.399 | 0.00 |
| 6606.934 | 0.00 |
| 7585.776 | 0.00 |
| 8709.636 | 0.00 |
| 10000.000 | 0.00 |

# INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2010/051821

A. CLASSIFICATION OF SUBJECT MATTER
INV. B01D9/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
B01D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 28 March 2011 | 06/04/2011 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016 | Haderlein, Andreas |

1

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# INTERNATIONAL SEARCH REPORT

International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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| A | US 3 583 856 A (LANDAU JOSEF ET AL) 8 June 1971 (1971-06-08) figure 1 | 1-44 |
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