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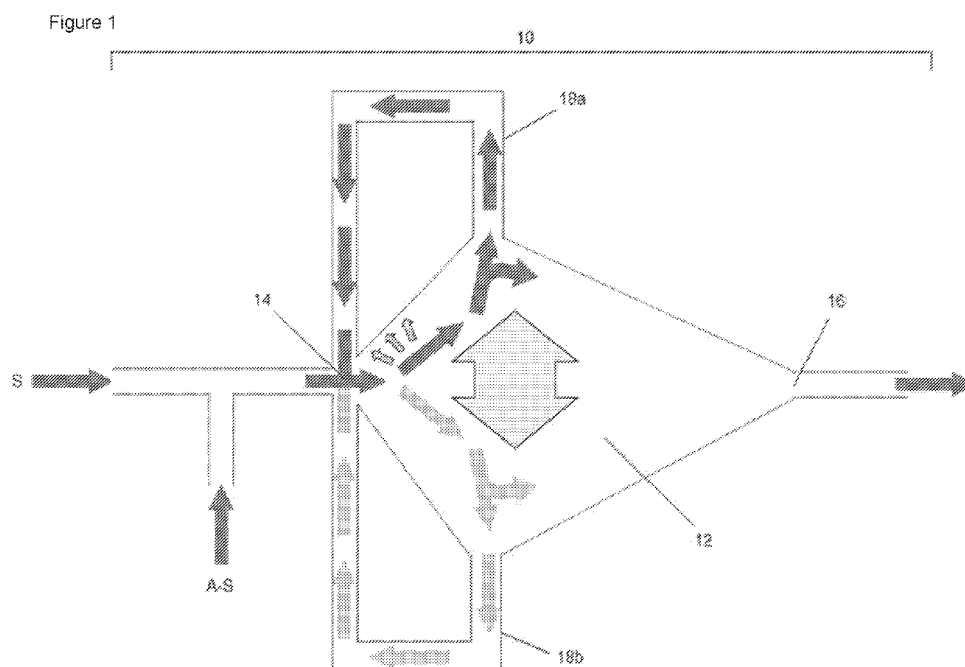
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(54) Title: CRYSTALLISATION METHOD AND APPARATUS



(57) Abstract: A method is provided for preparing a material in a fluidic oscillator (10) which comprises a chamber (12) having an inlet (14) and an outlet (16), and at least two feedback arms (18 a,b) through which fluid may pass from the chamber to the inlet to impart an oscillating flow onto a fluid as it is passed through the inlet. The method comprises passing a solution of the material, or a precursor to the material, through the inlet into the chamber; and precipitating the material in the chamber.



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CRYSTALLISATION METHOD AND APPARATUS

Field of the Invention

5 The present invention relates to a method for preparing a material. In particular, the invention relates to a method in which a fluidic oscillator is used to precipitate a material, such as a crystalline material, from a solution. The invention also relates to a fluidic oscillator apparatus which is suitable for carrying out such methods.

10 Background to the Invention

Crystallisation is an important step in the pharmaceutical and fine chemical industries, as it allows for increases in the purity of a material and may help to create particles. Many organic molecules in the pharmaceutical and fine chemical sectors are produced via
15 crystallisation. The quality of a crystalline product may be assessed by looking for variations in crystal habit, crystal form and crystal size distribution (CSD), characteristics which are crucial for downstream manufacturing processes as well as product performance. For example, medicinal properties like bioavailability and stability for a drug; rate of detonation for explosives; and activity and selectivity for catalysts can all be
20 affected by variations in the characteristics of a crystalline product.

The above-mentioned characteristics of crystalline products are dependent on:

- i. Spatio-temporal variation of super-saturation: this may be controlled by mixing, heat transfer, circulation time or residence time distributions and
25 different ways of realising super-saturation, for example, by cooling, using an anti-solvent, evaporation and combinations thereof;
- ii. Nucleation (primary and secondary) and growth kinetics; and
- iii. Physico-chemical properties: such as solubility, heat of crystallization, viscosity, density, surface charges, agglomeration and breakage
30 characteristics.

It is therefore essential, where possible, to control these parameters so that the desired characteristics of a crystalline product are obtained, with minimal variation in product

quality.

Typically, crystallisation is carried out in batch mode in mechanically agitated vessels (crystallisers). However, batch crystallisation techniques can suffer from problems such as poor utilisation of equipment, high maintenance costs and batch to batch variability. Moreover, batch processing also generally offers poor control on the CSD requiring an additional energy intensive milling operation to achieve target product size distributions. Batch processes can also be slow to adapt to changing market demands, for example, a need for larger or smaller particle sizes. Industries have therefore been driven towards continuous crystallisation processes.

Continuous crystallisation processes take place under steady state, and offer the potential for improvements in crystalline product quality control (such as control of CSD and polymorphic form), size of equipment footprint and energy and labour costs. Improvements in product quality can also simplify downstream processes such as filtration, and particle size modifying steps. Commonly used continuous crystallisers include stirred tanks (single or cascade) and tubular crystallisers with different types of agitation (for example oscillatory baffle crystalliser).

Despite progress in recent years, the existing methods for continuous crystallisation suffer from a number of limitations. For instance, the continuous stirred crystallisers suffer from broad residence time distribution – leading to large CSD – and limited heat transfer and mixing abilities. Large variations in shear stress and turbulent intensity within large stirred crystallisers can often lead to severe issues on scale-up. Whilst tubular crystallisers offer the possibility of multiple additions of anti-solvent and multi-jacket cooling, these devices suffer from undesired blockages which often occur because of accumulation and agglomeration of particles. Possible workarounds to address this problem often involve complicated and moving machinery (for example, oscillating baffle crystalliser) or, in some cases, even the addition of a second immiscible phase which wets tube walls and encases the crystallising phase.

Thus, there is a need for methods for producing materials which address one or more of these problems. In particular, there is a need for methods in which super-saturation is

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achieved throughout the solution, for example, as a result of fast mixing and fast cooling. There is also a need for methods in which the residence time distribution may be controlled, so as to obtain materials with the desired product characteristics.

5 Fluidic oscillators were developed almost 50 years ago. There has been a renewed interest in fluidic oscillators in recent years with the advent of microfluidics.

Fluidic oscillators exploit the Coanda effect, that is, the tendency of a jet of fluid to follow an adjacent flat or curved surface. A fluidic oscillator will typically comprise a chamber
10 having an inlet and an outlet, and at least two feedback arms through which fluid may pass from the chamber to the inlet to impart an oscillating flow onto a fluid as it is passed through the inlet.

In use, a jet of fluid is introduced into the chamber, some of which will adhere to a first
15 wall adjacent to the inlet and enter a first feedback arm. The fluid in the first feedback arm is recycled and reintroduced at the inlet in a direction which pushes the main inlet jet away from the first wall, to a second wall adjacent to the inlet on the other side of the chamber from the first wall. Here, the fluid enters a second feedback arm. The fluid in the second feedback arm is recycled and reintroduced at the inlet in a direction which
20 pushes the main inlet jet away from the second wall, back towards to first wall. In this way, fluid which is recycled through the feedback arms imparts an oscillating flow onto the jet of fluid passing through the inlet. More than two feedback arms may be positioned around the inlet to further control the oscillating jet flow of fluid through the inlet.

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Summary of the Invention

The present invention is based on the surprising discovery that a fluidic oscillator may be used in a method for preparing a material in which the material is precipitated from a
30 supersaturated solution or as a result of a precipitation reaction.

Thus, the present invention provides a method for preparing a material in a fluidic oscillator which comprises a chamber having an inlet and an outlet, and at least two

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feedback arms through which fluid may pass from the chamber to the inlet to impart an oscillating flow onto a fluid as it is passed through the inlet. The method comprises:

- a) passing a solution of the material, or a precursor to the material, through the inlet into the chamber; and
- 5 b) precipitating the material in the chamber.

The present invention further provides an apparatus for precipitating a material. The apparatus comprises:

- 1) a fluidic oscillator which comprises:
 - 10 a chamber having an inlet and an outlet and containing precipitated material, and at least two feedback arms through which fluid may pass from the chamber to the inlet to impart an oscillating flow onto a fluid as it is passed through the inlet; and
 - 2) a vessel connected to the inlet and containing a solution of the material, or a
- 15 precursor to the material, that is present in the chamber.

Also provided is the use of a fluidic oscillator in a method for precipitating a material from a solution.

20 Brief Description of the Drawings

Figure 1 is a cross-sectional diagram of a fluidic oscillator that may be used according to the present invention. More specifically, the diagram shows a fluidic oscillator (10) comprising a chamber (12) having an inlet (14) and an outlet (16), and two feedback
25 arms (18a, 18b) passing from the chamber (12) to the inlet (14). In use, a solution (S) comprising dissolved material is combined with anti-solvent (AS) before being passed through the inlet (14) into the chamber (12). Some of the solution passes into a first feedback arm (18a) and is recycled to the inlet (14) where it pushes the solution (S) passing through the inlet (14) towards the second feedback arm (18b). Solution recycled
30 via the second feedback arm (18b) then pushes the solution (S) back to the first feedback arm (18a). Thus, the feedback arms (18a, 18b) impart an oscillating flow onto the solution (S) as it passes through the inlet (14). Solution (S) comprising precipitated material is removed from the chamber (12) via the outlet (16).

Figure 2 is a cross-sectional diagram of fluidic oscillators arranged in series. More specifically, the diagram shows four fluidic oscillators (10, 20, 30, 40) linked in series. The fluidic oscillators (10, 20, 30, 40) are linked by a connection between the outlet (26) of one fluidic oscillator (20) to the inlet (34) of the following fluidic oscillator (30). Anti-solvent (AS) is added to the solution (S) before it passes through the inlet of the first fluidic oscillator (10) in the series. Valves control the addition of further anti-solvent before the inlets (34) of the remaining fluidic oscillators (20, 30, 40) in the series.

10 Figure 3 is a diagram showing cross-sections of fluidic oscillators having a variety of internal configurations. The cross-sections are taken through the two-dimensional plane which contains the inlet, outlet and points at which the two feedback arms meet the chamber. The diagram shows configurations WS and SL having a kite-shaped cross-section, but with the walls that extend from the inlet and outlet (and which sit within the
15 two-dimensional plane containing the inlet, outlet and points at which the feedback arms meets the chamber) tapering at different angles (θ). Configuration WS is preferred, and has a larger taper than configuration SL. Configuration OD has a cross-section based on an isosceles trapezium, and further comprises a kite-shaped wedge in the chamber.

20 Figure 4 shows results from computational fluid dynamics simulations of a fluidic oscillator. Specifically, Figure 4a shows results from simulations of the oscillations observed in a fluidic oscillator (expressed in terms of Frequency, f_z , and Strouhal number, St) across a range of flows (expressed in terms of Reynolds number, Re). Figure 4b shows results from simulations of the flow rate through the feedback arms
25 (expressed in terms of dimensionless fluctuating energy, ξ , and ratio of inlet flow rate, ϕ) across a range of flows in each of the fluidic oscillators depicted in Figure 3. Figure 4c shows results from simulations of the heat transfer (expressed in terms of Nusselt number, Nu) observed across a range of flows in each of the fluidic oscillators depicted in Figure 3, and a conventional straight pipe. Figure 4d shows results from simulations
30 of residence time distribution (θ representing time) in a fluidic oscillator operated at two different flow rates and a conventional continuous stirred-tank reactor and plug flow reactor.

Figure 5 is a cross-sectional diagram showing the geometries (in mm) of a preferred fluidic oscillator for use in the present invention.

Figure 6 shows scanning electron microscope images of paracetamol crystals that were preparing in a fluidic oscillator using a method of the present invention. Image a) was obtained at 250 times magnification, image b) was obtained at 500 times magnification and image c) was obtained at 1000 times magnification.

Figure 7 is a differential scanning calorimetry thermogram of the paracetamol crystals that were prepared in a fluidic oscillator using a method of the present invention.

Figure 8 is a scanning electron microscope image of crystalline nano-catalyst particles obtained in a precipitation reaction that was carried out in a fluidic oscillator using a method of the present invention.

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Figure 9 is an X-ray powder diffraction pattern of the crystalline nano-catalyst particles obtained in a precipitation reaction that was carried out in a fluidic oscillator using a method of the present invention.

20 Detailed Description of the Invention

The fluidic oscillators used in the present invention comprise a chamber having an inlet and an outlet, and feedback arms through which fluid may pass from the chamber to the inlet to impart an oscillating flow onto a fluid as it is passed through the inlet.

25

An advantage of using a fluidic oscillator, as opposed to a conventional stirred tank or an oscillating baffle crystalliser, is that it does not contain any moving parts. In other words, no mechanical agitation occurs during use of the fluidic oscillator. In spite of this, a very high degree of mixing is achieved as a result of the oscillating fluid flow through the inlet to the fluidic oscillator chamber.

30

According to a further advantage of using a fluidic oscillator in accordance with the present invention is that the process can be operated without the need for external

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energy sources such as, for example, electromagnetic radiation (for example microwaves or infrared).

According to the present invention, a material is prepared in a fluidic oscillator by a method in which a solution of the material, or a solution of a precursor to the material is passed through the inlet into the chamber. Material is then precipitated in the chamber.

The material that is prepared using the method of the present invention may be any solid material that is capable of being dissolved in a solvent, or any solid material that is capable of being prepared in a precipitation reaction. The method of the present invention is particularly suitable for preparing materials which benefit from the high levels of quality control associated with the use of the fluidic oscillator, such as therapeutic agents (including active pharmaceutical ingredients (APIs) and drugs), dyes and pigments, catalysts and explosives. The method is particularly suitable for preparing nano-materials, including nano-catalysts.

Any liquid solvent may be used to prepare the solution, provided that it is capable of forming a supersaturated solution with the material. Common solvents include water and alcohols (for example methanol and ethanol).

20

The solution may be passed through the inlet by any means, provided that the solution passes into the chamber with an oscillating flow. The solution will typically be introduced into the chamber in the form of a jet.

25 The solution is preferably passed through the inlet at a flow such that the Reynolds number is at least 250, preferably at least 400, and more preferably at least 500. The solution may be passed through the inlet at a flow such that the Reynolds number is up to 10,000, preferably up to 5,000, and more preferably up to 2,500. Thus, the solution may be passed through the inlet at a flow such that the Reynolds number may be from 30 250 to 10,000, preferably from 400 to 5,000, and more preferably from 500 to 2,500.

Reynolds number is a dimensionless parameter which is well known in the art as an indicator of flow. It is defined as a ratio of the product of hydraulic diameter (equal to

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diameter where the inlet has a circular cross-section, as will typically be the case), superficial velocity (equal to flow rate of the solution through the inlet (e.g. measured using a metering pump) divided by the cross-sectional area of the inlet) and density of the solution (e.g. measured according to ASTM D792-13) to dynamic viscosity of the solution (e.g. measured according to ASTM D445-17a).

In some instances, a solution of the material (rather than a precursor to the material) is passed through the inlet into the chamber. In these instances, precipitation may occur because the solution is present in the chamber as a supersaturated solution.

10 Supersaturated solutions are well-known in the art as unstable systems having a greater concentration of a material in solution than would exist at equilibrium.

The supersaturated state may be brought about in a number of different ways. For example, the method of the present invention may comprise adding anti-solvent to the solution so that the solution becomes supersaturated. Anti-solvents are well-known as solvents in which a particular product (in this case, the material) has low, or preferably substantially no, solubility. Thus, the addition of anti-solvent to the solution of material will induce precipitation of the material.

20 The anti-solvent is preferably added to the solution before the solution is passed through the inlet. This enables the anti-solvent to be thoroughly mixed into the solution as a result of the oscillating flow of the solution through the inlet. The anti-solvent may be added to the solution via a Y- or T-joint upstream of the inlet. The anti-solvent may also be added to the solution in the chamber of the fluidic oscillator, though this is less preferred.

The ratio by volume of solution to anti-solvent may be at least 0.02 : 1, preferably at least 0.05 : 1, and more preferably at least 0.1 : 1. The ratio by volume of solution to anti-solvent may be up to 50 : 1, preferably up to 20 : 1, and more preferably up to 10 : 1.

30 Thus, the ratio by volume of solution to anti-solvent may be from 0.02 : 1 to 50 : 1, preferably from 0.05 : 1 to 20 : 1, and more preferably from 0.1 : 1 to 10 : 1.

The method of the present invention may comprise cooling the solution so that the

solution becomes supersaturated. Cooling may be achieved by direct contact cooling of the solution, or by convective cooling.

Direct contact cooling can be achieved by using anti-solvent with a temperature which is 5 lower than the temperature of the solution before the anti-solvent has been added to it. The temperature of the anti-solvent may be at least 0.5 °C, preferably at least 1 °C, and more preferably at least 2 °C lower than the temperature of the solution before the anti-solvent has been added to it. The temperature of the anti-solvent may be up to 30 °C, preferably up to 20 °C, and more preferably up to 10 °C lower than the temperature of 10 the solution before the anti-solvent has been added to it. Thus, the temperature of the anti-solvent may be from 0.5 to 30 °C, preferably from 1 to 20 °C, and more preferably from 2 to 10 °C lower than the temperature of the solution before the anti-solvent has been added to it.

15 Direct contact cooling may also be achieved by (convectively) cooling the solution that is recycled through the feedback arms, for example by using cooling jackets on the feedback arms. The recycled fluid then (directly) cools the solution as it imparts an oscillating flow onto the solution passing through the inlet.

20 Convective cooling may be achieved by maintaining a lower temperature in the chamber than the solution that is passed through the inlet. The chamber may be at least 0.5 °C, preferably at least 1 °C, and more preferably at least 2 °C cooler than the temperature of the solution at the inlet. The chamber may be up to 30 °C, preferably up to 20 °C, and more preferably up to 10 °C cooler than the temperature of the solution at the inlet. 25 Thus, the chamber may be from 0.5 to 30 °C, preferably from 1 to 20 °C, and more preferably from 2 to 10 °C cooler than the solution at the inlet.

The temperature in the chamber may be controlled by cooling jackets. Thus, in some embodiments, cooling jackets are present on the outside of the chamber, for example, 30 covering at least 50 %, preferably at least 60 %, and more preferably at least 70 % of the surface area of the chamber. In some embodiments, cooling jackets are present on the feedback arms.

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Different mechanisms for bringing about a supersaturated state in the solution may be combined to enhance the efficacy of the precipitation process. For example, anti-solvent addition and cooling (such as direct and/or convective) may preferably be used together.

5 In other instances, a solution of a precursor to the material (rather than a solution of the material) is passed through the inlet into the chamber, and the material is precipitated in the chamber as the result of a precipitation reaction. Precipitation reactions are well-known in the art as reactions in which the reagents are soluble, but the product is insoluble, in the solvent being used for the reaction.

10

The precipitation reaction may be brought about by adding a reagent to the solution which is capable of reacting with the precursor to form the material. As described in connection with the anti-solvent, the reagent is preferably added to the solution before the solution is passed through the inlet. This enables the reagent to be thoroughly mixed
15 into the solution as a result of the oscillating flow of the solution through the inlet. The reagent may be added to the solution via a Y- or T-joint upstream of the inlet. The reagent may also be added to the solution in the chamber of the fluidic oscillator, though this is less preferred.

20 Where a precipitation reaction is carried out, the chamber may be cooled (for example as described above) or it may be heated. This will depend on the conditions required for the precipitation reaction to proceed.

During the method of the present invention, some of the solution that is introduced into
25 the chamber is recycled via the feedback arms in order to impart an oscillating flow onto the solution that is being passed through the inlet.

The ratio by volume of solution that passes through the feedback arms to solution passed through the inlet may be at least 1 : 100, preferably at least 3 : 100, and more
30 preferably at least 5 : 100. The ratio by volume of solution that passes through the feedback arms to solution passed through the inlet may be up to 70 : 100, preferably up to 50 : 100, and more preferably up to 30 : 100. Thus, the ratio by volume of solution that passes through the feedback arms to solution passed through the inlet may be from

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1 : 100 to 70 : 100, preferably from 3 : 100 to 50 : 100, and more preferably from 5 : 100 to 30 : 100.

The feedback arms that are present in the fluidic oscillator help to control the particle size distribution of the materials that are precipitated therein. Without wishing to be bound by theory, this is believed to be because smaller particles of precipitated material are more likely to be recycled through the feedback arms than larger particles, thereby increasing the residence time and, thus, the size of the smaller particles so that they more closely match the larger particles.

10

However, the feedback arms provide further opportunities for controlling the properties of the material that is prepared in the fluidic oscillator.

In embodiments, the feedback arms are heated, for example, to ensure that the material does not precipitate during recycle of the solution to the inlet. In other embodiments, the feedback arms may be cooled, for example as described above. Heating and cooling jackets may be used to control the temperature in the feedback arms.

In some embodiments, the feedback arms comprise at least three, preferably at least five, and more preferably at least 7, bends such that the path of a fluid through a feedback arm is disrupted. The bends may be curved or they may be in the form of zigzags. Without wishing to be bound by theory, it is believed that bends in a feedback arm encourage preferential recycling of smaller particles.

Other features of the feedback arms may also be adjusted, for example, the length, the shape, the width, the point of connection (such as its location and design) between the feedback arms and the chamber and/or inlet, the internal surface (such as material and texture), *etc.*

The fluidic oscillator used in the present invention comprises at least two feedback arms. Preferably, the fluidic oscillator comprises only two feedback arms. These feedback arms will typically be positioned on opposing sides of the inlet. The use of two feedback arms has been shown to provide excellent mixing characteristics across flow rates. More

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than two feedback arms may also be used, though this is less preferred.

The chamber used in the fluidic oscillator may be of any shape, provided that a sufficient proportion of the solution introduced into the chamber passes through the feedback arms
5 to impart an oscillating flow onto the solution as it passes through the inlet.

The cross-section of the chamber is preferably a geometric kite, that is, a quadrilateral which comprises two pairs of equal-length sides that are adjacent to each other. The inlet and the outlet may be positioned at the junction of the equal-length sides. The
10 feedback arms may be positioned at the junction of sides of different lengths. It will be appreciated that cross-section is used to denote a two-dimensional plane which contains the inlet, outlet and point at which the feedback arms meet the chamber. Without wishing to be bound by theory, it is believed that a kite-shaped cross-section provides excellent circulation of the solution through the fluidic oscillator and, therefore, a good
15 particle size distribution with minimal clogging.

The 'front' and 'back' of the chamber, that is, the walls of the chamber sitting in front and behind the cross-section, may be flat or curved.

20 One or more wedges may be present in the chamber to help direct the flow of solution, though this is generally not required.

The walls of the chamber extending from the inlet are preferably tapered towards the inlet. The angle between the walls extending from the inlet (θ) may be at least 5 °,
25 preferably at least 10 °, and more preferably at least 12 °. The angle between the walls extending from the inlet may be up to 150 °, more preferably up to 120 °, and still more preferably up to 90 °. Thus, the angle between the walls extending from the inlet may be from 5 to 150 °, more preferably from 10 to 120 °, and still more preferably from 12 to 90 °.

30

The walls of the chamber extending to the outlet, for example in a chamber having a kite-shaped cross-section, are preferably tapered towards the outlet. The angle between the walls extending to the outlet (θ') may be at least 3 °, preferably at least 5 °, and more

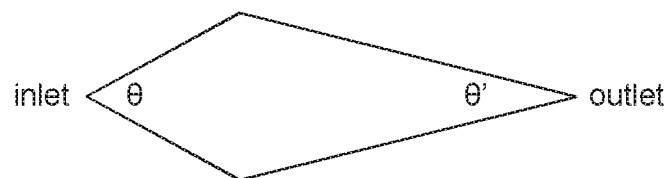
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preferably at least 8° . The angle between the walls extending from the inlet may be up to 130° , more preferably up to 100° , and still more preferably up to 80° . Thus, the angle between the walls extending from the inlet may be from 3 to 130° , more preferably from 5 to 100° , and still more preferably from 8 to 80° .

5

The walls of the chamber extending from the inlet and to the outlet are preferably those falling within a two-dimensional plane which contains the inlet, outlet and point at which the feedback arms meet the chamber. Thus, in the case of a chamber having a kite-shaped cross-section, θ and θ' are identified as follows:

10



The method of the present invention preferably further comprises removing the precipitated material from the chamber through the outlet.

15

The outlet may be connected to a unit in which the precipitated material is further processed, for example, by filtering, drying and/or size modification (such as grinding or agglomerating the precipitated material). However, since the use of a fluidic oscillator enables particle size and particle size distribution to be closely controlled, in some
20 embodiments, the method does not comprise modifying the size of the precipitated material.

The precipitated material will generally be in the form of particles. The particle size distribution is preferably such that at least 60% , preferably at least 75% , and more
25 preferably at least 90% of the particles have a particle size which is equal to the Sauter mean-average diameter of the particles $\pm 50\%$.

The mean particle size, Sauter mean diameter and particle size distribution may be measured using laser diffraction methods. A suitable instrument is a laser diffraction
30 particle size analyser, for example Sympatec HELOS & RODOS dry dispersion unit, Sympatec Instruments, UK. The laser diffraction method may comprise feeding

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approximately 15 to 20 mg of the sample into the analyser under an air pressure of 4 bars at a aspirator speed of around 30 mm/sec (for example using an ASPIROS unit). Counting may be triggered at an optical concentration of one per cent (1 %).

- 5 In preferred embodiments, the material precipitates in a crystalline form (rather than an amorphous form).

The method of the present invention may comprise passing the solution through a single fluidic oscillator, and then processing the material that precipitates in the single fluidic
10 oscillator into a product, for example a pharmaceutical formulation, a catalyst, *etc.* However, in some embodiments, the method comprises passing the solution through two or more fluidic oscillators. The material precipitates in the chamber of at least one, and preferably each, of the fluidic oscillators. By using multiple fluidic oscillators in series, it is believed that a flow close to plug flow may be achieved.

15

The solution may be passed through two fluidic oscillators, or preferably at least three, and more preferably at least four fluidic oscillators. It will be appreciated that the solution will typically comprise some precipitated material once it is passed to the second and any subsequent fluidic oscillators.

20

The fluidic oscillators are preferably linked in series, that is, with the outlet of one fluidic oscillator connected to the inlet of the next fluidic oscillator. The fluidic oscillators may be arranged in a stack so as to provide a compact precipitation unit.

- 25 The use of two or more fluidic oscillators enables greater control over the precipitation process by fine tuning of the conditions in each of the fluidic oscillators. Thus, in embodiments, the conditions in the two or more fluidic oscillators, for example, the temperatures and/or amounts of anti-solvent in the chambers, are preferably not all the same. Preferably, the conditions in each fluidic oscillator are different. In this way, the
30 solution may be maintained in a supersaturated state throughout the series of fluidic oscillators.

For example, the temperature may decrease in successive chambers through which the

solution passes. As a further example, anti-solvent may be added to the solution as it is passed through the two or more fluidic oscillators, for instance each time it is passed through a fluidic oscillator. The anti-solvent is preferably added before the solution is passed through the inlet of each fluidic oscillator. One or more valves may be used to
5 control the addition of the anti-solvent to the fluidic oscillators.

The method of the present invention is preferably carried out as a continuous process, though it may be carried out batch-wise. Where the process is carried out batch-wise, the outlet of the chamber is preferably connected to the inlet of the chamber. In this way,
10 the fluid may be recycled through the fluidic oscillator, for example for a defined period of time or until desired precipitant properties, such as particle size, are obtained.

The use of a fluidic oscillator is advantageous as it enables the quality of the product to be closely controlled. Thus, in embodiments, the method of the present invention
15 comprises:

- (i) monitoring one or more properties of the precipitated material;
- (ii) comparing the one or more properties to target properties; and
- (iii) modifying one or more conditions in the fluidic oscillator where the target properties are not being met.

20

Steps (i) to (iii) may be repeated as part of an iterative feedback process in which the quality of the material that is produced by the method is maintained and/or optimised. The feedback process is preferably an automated feedback process which is controlled by a computer system.

25

The one or more properties of the precipitated material may be selected from: particle size, particle size distribution, particle shape, solid form (such as crystalline, amorphous, polymorphic) and surface morphology.

30 The one or more conditions in the fluidic oscillator that may be modified include: the temperature, concentration and flow rate of the solution that is passed through the inlet; the temperature and flow rate of the anti-solvent; the ratio of solution to anti-solvent; the ratio of solution that passes through the feedback arms to solution passed through the

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inlet; temperature in the feedback arms; temperature in the chamber; and geometry (such as shape, length, *etc.*) of the feedback arms.

For instance, mixing has been found to be fairly independent to flow rate. This means
5 that residence time (and therefore particle size distribution) may be adjusted by adjusting the flow rate through the inlet without significantly impacting the degree of mixing.

The use of a fluidic oscillator is also advantageous because it enables the conditions in the oscillator to be rapidly adjusted to respond to market demand, that is, where the
10 product is suddenly required to possess different properties (for example particle size).

Thus, in embodiments, the method comprises:

- (a) preparing a first precipitated material; and
- (b) modifying one or more conditions in the fluidic oscillator so that a second precipitated material is prepared,

15 wherein one or more properties differ between the first and second precipitated materials.

The one or more properties and one or more conditions may be selected from those listed above in connection with the iterative process.

20

According to the present invention, an apparatus is provided which may be used to carry out the methods disclosed herein. The apparatus comprises a fluidic oscillator (for example as described herein) containing precipitated material in the chamber, and a vessel connected to the inlet and containing a solution of the material, or a solution of a
25 precursor to the material, that is present in the chamber. The vessel may be a storage tank. The vessel may be connected to the inlet via a pipe.

The apparatus may further comprise one or more units for further processing the precipitated material (for example filtering, drying and/or size modifying units as
30 described above), the one or more units being connected to the outlet of the fluidic oscillator.

The apparatus may comprise an area where the precipitated material is collected which

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is connected to the outlet of the fluid oscillator or, where one or more units for further processing the material are used, downstream of the one or more units.

According to the present invention, a fluidic oscillator is used in a method for precipitating
5 a material from a solution, for example, according to a method disclosed herein. The solution may comprise the material or a precursor to the material, such as described above.

The following non-limiting Examples illustrate the present invention.

10

Examples

Example 1: simulations of fluidic oscillator performance

15 Computational fluid dynamics simulations were carried out to determine whether it is viable to use a fluidic oscillator for crystallising materials.

In a first simulation, the oscillations observed in a fluidic oscillator (expressed in terms of Frequency, f_z , and Strouhal number, St) were simulated across a range of inlet flows
20 (expressed in terms of Reynolds number, Re). The relevant definitions are:

$$Re = \frac{\rho u D_H}{\mu}, \text{ where: } D_H = \frac{4 A_{jet}}{P_i} = [m]$$

and:

$$St = \frac{f D_H}{u}$$

where ρ is density of solution, u is superficial velocity at the inlet (ratio of flow rate and
25 cross sectional area of inlet), μ is the dynamic viscosity of the fluid, D_H is hydraulic diameter of inlet, A_{jet} is cross sectional area of inlet, P_i is perimeter of inlet, f is oscillation frequency of jet and St is Strouhal number. The results of the first simulation are shown in Figure 4a. It can be seen that sustained oscillations were observed in the simulation across a wide range of flows. The oscillation frequency was shown to increase linearly
30 with flow. Strouhal number was, however, largely independent of flow, thereby suggesting that the degree of oscillation can be controlled by varying the flow of solution

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through the inlet, without compromising mixing.

In a second simulation, the flow rate through the feedback arms (expressed in terms of dimensionless fluctuating energy, ξ , and ratio of inlet flow rate, ϕ) were simulated across a range of flows (expressed in terms of Reynolds number, Re) in each of the fluidic oscillators depicted in Figure 3 (denoted in Figure 3 as WS, SL and OD). The relevant definition is:

$$\xi = \frac{\text{fluctuating kinetic energy}}{\text{volumetric mean kinetic energy}} = \frac{\frac{1}{2} \left((v'_x)^2 + (v'_y)^2 \right)_i}{\frac{1}{V_R} \int \frac{1}{2} \left(\bar{v}_x^2 + \bar{v}_y^2 \right)_i dV}$$

where v'_x and v'_y are fluctuating velocity in x and y direction respectively, $\bar{v}_x$ and $\bar{v}_y$ are mean velocity in x and y direction respectively and V_R is the volume of the crystallisation chamber. The results of the second simulation are shown in Figure 4b. It can be seen that different flow rates through the feedback arms were simulated for the different oscillators, thereby suggesting that feedback arm geometry may be used as a tool for controlling crystallisation processes.

In a third simulation, the heat transfer (expressed in terms of Nusselt number, Nu) observed across a range of flows (expressed in terms of Reynolds number, Re) was simulated in each of the fluidic oscillators depicted in Figure 3, and a conventional straight pipe. The results of the third simulation are shown in Figure 4c. It can be seen that each of the fluidic oscillators exhibited good heat transfer in the simulation, with excellent heat transfer observed at higher flows as compared to a straight pipe, particularly in the case of the WS and SL fluidic oscillators.

In a fourth simulation, the residence time distribution (θ denoting time) was simulated in a fluidic oscillator operated at two different flow rates and a conventional continuous stirred-tank reactor and plug flow reactor. The results of the fourth simulation are shown in Figure 4d. It can be seen that the residence time distribution, which is a function of the ratio of back flow through the feedback arms with inlet flow rate (among other things), in the fluidic oscillator is shown in the simulation to be close to that observed in a

continuous stirred tank reactor.

The results indicate that it is viable to use a fluidic oscillator for crystallising materials.

5 Example 2: anti-solvent crystallisation of paracetamol

Following the successful results obtained using computational fluid dynamics simulations, a fluidic oscillator was constructed in glass. The fluidic oscillator had the dimensions (in mm) shown in Figure 5 and a depth of 6 mm.

10

Recrystallisation of paracetamol was carried out using the fluidic oscillator.

Acetaminophen (paracetamol) with a purity of >98 % was sourced from Merck. The methanol was of reagent grade with a purity of >99 % sourced from Sigma Aldrich.

15 Deionised water was used as an anti-solvent.

350 g of paracetamol was dissolved in 1 L of methanol. The paracetamol solution was fed to the fluidic oscillator at a rate of 250 ml/min. The deionised water anti-solvent was fed to the crystalliser at a rate of 800 ml/min. The product was collected from the outlet,
20 filtered and dried. The obtained paracetamol crystals were subsequently analysed.

The morphology of the paracetamol crystals was studied using scanning electron microscopy (SEM). Self-adhesive carbon mounts were used to mount samples on aluminium pin stubs (Agar Scientific, Stansted, UK). SEM images of the mounted
25 samples were collected using a FEI Quanta 400 scanning electron microscope (Cambridge UK) under vacuum and XTM microscope control software V 2.3. The images are shown in Figure 6 with image a) obtained at 250 times magnification, image b) obtained at 500 times magnification and image c) obtained at 1000 times magnification.

30

The paracetamol crystals were also analysed using differential scanning calorimetry (DSC) and X-ray powder diffraction (XRPD). DSC was performed using DSC Q2000 from TA instruments. Approximately, 2 to 4 mg of the sample was heated in the sealed

standard aluminium pan from 35 to 250 °C at a heating rate of 10 °C/min under a nitrogen atmosphere. DSC data were analysed using the TA Universal analysis 2000 software, version 4.5A (TA Instruments, Inc.). XRPD was carried out at a scanning range of 5 to 30 ° 2 θ with step size of 0.02 ° and a 1 s per step time by a Philips 5 automated diffractometer. Cu K α radiation was used with a voltage of 40 kV and a current of 35 mA. A DSC thermogram of the paracetamol crystals is shown in Figure 7. The DSC and XRPD analysis confirmed that the paracetamol crystals obtained using the fluidic oscillator were paracetamol Form I.

10 Particle size was assessed using a laser diffraction particle size analyser (Sympatec HELOS & RODOS dry dispersion unit, Sympatec Instruments, UK). Approximately 15 to 20 mg of the sample was fed into the analyser by using an ASPIROS unit, under an air pressure of 4 bars at an aspirator speed of 30 mm/sec. Trigger conditions (vacuum) were at five sec at an optical concentration of one per cent (1 %). The paracetamol
15 crystals had a mean particle size (arithmetic mean volume distribution, X50) of nearly 60 microns and a Sauter Mean Diameter (SMD) of about 15 microns.

Example 3: reactive precipitation of a nano-catalyst

20 Reactive precipitation of a nano-catalyst was carried out using the same fluidic oscillator as was used in Example 2.

Potassium permanganate (KMnO₄) with a purity of >99% was sourced from Alfa Aesar. Maleic acid with a purity of > 99% was sourced from Sigma Aldrich. Deionised water
25 was used as a solvent.

12.65 g of KMnO₄ was dissolved in 0.8 L of deionised water and 3.09 gm of maleic acid was dissolved in 0.2 L of deionised water. This KMnO₄ solution was fed to the crystalliser at a rate of 800 ml/min. The maleic acid solution was fed to the crystalliser at a rate of
30 200 ml/min. The product was collected from the outlet. It was allowed to age for about half an hour, filtered and dried. The obtained nano-catalyst particles were subsequently calcined and analysed.

The morphologies of the nano-catalyst particles were characterised using SEM using a method similar to that disclosed in Example 2. The samples were prepared by mounting a thin layer of the crushed sample onto a specimen stub, with double-sided carbon tape (which provides a drainage path for scanning electron current and acts as an adhesive for the sample). Due to gas molecules interfering with the procedure, the SEM was carried out under vacuum. Images of the samples were taken in the range of 100 to 10,000 times magnification. An SEM image of the crystalline nano-catalyst particles is shown in Figure 8. It can be seen that the particles of similar size and shape were obtained.

10

The nano-catalyst particles were further analysed using XRPD methods. The XRPD patterns were obtained carried out using a PANalytical X'Pert Pro X-ray Diffractometer. The X-ray source was copper (Cu) with a wavelength of 1.5405 Å. A spinning gauge was used *ex-situ* to carry out all the measurements. The diffractograms were recorded from 4 to 75 ° with a step size of 0.017 °. Figure 9 shows XRPD patterns of the nano-catalyst particles. The patterns shows that the nano-catalyst was obtained in a crystalline form.

Claims

1. A method for preparing a material in a fluidic oscillator which comprises a chamber having an inlet and an outlet, and at least two feedback arms through which fluid may pass from the chamber to the inlet to impart an oscillating flow onto a fluid as it is passed through the inlet, said method comprising:
 - passing a solution of the material, or a precursor to the material, through the inlet into the chamber; and
 - precipitating the material in the chamber.
2. The method of Claim 1, wherein a solution of the material is passed through the inlet into the chamber, and the solution is present in the chamber as a supersaturated solution.
3. The method of Claim 2, wherein the method comprises adding anti-solvent to the solution so that the solution becomes supersaturated.
4. The method of Claim 3, wherein:
 - the anti-solvent is added to the solution before the solution is passed through the inlet, for example via a Y- or T-joint;
 - the ratio by volume of solution to anti-solvent passed through the inlet is from 0.02 : 1 to 50 : 1, preferably from 0.05 : 1 to 20 : 1, and more preferably from 0.1 : 1 to 10 : 1; and/or
 - the temperature of the anti-solvent is lower, for example from 0.5 to 30 °C lower, preferably from 1 to 20 °C lower, and more preferably from 2 to 10 °C lower, than the temperature of the solution before the anti-solvent has been added to it.
5. The method of any of Claims 2 to 4, wherein the temperature of the solution that is passed through the inlet is higher than the temperature in the chamber, so that the solution becomes supersaturated in the chamber.

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6. The method of Claim 5, wherein cooling jackets are present on the outside of the chamber, for example covering at least 50 %, preferably at least 60 %, and more preferably at least 70 % of the surface area of the chamber.
7. The method of Claim 1, wherein a solution of a precursor to the material is passed through the inlet into the chamber, and the material is precipitated in the chamber as the result of a precipitation reaction.
8. The method of any of Claims 1 to 7, wherein:
 - the solution is passed through the inlet at a flow such that the Reynolds number is at least 250, preferably at least 400, and more preferably at least 500, and/or the solution is passed through the inlet at a flow such that the Reynolds number is up to 10,000, preferably up to 5,000, and more preferably up to 2,500;
 - and preferably:
 - the solution is passed through the inlet at a flow such that the Reynolds number is from 250 to 10,000, preferably from 400 to 5,000, and more preferably from 500 to 2,500.
9. The method of any of Claims 1 to 8, wherein the ratio by volume of solution that passes through the feedback arms to solution passed through the inlet is from 1 : 100 to 70 : 100, preferably from 3 : 100 to 50 : 100, and more preferably from 5 : 100 to 30 : 100.
10. The method of any of Claims 1 to 9, wherein:
 - the feedback arms comprise at least three, preferably at least five, and more preferably at least 7, bends such that the path of a fluid through a feedback arm is disrupted, and preferably wherein the bends are in the form of zigzags; and/or
 - the feedback arms are heated or cooled.
11. The method of any of Claims 1 to 10, wherein:
 - the cross-section of the chamber is a geometric kite;

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the walls of the chamber extending from the inlet are tapered towards the inlet, and the angle between the walls is preferably from 5 to 150 °, more preferably from 10 to 120 °, and still more preferably from 12 to 90 °; and/or

the walls of the chamber extending to the outlet are tapered towards the outlet.

12. The method of any of Claims 1 to 11, wherein the method further comprises removing precipitated material from the chamber through the outlet.
13. The method of any of Claims 1 to 12, wherein the material precipitates in the form of particles, and the particle size distribution is preferably such that at least 60 %, preferably at least 75 %, and more preferably at least 90 % of the particles have a particle size which is equal to the Sauter mean diameter of the particles $\pm$ 50 %.
14. The method of any of Claims 1 to 13, wherein the method comprises passing the solution through two or more fluidic oscillators, wherein material precipitates in the chamber of at least one, and preferably each, of the fluidic oscillators.
15. The method of Claim 14, wherein:
 - the two or more fluidic oscillators are linked in series;
 - the conditions in the chambers of the two or more fluidic oscillators are not all the same, for instance the temperature decreases in successive chambers through which the solution passes; and/or
 - anti-solvent is added to the solution as it is passed through the two or more fluidic oscillators, and preferably each time the solution is passed through a fluidic oscillator.
16. The method of any of Claims 1 to 15, wherein the method is carried out as a continuous process.
17. The method of any of Claims 1 to 16, wherein the method comprises:
 - (i) monitoring one or more properties of the precipitated material;

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- (ii) comparing the one or more properties to target properties; and
- (iii) modifying one or more conditions in the fluidic oscillator where the target properties are not being met.

wherein steps (i) to (iii) are preferably repeated as part of a feedback process, preferably an automated feedback process.

18. The method of any of Claims 1 to 17, wherein the method comprises:

- (a) preparing a first precipitated material; and
- (b) modifying one or more conditions in the fluidic oscillator so that a second precipitated material is prepared,

wherein one or more properties differ between the first and second materials.

19. The method of Claim 17 or Claim 18, wherein:

the one or more properties of the precipitated material are selected from: particle size, particle size distribution, particle shape, solid form (for example crystalline, amorphous, polymorphic) and surface morphology; and/or

the one or more conditions in the fluidic oscillator that are modified are selected from: the temperature, concentration and flow rate of the solution that is passed through the inlet; the temperature and flow rate of the anti-solvent; the ratio of solution to anti-solvent; the ratio of solution that passes through the feedback arms to solution passed through the inlet; temperature in the feedback arms; temperature in the chamber; and geometry (for example shape, length, etc.) of the feedback arms.

20. The method of any of Claims 1 to 19, wherein:

the material is selected from therapeutic agents, dyes and pigments, catalysts and explosives;

the material is precipitated as a nano-material; and/or

the material precipitates as a crystalline material.

21. An apparatus for precipitating a material, for instance using a method as defined in any of Claims 1 to 20, said apparatus comprising:

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a fluidic oscillator which comprises:

a chamber having an inlet and an outlet and containing precipitated material, and

at least two feedback arms through which fluid may pass from the chamber to the inlet to impart an oscillating flow onto a fluid as it is passed through the inlet, and

a vessel connected to the inlet and containing a solution of the material, or a precursor to the material, that is present in the chamber.

22. Use of a fluidic oscillator in a method for precipitating a material from a solution.
23. Use of a fluidic oscillator for controlling particle size and/or particle size distribution in a method for precipitating a material from a solution.
24. The use of Claim 22 or Claim 23, wherein the solution comprises the material or a precursor to the material.
25. The use of any one of Claims 22 to 24, wherein the fluidic oscillator is used in a method as defined in any of Claims 1 to 20.

Figure 1

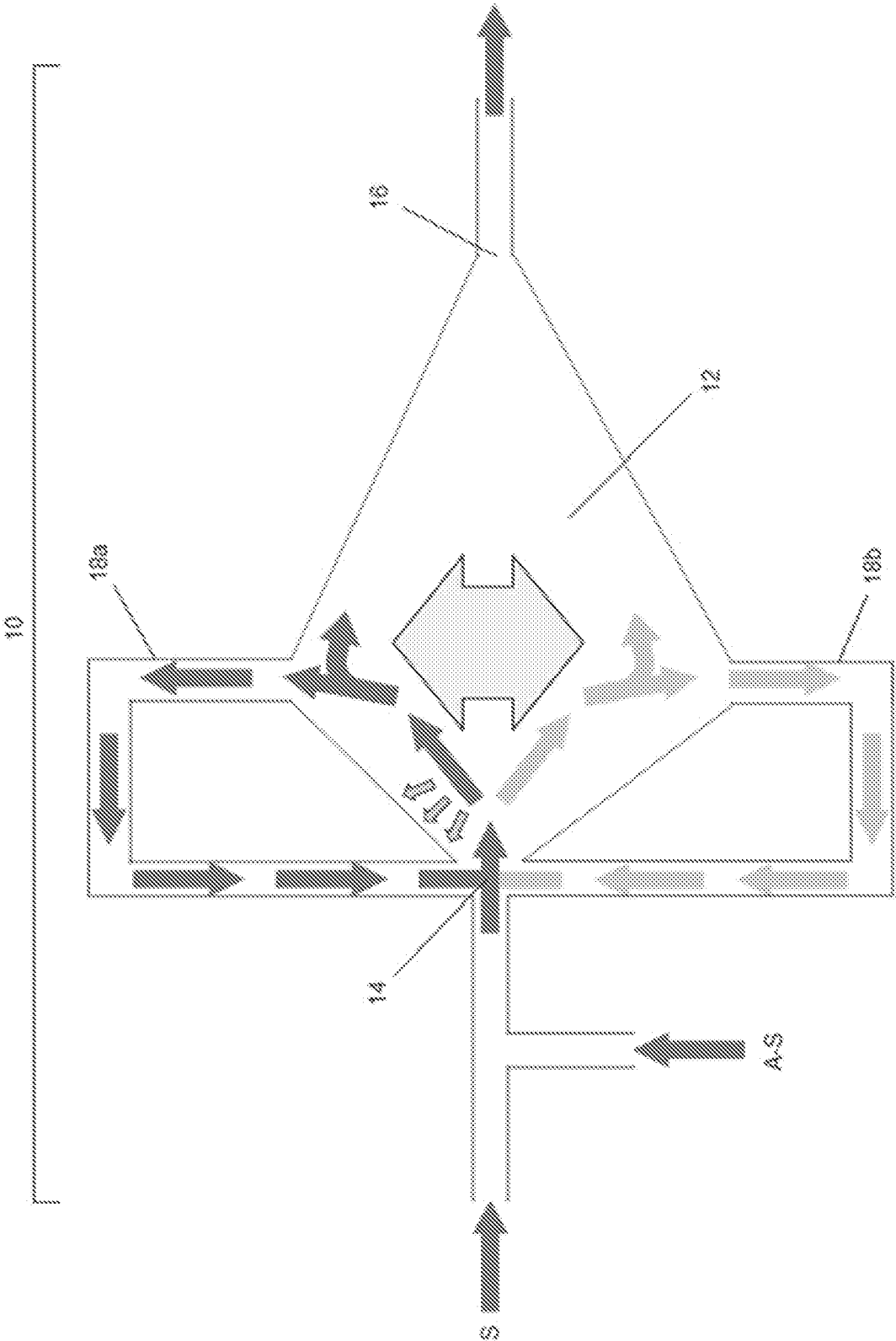


Figure 2

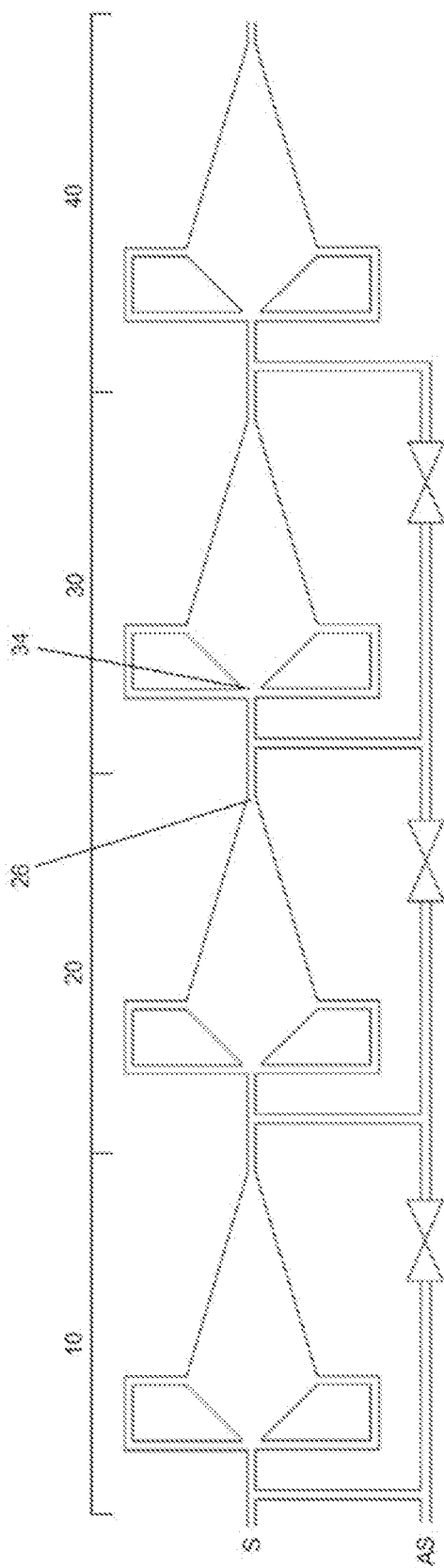


Figure 3

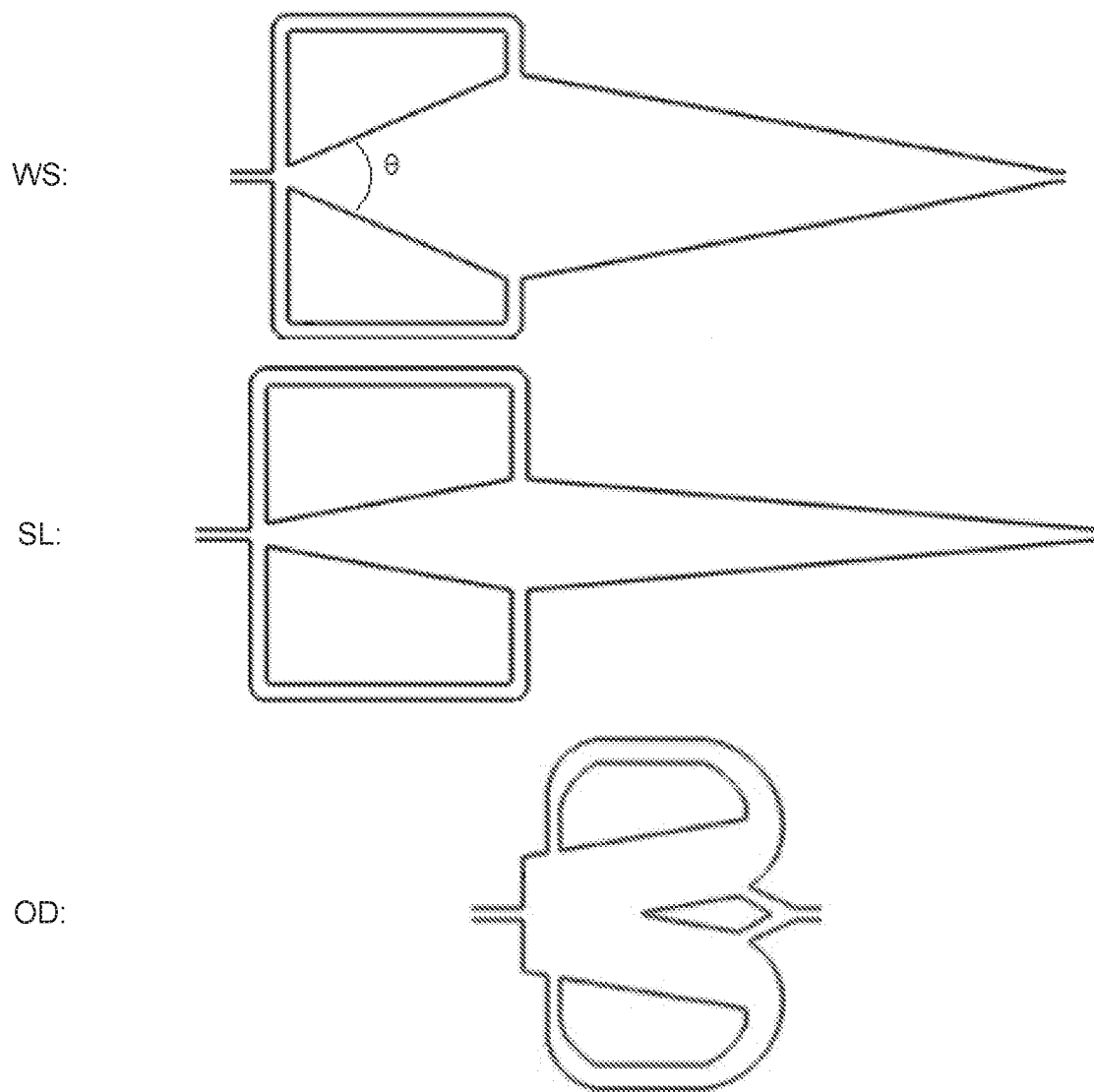


Figure 4a

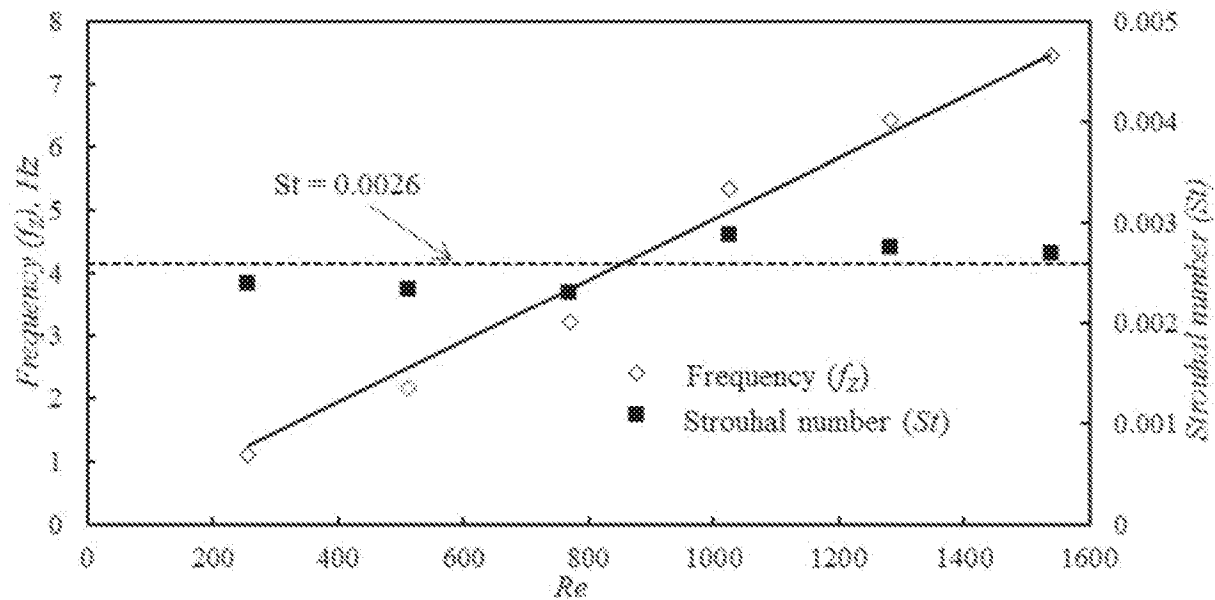


Figure 4b

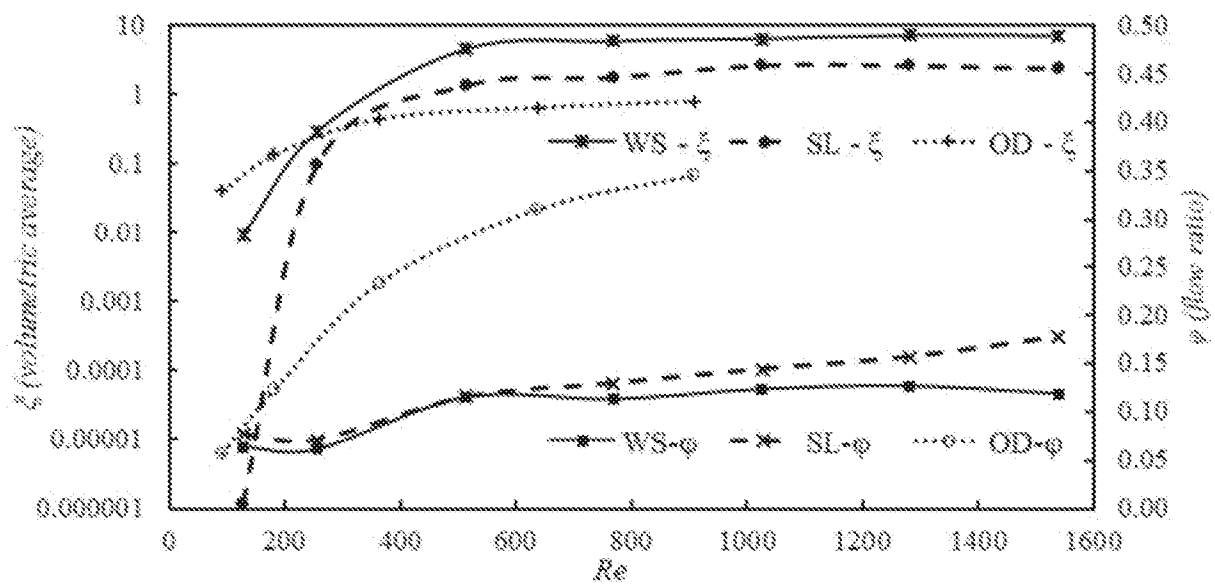


Figure 4c

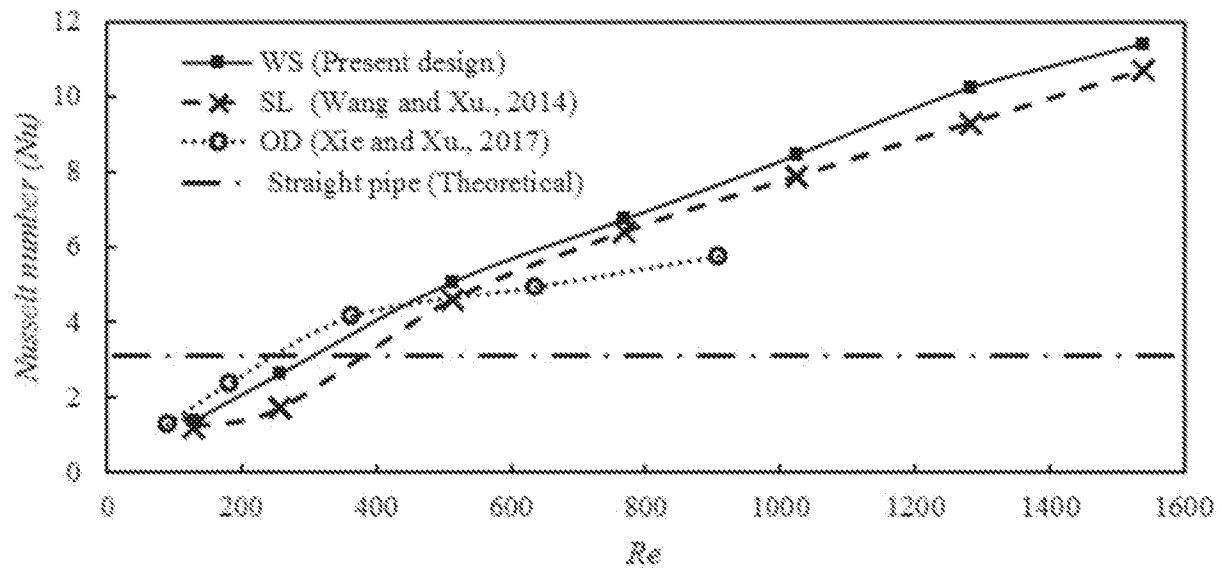


Figure 4d

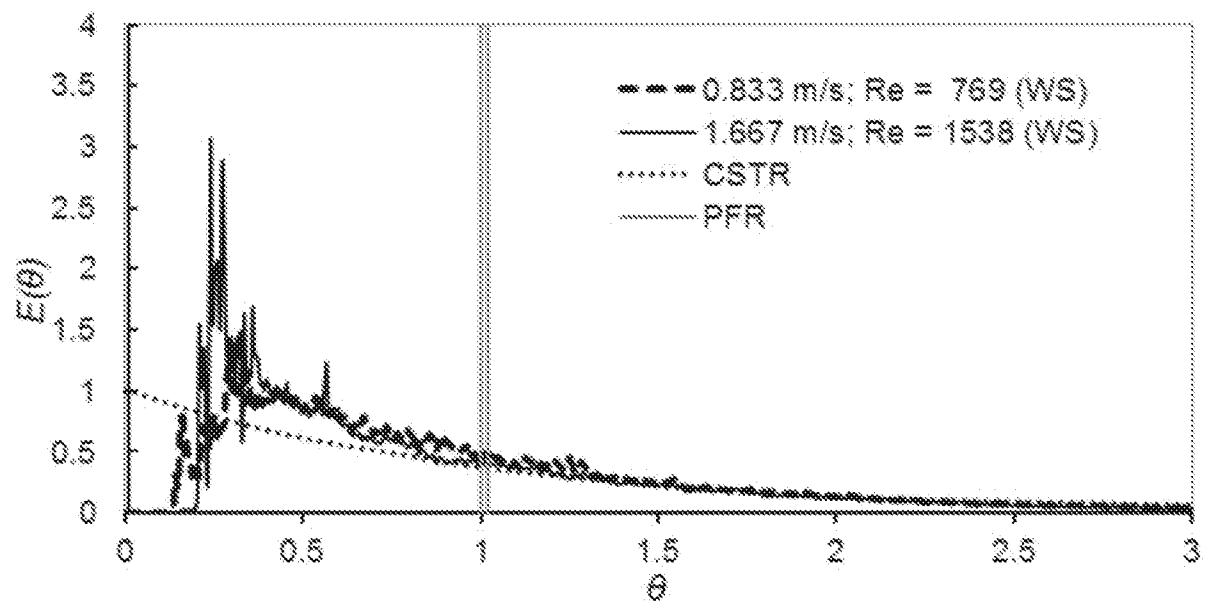


Figure 5

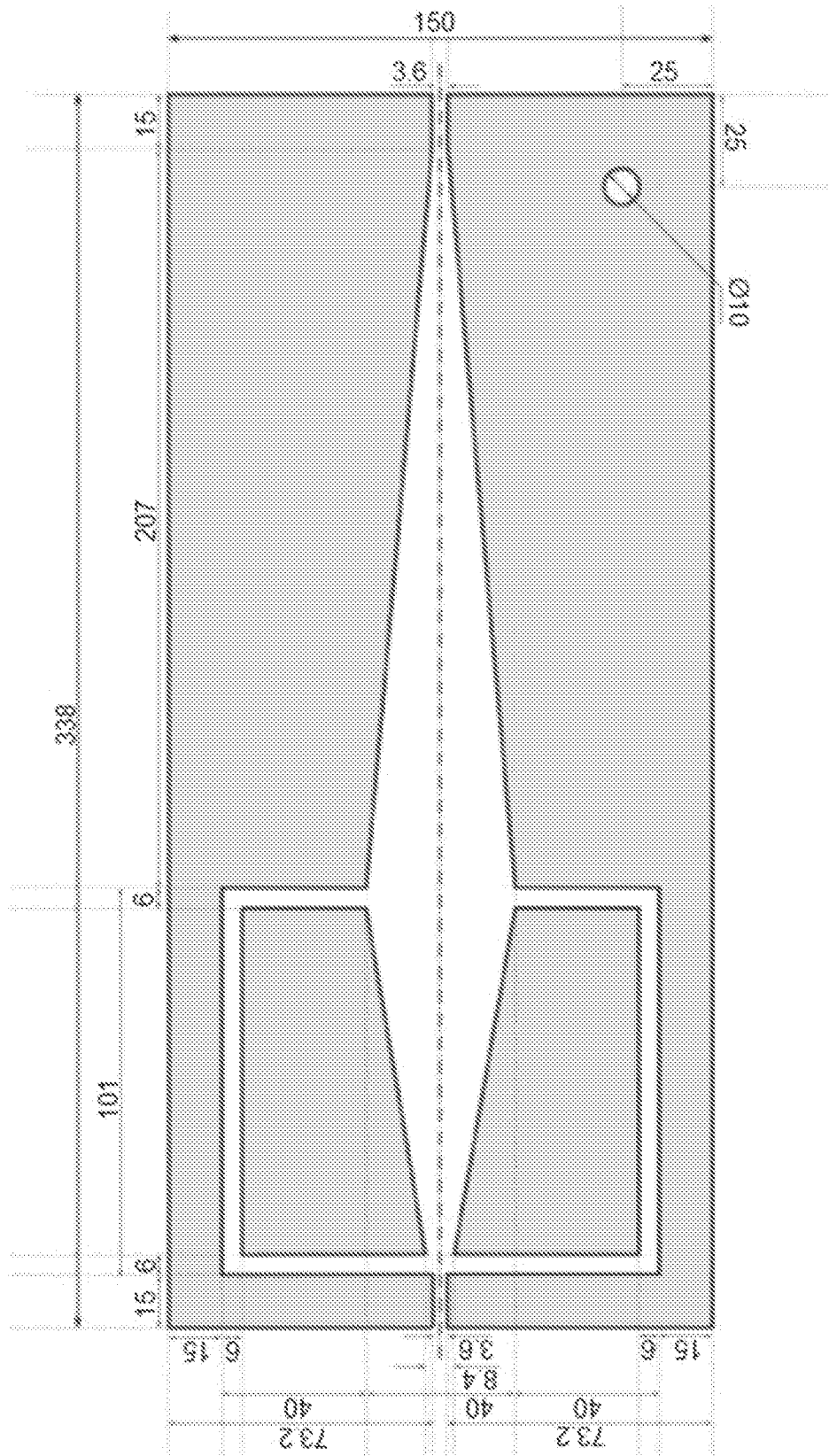
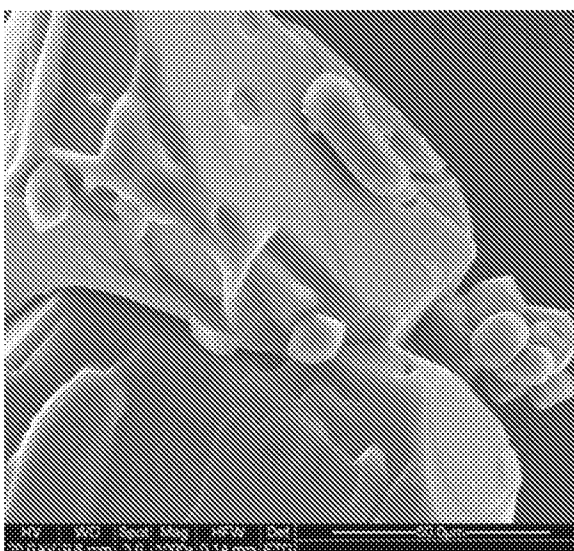
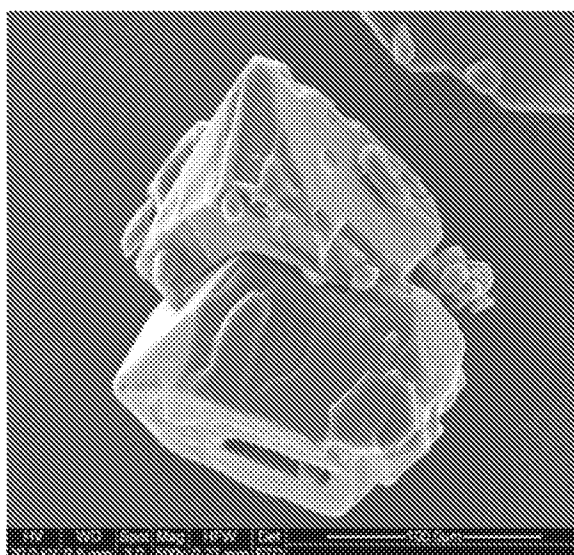
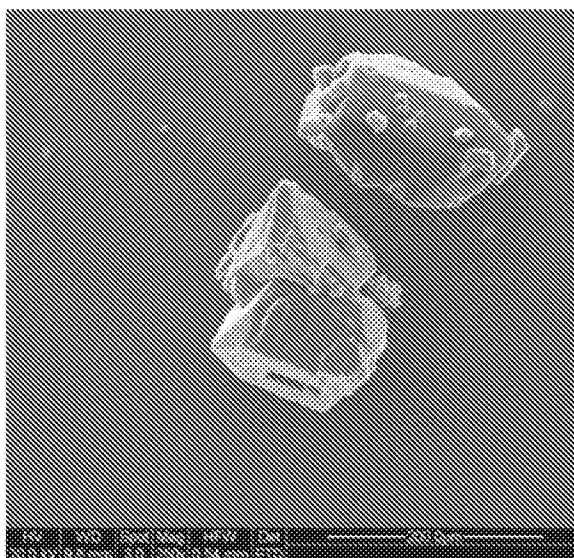


Figure 6



8/9

Figure 7

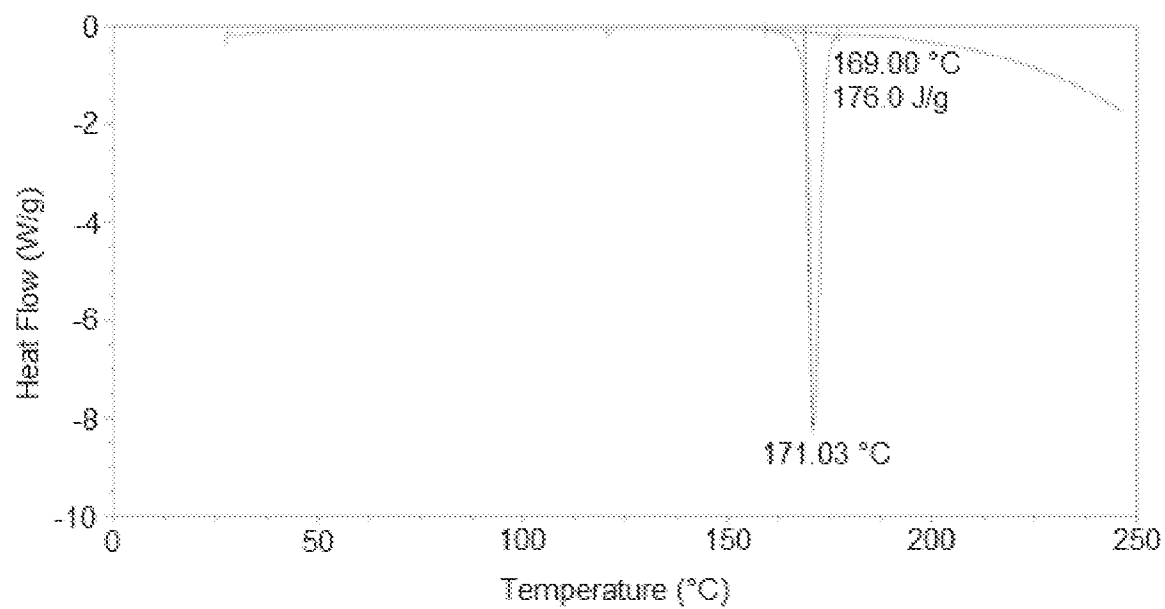


Figure 8

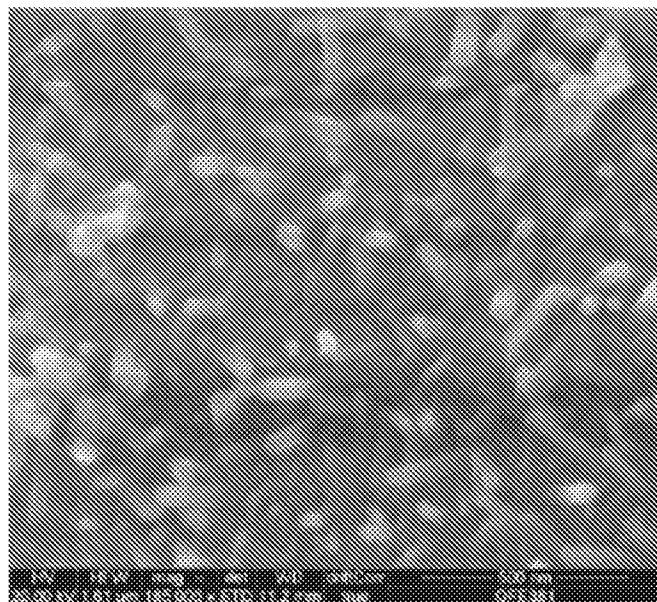
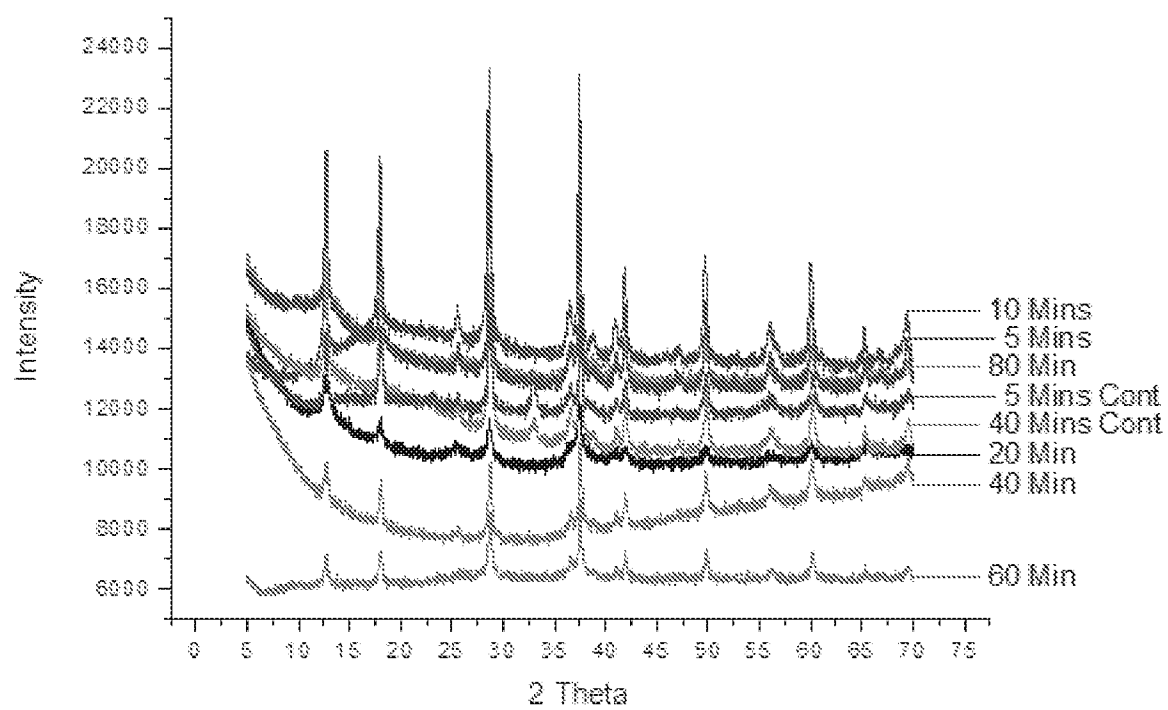


Figure 9



INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2019/051795

A. CLASSIFICATION OF SUBJECT MATTER

INV. B01D9/00 B01F5/04 B01F15/02
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 B01F C30B B01J G01F

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 practicable, search terms used)

EP0-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2016/015991 A1 (VOITH PATENT GMBH [DE]) 4 February 2016 (2016-02-04)	1,7, 10-13, 16-25
Y	claims; figures page 13, lines 16-26	2-6,8,9, 14,15
X	----- ULRICH JOACHIM: "Crystallization", KIRK OTHMER ENCYCLOPEDIA OF CHEMICAL TECHNOLOGY, XX, XX, vol. 8, 16 August 2002 (2002-08-16), pages 95-147, XP002521007, DOI: 10.1002/0471238961.0318251918152119.A01.PU B2	21
Y	page 134 - page 135 ----- -/--	2-6



Further documents are listed in the continuation of Box C.



See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search

12 September 2019

Date of mailing of the international search report

25/09/2019

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Kleiminger, Lisa

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2019/051795

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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X	----- CONG XU ET AL: "High-Throughput Production of Droplets Using Mini Hydrodynamic Focusing Devices with Recirculation", INDUSTRIAL & ENGINEERING CHEMISTRY RESEARCH, vol. 54, no. 25, 16 June 2015 (2015-06-16), pages 6551-6558, XP055620546, ISSN: 0888-5885, DOI: 10.1021/acs.iecr.5b01114	21
Y	figures page 6553	8,9
Y	----- CONG XU ET AL: "Countercurrent Droplet-flow-based mini extraction with pulsed feeding and without moving parts : Separations: Materials, Devices and Processes", AIChE JOURNAL, vol. 62, no. 10, 1 October 2016 (2016-10-01), pages 3685-3698, XP055620531, US ISSN: 0001-1541, DOI: 10.1002/aic.15267 figures abstract -----	8,9,14, 15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2019/051795

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