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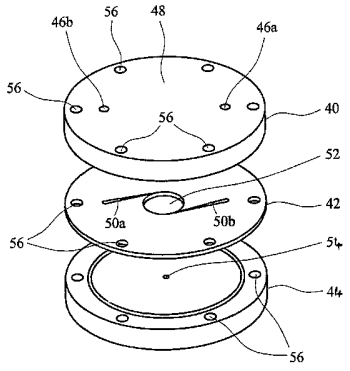
(54) Title: PROCESS FOR PREPARING PARTICLES AND APPARATUS



(57) Abstract: Apparatus (2) includes a vessel (4) for containing a formulation. The outlet (6) of vessel (4) is connected to an inlet (8) of a mixer (10). A second vessel (12) for containing a hydrofluorocarbon solvent is arranged for the delivery of the solvent via a pump (20) into the mixer (10) via a line (27). Downstream of the mixer (10) is a filter (26) for collecting particles prepared using the apparatus. A mixer (10) may be arranged for the turbulent mixing of fluid streams entering into them so that highly turbulent mixing of the fluorocarbon with the formulation is achieved, leading to efficient production of small particles.

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Process for preparing particles and apparatus

This invention relates to a process for preparing particles of a substance and apparatus, for example a mixer, for preparing particles or for use in other applications.

Applicant's earlier patent applications PCT/GB00/04350 and PCT/GB02/05017 describe methods for producing particles in an advantageous manner. However, problems still exist. For example, there is a need to provide greater control over operation of apparatus for producing particles thereby allowing the production of particles consistently, efficiently and of small sizes.

It is an object of the present invention to address the aforementioned problems and problems discussed generally in PCT/GB00/04350 as PCT/GB02/05017, particularly the introduction thereof.

According to a first aspect of the invention, there is provided a process for preparing particles of a substance comprising:

(a) selecting a first formulation including a first substance or a precursor of a first substance;
(b) selecting a second formulation which includes a fluorocarbon;
(c) directing said first or said second formulation into a mixing device which is arranged to cause fluid directed into it to travel, for example rotate, about an axis;

(d) contacting said formulation directed into the mixing device with the other one of either said first or said second formulation, wherein particles comprising said first substance form after, for example as a result of, contact of the first and second formulations.

By causing the fluid to travel about an axis substantial kinetic energy and/or turbulence may be imparted to the fluid and this is found to advantageously facilitate mixing of a said fluorocarbon with a said first formulation.

Said mixing device is preferably arranged to define a first travel path for the formulation directed into it in step (c).

Said first travel path preferably includes a curved component, suitably downstream of an inlet of the travel path, which is arranged to cause fluid directed into the first travel path to travel about a said axis. Said curved component preferably has an axis about which fluid directed into the mixing device is arranged to travel, for example rotate, as described in step (c).

A part of said first travel path preferably extends transversely, for example perpendicularly, to said axis. Said part of said travel path preferably extends substantially tangentially to the curved component of the travel path.

Said curved component of said first travel path is preferably defined by a chamber. Said chamber preferably

comprises an outer wall which includes a curved cross-section which preferably includes a curved region which extends around the entirety of said axis of said travel path about which fluid directed into the mixing device is arranged to travel. Said curved region is preferably circular.

Said first travel path preferably includes a constriction, suitably downstream of said curved component and/or said chamber. Said constriction preferably defines a part of an outlet travel path via which fluid can exit the mixing device. Preferably, a part of the first travel path extends transversely to, preferably substantially perpendicular to, at least a part of the outlet travel path.

Preferably, in the mixing device, fluid is arranged to travel, for example to rotate, about a said axis in step (c) and also to travel in the direction of said axis.

Preferably, the ratio of the sum of the cross-sectional areas of each inlet of the mixing device to the sum of the cross-sectional area(s) of each outlet of the device is in the range 1:2 to 10:1. Preferably, the ratio is in the range 1:1 to 5:1. Whilst the mixing device preferably has a plurality of inlets, it preferably has only one outlet via which particles of said first substance formed in the process together with associated fluid pass out of the device.

Preferably, the cross-sectional area of each inlet of the mixing device is designed so that the linear velocities of

flows through the inlets are similar or substantially similar.

Preferably, in step (c), said second formulation is directed into the mixing device and caused to travel about said axis. Preferably, in step (d), the second formulation which has been caused to travel about said axis is contacted with said first formulation.

Preferably, in step (d), the formulation directed into the mixing device in step (c) is contacted with the other one of said first or said second formulations by directing the other one of said first or second formulations transversely into a flow path of the formulation directed into the mixing device in step (c).

Said mixing device is preferably arranged to define a second travel path for a second stream of solvent formulation directed into it in step (c).

A part of said second travel path preferably extends transversely, for example perpendicular, to said axis referred to in step (c). Where said first travel path includes a curved component, said part of said second travel path preferably extends substantially tangentially to the curved component.

When said mixing device includes a chamber, said second travel path is preferably arranged to communicate with said chamber. Preferably, said first and second travel paths are arranged to deliver fluid in the same rotational direction into the chamber.

Said mixing device preferably comprises a first body and a second body which preferably are releasably securable to one another. The first body preferably includes a first fluid inlet which preferably extends, preferably in a substantially straight line, from one side of the body to an opposite side thereof. Preferably, in the method, the other one of said formulations is directed through said first fluid inlet in step (d). Preferably, said first formulation is directed through said first fluid inlet.

Said first body preferably includes a first face which is preferably arranged to cooperate with said second body to define, in part, a fluid travel path of the mixing device. Said second body preferably defines at least part of said first travel path which preferably includes an inlet for said formulation directed into the mixing device in step (c). Preferably a part, for example said first face, of said first body and a part, for example a face, of said second body, cooperate to define a part of said first fluid travel path. Said second body preferably defines at least part of said second travel path when provided. Preferably, a said part, for example said first face, of said first body and a part, for example a said face, of said second body cooperate to define a part of said second fluid travel path. Said first body and said second body preferably make face to face contact.

In a first embodiment, the mixing device may include a first body which includes a said first fluid inlet and a second inlet, wherein said inlets preferably extend substantially parallel to one another, preferably from one side of the body to an opposite side thereof. Said first and second inlets are preferably arranged to receive the

first and second formulations respectively. Said second body preferably defines at least a part of said first travel path and said second travel path, wherein said paths extend transversely to a said chamber of the mixing device and are arranged to direct fluids flowing in the paths into one another in step (d). Said first and second travel paths are preferably elongate channels which preferably extend tangentially to said chamber. Said chamber preferably has a curved, more preferably circular, cross-section, at least in a region which is connected to the first and second fluid travel paths.

In the first embodiment, the mixing device may include a third body, which may be releasably secured to the second body, and which preferably includes an outlet, preferably a single outlet, of the device. Said second body and said third body preferably make face to face contact.

In the first embodiment, preferably said first formulation is directed through said first fluid inlet and said second formulation is directed through said second fluid inlet. Preferably both said first and second formulations are directed into the mixing device and caused to travel, for example, rotate about said axis, the fluids suitably mixing during said travel resulting in particle formation in step (d). A mixture of fluids and particles may then pass out of the mixing device and particles isolated.

In a second embodiment, said first or second formulation may be caused to travel, for example, to rotate about said axis and the other one of said first or second formulation may be contacted with the formulation travelling about said axis at a position downstream of a position at which

travel of said fluid about said axis has been initiated. Said position downstream is preferably spaced, in the direction of said axis, from a position at which a said formulation is initially caused to travel about said axis. In said second embodiment, the mixing device may comprise a chamber into which said first or second formulation is arranged to be directed. The chamber may be arranged to cause fluid directed into it in step (c) to travel, preferably rotate, about a said axis. The chamber preferably includes a first end and a second end and preferably said axis extends between the first and second ends. Said mixing device preferably includes a first conduit means for delivering fluid into the chamber at a position towards said first end and a second conduit means for delivering fluid into the chamber at a position towards the second end. Thus, the arrangement is suitably such that fluid passing into the chamber via said second conduit means contacts fluid in the chamber which has been delivered into the chamber upstream of said second conduit means, which has passed through the chamber and been caused to rotate about said axis as it moves towards said second end. Said first conduit means preferably extends transversely to said chamber of the mixing device. It preferably comprises an elongate channel which suitably extends tangentially to the chamber.

Said chamber preferably tapers inwardly on moving from said first end to said second end. Suitably, the ratio of the cross-sectional area of the chamber at said first end is at least twice, preferably at least five times, more preferably at least ten times, the cross-sectional area of the chamber at the second end. Said second conduit means is preferably arranged to direct fluid into said chamber

in a direction which is not tangential to the travel, for example rotation, of the fluid about said axis. Said second conduit means is preferably arranged to direct fluid into said chamber at an angle of less than 90°, suitably less than 80°, preferably less than 60°, more preferably less than 45° especially less than 30° to the axis about which fluid is caused to travel in accordance with step (c) above. Preferably, said second conduit means is arranged to direct fluid in a direction substantially parallel to said axis and, more preferably, substantially coaxial thereto. Alternatively, but less preferred, the fluid may be directed radially to said axis.

Said chamber of said second embodiment is preferably substantially annular in cross-section such that fluid flowing therein between said first and second ends preferably passes between inner and outer walls of the chamber. Advantageously, by providing an annular chamber, fluid flowing therethrough cannot collapse into a centre, as might happen if the chamber was cylindrical and had a circular cross-section. This helps to maintain the speed and rotatory flow of fluid in the chamber which may facilitate mixing. Preferably said inner and outer walls may be shaped so that the width of a gap between the inner and outer walls is either substantially constant between said first and second ends or the gap tapers inwardly between the first and second ends. Said chamber may include a stepped region, suitably between said first and second ends, which defines an abrupt change of shape of the chamber.

Said inner wall is preferably defined by a bulbous member, for example a plug type member, which is received within a receptacle and cooperates therewith to define said chamber. Preferably, said second conduit means is defined in said bulbous member and preferably extends between first and second parts, for example first and second ends of said bulbous member. Preferably downstream of the bulbous member, the mixing device includes an outlet. Preferably, the ratio of the sum of the cross-sectional areas of all fluid inlets into the mixing device to the sum of the cross-sectional areas of all fluid outlets is at least 2, preferably at least 3.

Said second embodiment may include a third conduit means also for delivering fluid into the chamber at a position towards said first end. Said second conduit means preferably extends transversely to said chamber of the mixing device. It preferably comprises an elongate channel which suitably extends tangentially to the chamber. Said first and third conduit means are preferably arranged to deliver fluid into the chamber in opposite directions from diametrically opposite sides of the chamber.

Said second embodiment preferably includes first and second bodies as referred to above which are preferably arranged to define parts of first and second travel paths as described. Said first travel path may be defined at least in part by said first conduit means and said second travel path may be defined by said third conduit means, when provided.

In the second embodiment, preferably said second formulation is directed into the mixing device and arranged to travel, for example rotate, about said axis. Preferably, separate streams of said second formulation are directed into the mixing device via said first and third conduit means and each is arranged to rotate about said axis. Said first formulation is preferably contacted with said second formulation after said second formulation is travelling as described and suitably at or towards the second end of the chamber as described. When said mixing device comprises a bulbous member which includes a second conduit means, said first formulation preferably passes through said second conduit means. In operation, said first formulation (which may not be rotating about an axis) may contact the second formulation which is travelling about said axis whereby the two fluids mix resulting in particle formation in step (d). A mixture of fluids and particles may then pass out of the mixing device and particles isolated.

In the method said first formulation and said second formulation (and preferably any other formulation used in the method if provided) are preferably in a non-supercritical state.

By the term "in a non-supercritical state" we mean that the referenced formulation is not at or above its critical temperature and critical pressure simultaneously.

A fluorocarbon solvent used in the preparation of said particles may be selected from a C_{1-4} fluorinated hydrocarbon, a perfluorocarbon and a C_{1-4} hydrofluorocarbon ether.

A said hydrofluorocarbon ether preferably comprises one or more carbon, fluorine, hydrogen and oxygen atoms only. It may include up to 10, preferably up to 8, more preferably, up to 6, fluorine atoms. It preferably includes at least 2, more preferably at least 3 fluorine atoms. It is preferably aliphatic and/or saturated. An example of a hydrofluorocarbon ether is 1,1,1,2,2-pentafluorethyl methyl ether.

Preferably, the fluorocarbon solvent used is a said C_{1-4} fluorinated hydrocarbon, rather than a said hydrofluorocarbon ether.

Said C_{1-4} fluorinated hydrocarbon is preferably non-chlorinated. Preferably, it comprises one or more carbon atoms, one or more fluorine atoms together with one or more other atoms selected from hydrogen atoms and iodine atoms. More preferably, it comprises one or more carbon, fluorine and hydrogen atoms only. Preferably, said fluorinated hydrocarbon is a C_{1-3}, more preferably a C_{2-3}, fluorinated hydrocarbon. Especially preferred is a C_2 fluorinated hydrocarbon.

Said fluorinated hydrocarbon may include 10 or fewer, suitably 8 or fewer, preferably 7 or fewer, more preferably 5 or fewer, especially 4 or fewer, fluorine atoms. Preferably, said fluorinated hydrocarbon includes at least 2, more preferably at least 3, fluorine atoms.

Said fluorinated hydrocarbon is preferably aliphatic. It is preferably saturated.

Said fluorinated hydrocarbon may have a boiling point at atmospheric pressure of less than 20°C, preferably less than 10°C, more preferably less than 0°C, especially less than -10°C. The boiling point may be greater than -90°C, preferably greater than -70°C, more preferably greater than -50°C, especially greater than -40°C.

Said fluorocarbon solvent is preferably selected from iodotrifluoromethane, CF_3H (HFC-23, trifluoromethane), CH_3F (HFC-41, fluoromethane), CH_2F_2 (HFC-32, difluoromethane), CF_3CF_2H (HFC-125, pentafluoroethane), CF_3CH_3 (HFC-143 A, 1,1,1-trifluoroethane), HCF_2CH_3 (HFC-152 A, 1,1-difluoroethane), CF_3CHFCF_3 (HFC-227 EA, 1,1,1,2,3,3,3-heptafluoropropane), $CF_3CF_2CF_2H$ (HFC-227 CA, 1,1,1,2,2,3,3-heptafluoropropane), $CF_3CH_2CF_3$ (HFC-236 FA, 1,1,1,3,3,3-hexafluoropropane), $CF_3CF_2CH_3$ (HFC-245 CB, 1,1,1,2,2-pentafluoropropane), $CF_3CF_2CH_2F$ (HFC-236 CB, 1,1,1,2,2,3-hexafluoropropane), $HCF_2CF_2CF_2H$ (HFC-236 CA, 1,1,2,2,3,3-hexafluoropropane), CF_3CHFCF_2H (HFC-236 EA, 1,1,1,2,3,3-hexafluoropropane), and CH_2FCF_3 (HFC-134A, 1,1,1,2-tetrafluoroethane).

Preferably, said fluorocarbon solvent formulation includes a first solvent selected from iodotrifluoromethane, 1,1,1,2,3,3,3-heptafluoropropane (R-227 EA), 1,1,1,2,2,3,3-heptafluoropropane (R-227CA) and 1,1,1,2-tetrafluoroethane.

More preferably, said fluorocarbon solvent formulation includes a first solvent selected from 1,1,1,2,3,3,3-heptafluoropropane (R-227EA) and 1,1,1,2-tetrafluoroethane, with 1,1,1,2-tetrafluoroethane being especially preferred.

Although substantially pure solvent, for example HFC 134A may be used in some applications as the second formulation, since it is a very poor solvent, it may be mixed with small quantities of other co-solvents as described hereinafter to adjust the solvation properties.

Thus, the second formulation may include a co-solvent, which may also be, but is preferably not, a C_1-C_4 hydrofluorocarbon of the type described herein. The co-solvent is suitably selected to affect the boiling point and/or dissolution properties of the fluorocarbon in the second formulation.

The co-solvent may be selected from C_{2-6} hydrocarbons, which may be alicyclic or aliphatic. They are preferably alkanes or cycloalkanes such as ethane, n-propane, iso-propane, n-butane or iso-butane.

The co-solvent may also be a hydrocarbon ether, particularly a dialkylether, such as dimethyl ether, methyl ethyl ether or diethyl ether.

The co-solvent may also be a hydrocarbon with polar properties, such as those with dielectric constants of greater than 5. Suitable dielectric hydrocarbon co-solvents include alcohols, for example methyl, ethyl and isobutyl alcohols, and ketones, such as acetone.

Suitably, the second formulation comprises a major portion of said C_1-C_4 hydrofluorocarbon as described hereinbefore. Preferably, at least 90 wt%, more preferably at least 93 wt%, especially at least 97 wt% of the second formulation

comprises a C_1-C_4 hydrofluorocarbon as described hereinbefore. The balance may be made up of one or more co-solvents as described above. Where the second formulation includes a co-solvent, it may comprise 1-50wt%, preferably, 2-30wt% and more preferably 2-20wt% co-solvent as described herein.

Preferably, the co-solvent forms an azeotropic mixture with the fluorocarbon so that its proportion in the second formulation may remain constant even though the second formulation may be redistilled many times.

Preferably, the first formulation comprising the first substance or precursor is a solution. The solution may be a true solution or a colloidal solution. The colloidal solution may be a sol, emulsion, gel or other colloidal matrix.

The first formulation suitably includes an organic solvent as the formulation carrier solvent. Said first formulation could comprise water, for example greater than 50wt% water. Preferably, the first substance is soluble in the organic solvent.

Suitable organic solvents of the first formulation include alcohols, especially aliphatic alcohols such as methanol, ethanol, 1-propanol or 2-propanol; ketones, especially aliphatic ketones, with dialkyl ketones such as acetone or methyl isobutyl ketone being preferred; organic acids, preferably acetic acid; amides, such as N,N'-dialkylamide or alkylamide; carboxylic acid derivatives, for example, anhydrides such as acetic anhydride; cyanide derivatives, for example, hydrogen cyanide or any alkyl cyanide;

ammonia; sulphur containing molecules; acetates, with methyl acetate, ethyl acetate and butyl acetate being preferred; ethers, with dimethyl ether and diethyl ether being preferred; alkanes or alkane derivatives, with dichloromethane and dichloroethane being preferred; tetrahydrofuran; toluene; hexane; heptane and petroleum ether mixtures.

Especially preferred solvents of said first formulation are selected from acetic acid, methanol, ethanol, toluene, cyclohexane and acetone.

The organic solvent of the first formulation may comprise a combination of two or more of the above, in any ratio. Preferably, the organic solvent is miscible with the fluorocarbon in the second formulation.

Typically, the process of the present invention permits substantially instantaneous mixing and/or interdispersion of the solvent, for example organic solvent, of the first formulation with the second formulation.

Suitably, the first substance of the first formulation is insoluble or sparingly soluble in the second formulation.

Preferably, the solubility of the first substance in the second formulation is less than 20% weight by weight (w/w), more preferably less than 10% w/w, especially less than 5% w/w, most especially less than 2% w/w.

Preferably, the solubility of the first substance in the second formulation is only up to 1% w/w, more preferably

only up to 0.5% w/w, especially only up to 0.3% w/w, most especially only up to 0.1% w/w.

Suitably, if the first substance is soluble in the organic solvent of the first formulation and insoluble or only sparingly soluble in the second formulation then this permits the formation of small particles of the first substance.

Suitably, the first substance is an active ingredient selected from flavours, fragrances, plastics, polymers, bio-polymers, pigments, dyes, and biologically active compounds such as pharmaceuticals, synthetics and semi-synthetic drugs and pesticides. In an especially preferred embodiment, said first substrate is a pharmaceutically active compound.

Said first formulation preferably includes said first substance.

Suitably, the temperature of the first and second formulations (and preferably and other solvent formulation used in the process) are each independently greater than or equal to -20°C, preferably greater than or equal to 0°C. Suitably, the temperature of the first and second formulations (and preferably any other one used) are each independently less than or equal to 75°C, preferably less than or equal to 40°C.

Suitably, the vapour pressure of the first and second formulations (and preferably any other one used) are each independently less than or equal to 35 bar G, preferably

less than or equal to 20 bar G, at the preferred temperatures mentioned above.

A preferred temperature range of the first and second solvent formulations (and preferably any other ones present) is 0 to 40°C, which typically produces a vapour pressure of 2 bar G to 20 bar G for the formulations. As stated previously a highly preferred second formulations is HFC 134A which has a critical temperature of greater than 100°C and a critical pressure of greater than 40 bar G. Consequently, when the process of the present invention is operated within the preferred temperatures and pressures, particularly with regard to HFC 134A, it is evident that the formulations are in a non-supercritical state (e.g. they are not simultaneously above the critical temperature and critical pressure).

The method preferably includes a separation process after step (d) which causes separation of particles from solvents in the first and second formulations.

The separation process may include passing a mixture produced in step (d) through a separation means, for example a filter, so that particles of the first substance can be isolated, for example collected on the filter, and the mother liquors derived from the first and second formulations can be isolated, for example by passing through the filter.

Preferably, the method involves causing the application of a back pressure, suitably from a position downstream of the mixing device and preferably downstream of the separation means when provided. A back pressure device may be

provided downstream of the mixing device. The back pressure device may comprise a means (hereinafter "a restrictor device") for restricting flow of fluid downstream of the mixing device. Said restrictor device may comprise a constriction in a fluid flow path downstream of the mixing device. Suitably, the ratio of the sum of the areas of the cross-sections of all inlets into the mixing device to the sum of the cross-sectional areas of all oulets from the device is greater than 1, preferably greater than 1.2, more preferably greater than 1.5. The cross-sectional area of the restrictor device may be selected so that a given flow rate to allow operating conditions of pressure and temperature is achieved.

The method may involve varying the level of back pressure between two different preparations of particles using said process. The back pressure could be adjusted by said restrictor device having a variable orifice size. For example, said restrictor device could comprise a valve which is arranged to define orifices of different sizes. Preferably, however, back pressure is adjusted by providing a means for interchanging restrictor devices. For example, a restrictor device with an inlet of relatively small cross-sectional area may facilitate provision of a relatively high back pressure; and a restrictor device with an inlet of relatively large cross-sectional area may facilitate provision of a relatively low back pressure.

In one embodiment, the method may include selecting both a first and a second substance and forming particles which comprise said first and second substances. Said particles may comprise a substantially homogenous mixture of said first and second substances or one of either said first or

second substance may coat the other one of said first or second substances.

When first and second substances are provided, both of said substances may be included in said first formulation or said substances may be included in separate formulations.

In one embodiment said first and second substances may comprise respective first and second active, for example pharmaceutically active, ingredients. In another embodiment, said first substance may be an active ingredient and said second substance may be selected from stabilisers; dispersion agents; surfactants; taste enhancing or masking additives; antioxidants; hygroscopic prevention agents; and, any other pharmaceutically or veterinary acceptable additive or excipients.

Particles having a size of less than or equal to 200 microns, preferably less than or equal to 100 microns, more preferably less than or equal to 50 microns, more preferably less than or equal to 20 microns, most preferably less than or equal to 10 microns may be produced in accordance with the present invention.

Particles having a size of greater than or equal to 0.5 microns, more preferably greater than or equal to 1 micron may be produced in preferred embodiments of the present invention.

Most preferably, the process of the present invention may produce particles having a specified range of particle sizes and crystalline form by design. Suitably, the process of the present invention may produce particles having a

defined crystalline form having a size in the range of 1 to 3 microns, 5 to 10 microns, 10 to 20 microns and 20 to 50 microns.

For the avoidance of doubt, the aforementioned particle sizes represent a maximum dimension of the particles.

According to a second aspect of the invention, there is provided a process for preparing particles of a substance comprising:

(a) selecting a first formulation including a first substance or a precursor of a first substance;
(b) selecting a second formulation;
(c) directing said first or said second formulation into a mixing device which is arranged to cause fluid directed into it to travel, for example rotate, about an axis;
(d) contacting the formulation travelling about said axis at a position downstream of a position at which travel of said fluid about said axis has been initiated, wherein particles of said first substance form after, for example as a result of, contact of the first and second formulations.

Preferably, said mixing device comprises a chamber which includes a first end and a second end, a first conduit means being provided for delivering fluid into the chamber at a position towards said first end and a second conduit means being provided for delivering fluid into the chamber at a position towards said second end, the arrangement being such that fluid passing into the chamber via said second conduit means contacts fluid which has been

delivered into the chamber via said first conduit means, from a position upstream of said second conduit means, and has been caused to rotate about said axis as it moves towards said second end, and particles of said first substance form after, for example as a result of, contact of the first and second formulations.

According to a third aspect of the invention, there is provided a process for preparing particles of a substance comprising:

(a) selecting a first formulation including a first substance or a precursor of a first substance;
(b) selecting a second formulation;
(c) directing said first or said second formulations into a mixing device which is arranged to cause fluid directed into it to rotate about an axis within an annular cavity and to pass axially along the cavity;
(d) contacting the formulation rotating about said axis with the other one of either said first or second formulation, wherein particles of said first substance form after, for example as a result of, contact of the first and second formulations.

Preferably, the formulation rotating about said axis is contacted downstream of a position at which rotation of said formulation is initiated. Said annular cavity suitably includes a first end and a second end, a first conduit means being provided for delivering fluid into the annular cavity at a position towards said first end and a second conduit means being provided for delivering fluid into the chamber at a position towards said second end, the

arrangement being such that fluid passing into the annular cavity via said second conduit means contacts fluid which has been delivered into the cavity via said first conduit means, from a position upstream of said second conduit means, and has been caused to rotate about said axis as it moves towards said second end.

Preferably, in the process, the speed of rotation of the formulation about said axis increases on moving from said first to said second end thereof. This may be achieved by the annular cavity tapering inwardly and/or the annulus having a reducing diameter on moving from said first to said second end thereof.

Said second formulation of the second and third aspects may be selected from the solvents described above as co-solvents. The second formulation may comprise C_{2-6} hydrocarbons, which may be alicyclic or aliphatic, with alkanes or cycloalkanes such as ethane, n-propane, iso-propane, n-butane or iso-butane, being especially preferred; a hydrocarbon ether, preferably a dialkylether, with dimethyl ether, methyl ethyl ether and diethyl ether being especially preferred; and a hydrocarbon with polar properties, such as those with dielectric constants of greater than 5 for example, alcohols, for example methyl, ethyl and isobutyl alcohols, and ketones, such as acetone. Preferred solvents may be selected from ketones, ethers, alcohols and carbon dioxide (in a supercritical or liquid state).

The process of the second and third aspects may have any feature of the process of the first aspect.

According to a fourth aspect of the invention, there is provided a mixing device comprising:

(a) a chamber which includes a first end and a second end;

(b) a first conduit means for delivering fluid into the chamber at a position towards said first end wherein said chamber is arranged to cause fluid directed into it via said first conduit means to rotate about an axis and move towards said second end;

(c) a second conduit means being provided for delivering fluid into the chamber at a position toward said second end wherein said chamber is arranged to cause fluid directed into it via said second conduit means to contact fluid directed into said chamber via said first conduit means.

Said chamber preferably defines an annular cavity downstream of said first end, said cavity being arranged for passage of fluid from said first conduit means towards said second end of the chamber. Said second conduit means is preferably arranged to direct fluid into the cavity at said position towards said second end.

Said first conduit means is preferably arranged to delivery fluid substantially tangentially to the annular cavity.

Said second conduit means is preferably arranged to deliver fluid at an angle x of less than 90° to an elongate axis of the annular cavity. Suitably x is less than 60°, preferably less than 45°, more preferably less than 30°. Fluid is suitably arranged to be delivered in a direction

which is substantially parallel, preferably substantially co-axial, to said elongate axis.

Said chamber preferably tapers inwardly on moving from said first end to said second end. Said second conduit means is preferably arranged to deliver fluid at an apex of a tapered region of the chamber. Such a tapered region may advantageously increase the speed of fluid flowing from said first conduit means.

Said mixing device preferably includes an outlet conduit means, downstream of said chamber. Said outlet conduit means preferably has a cross-sectional area which is substantially the same as or less than the cross-sectional area of all inlets into the chamber of the mixing device. Preferably, in the mixing device, the sum of the cross-sectional areas of all inlets is substantially the same as or greater than the sum of the cross-sectional areas of all outlets from the device.

Any features of any aspect of any invention or embodiment described herein may be combined with any feature of any aspect of any other invention or embodiment described herein.

Specific embodiments of the invention will now be described, by way of example, with reference to the accompanying drawings in which:

Figure 1 is a schematic representation of apparatus for producing particles;

Figure 2 is an exploded perspective view of a first mixing device;

Figure 3 is a graph of volume (%) vs. particle size (μm) for particles produced as described in Example 1;

Figure 4 is an exploded perspective view of half of a second mixing device;

Figure 5 is a schematic cross-sectional view of parts of the device of figure 2 in an assembled state;

Figures 6 to 8 illustrate alternative configurations of parts of apparatus for producing particles; and

Figure 9 is a graph of flow rate vs.pressure/temperature when using R-134a in the apparatus of Figure 1 with a series of different back pressure device nozzle diameters.

In the figures, the same or similar parts are annotated with the same reference numerals.

Referring to Figure 1, the apparatus 2 includes a first vessel 4 for containing a formulation having an inlet 5 at its upper end and an outlet 6 at its lower end. Vessel 4 may also be equipped with a motor driven stirrer (not shown), or other suitable agitation means, and a filtration grid (not shown) placed over the outlet 6.

The outlet 6 of the first vessel 4 is connected to a formulation pump 7 which in turn is connected, via line 31, to an inlet 8 of a mixer 10.

A second vessel 12 for containing a hydrofluorocarbon solvent (HFC) is connected via an inlet 14 at is upper end to a condenser 16 and connected via an outlet 18 at its lower end to a pump 20. The pump 20 is arranged to deliver HFC solvent into the mixer 10 via a line 27 incorporating heating/cooling device 32.

Downstream of the mixer 10 is a filter 26 for collecting particles prepared using the apparatus. Downstream of the filter is a back pressure device 28 arranged to increase the pressure within the mixer 10 and filter 26. The back pressure device may be in the form of a constricted flow nozzle, as described further below. Downstream of the device 28, there is an evaporation vessel 29 having an outlet 30 at its upper end connected to a compressor 34 which in turn is connected to the second vessel 12 via the condenser 16.

The whole apparatus 2 is connected via a network of pipes, pressure and temperature gauges, flow and pressure control valves to permit selection and maintenance of optimum critical parameters of flow, temperature and pressure in each part of the apparatus.

In operation of the apparatus 2, liquid hydrofluorocarbon is metered into the second vessel 12, then it is fed from the second vessel 12 to the mixer 10 via pump 20. The hydrofluorocarbon passes through the in-line filter 26 via the back pressure device 28 and into the evaporation vessel 29. As a result of the reduced pressure in the evaporation vessel 29 the hydrofluorocarbon evaporates and passes through the outlet 30, whereby it is recycled continuously by evaporation with the aid of compressor 34 and condenser

16. The recondensed hydrofluorocarbon is returned back into the second vessel 12.

A formulation comprising a substance to be prepared as small particles in solution with an organic solvent is metered into the first vessel 4 and then fed to the mixer 10 via pump 7. The HFC stream and the formulation are contacted in the mixer 10. As a result of the high affinity of the HFC to the organic solvent of the formulation there is mass transfer of the organic solvent into the HFC which causes the substance to precipitate as small particles.

The flow of the resultant suspension comprising particles of the substance is passed through the in-line filter 26. The particles collect on the filter 26 and the resulting mother liquors comprising the organic solvent and HFCs, now depleted of solid particles, pass into vessel 29 where the HFC is evaporated and recycled as described above leaving the organic solvent in the evaporation vessel 29 for disposal or recovery at a later stage.

At the end of the run, the HFC recycling can be maintained for a predetermined time to effect washing of the collected solid by removing any trace contamination of the carrier organic solvent from the formulation.

Optionally, heat can be supplied to the evaporation vessel 29 by conduction via the walls of the vessel 29 or by introduction of microwave energy into the chamber of vessel 29. All of the vessels may be jacketed to provide a means of temperature control.

A first mixing device 10a for use as mixer 10 in apparatus 2 is shown in figure 2. The device 10a includes three stainless steel machined circular plates 40, 42, 44. A top plate 40 includes two diametrically spaced apart cylindrical inlets 46a, 46b which extend perpendicular to the plane of face 48 of plate 40 and terminate directly above respective channels 50a, 50b in plate 42. Plate 42 includes a central small diameter circular opening 52 which defines a mixing chamber of the device 10a. The channels 50a, 50b extend tangentially to the opening 52 and are arranged to deliver fluids into the mixing chamber. The plate 44 includes a central narrow diameter outlet 54.

Plates 40, 42, 44 are secured together by bolts (not shown) which extend through aligned bolt holes 56 in the plates.

In use, liquid HFC is pumped into the mixer via inlet 46a and a liquid formulation comprising a substance to be prepared as small particles in solution is pumped into the mixer via inlet 46b. The respective fluid flows pass through inlets 46a, 46b into respective channels 50a, 50b. As the fluids flow along the narrow diameter channels 50a, 50b towards the mixing chamber 52, high kinetic energy is imparted to each fluid stream. The streams then flow tangentially in opposing directions into the chamber 52 and contact one another with the result that they mix rapidly. The mixture then exits the chamber 52 through axially aligned outlet orifice 54. Any particles produced are collected as the mixture passes through the in line filter 26 from which they may be isolated.

As mentioned above, the back pressure device 28 is arranged to increase the pressure within the mixer 10 and filter 26.

In addition the temperature at which the fluids are mixed may be advantageously increased using the heating/cooling device 32. As a consequence the vapour pressure will also be increased. In this regard, the back pressure device is arranged to provide a constriction in the fluids flow path immediately downstream of the filter 26 so that on the one hand the pressure in the mixer 10 and filter 26 is maintained at a level above the fluid vapour pressure to ensure the HFC remains in the liquid state and, on the other hand, the pressure inside the evaporation vessel 29 is sufficiently low to allow evaporation of the HFC. As the temperature of the HFC increases its surface tension and viscosity decrease. This is found to facilitate more rapid and efficient mixing, in mixer 10, with the liquid formulation comprising the substance to be prepared as small particles. It is found that the higher the temperature, hence the higher the pressure, in the mixer 10, the smaller the particle size produced.

The temperature in the mixer/filter may be in the range -10 to 75°C and the operating pressure in the range 2 to 40 barg. Fig 9 is an illustration of the relationship between temperature, operating pressure, aperture of back pressure device and fluids flow rates. In figure 9, the axis equates operating temperatures and pressures. The actual vapour pressure of R134a is 0 barg at -26°C. However, in the apparatus of Figure 1, the vapour pressure is increased, using the back pressure device 28, by 5 barg at that temperature (and all other temperatures) to ensure

the R134a is liquid in the mixer and to prevent the system collapsing.

The back pressure device 28, the compressor 34, condenser 16 and heating/cooling device 32 can be varied to control particles sizes produced because the aforementioned can be used to manipulate temperature and pressure, and hence physicochemical properties of the fluids, within the mixing chamber 10. For example, the device 28, compressor 34, condenser 16, and heating/cooling device 32 may be set up to deliver HFC at 15°C to the mixer 10 and effect an operating pressure within mixer 10 and filter 26 of 6-8 bar requiring a pressure difference between respective points upstream and downstream of the mixer and filter of 2-4 bar. Under these conditions the mixing of HFC and the other formulation(s) may be relatively slow. Figure 9 facilitates the selection of an appropriately sized back pressure nozzle for a given flow rate. For example, if the desired flow rate is 10 ml/min then a nozzle size of 130μm is required to maintain a steady state under the aforementioned conditions. Similarly, for a desired flow rate of 60ml/min, the required nozzle size to maintain the aforementioned conditions is 330μm. On the other hand, if the requirement is to produce smaller sized particles, the temperature within the mixer and filter has to be higher. For example a temperature of about 40°C will effect an operating pressure of about 15bar. Referring to illustration in fig 9, at a desired flow rate of 50ml/min, a nozzle size of 230μm is essential to maintain the aforementioned conditions of temperature and pressure.

Examples 1 to 18 describe the preparation of solid particles using the apparatus of figures 1 and 2.

Example 1

A 1.5% w/v solution of a proprietary pharmaceutical compound in methanol was prepared and charged into the formulation storage vessel 4. HFC134a was re-cycled through the apparatus at a flow rate of 120 ml/min until a steady state with respect to flow-rate, pressure of 12 barg and temperature of 25°C was reached. The solution was then pumped into the mixing device at a flow rate of 2ml/min. The flow was maintained for a period of 8 minutes. The HFC134a flow was maintained for a further 10 minutes. The in-line filter 26 was then dismantled and white crystalline material was isolated. Inspection under a light microscope revealed rod shape crystals with a size range of 1-20μm as measured using a Malvern Mastersizer, and graphical represented in figure 3.

Example 2

A solution containing 5% w/v adipic acid in ethanol was prepared and treated as described in Example 1. White crystalline solid product was isolated from the inline filter an examination of which under a light microscope showed fine, well defined thin needle crystals of about 10-30 μm in length.

Example 3

A solution containing 5% w/v resorcinol in ethanol was prepared and treated using the method described in Example 1. White crystalline solid product was isolated from the inline filter, an examination of which under a light microscope showed well defined crystalline particles that were rod shaped of about 10-30 μm in length.

Example 4

A saturated solution of copper (II) sulphate in methanol was prepared and treated using the method described in Example 1. Powdery blue product was isolated from the inline filter, an examination of which under a light microscope showed well defined spherical crystalline particles around 1μm in diameter.

Example 5

A solution containing 5% w/w each of adipic acid and resorcinol in ethanol was prepared and charged into the formulation storage vessel and the experiment was completed using the method described in Example 1. At the end of the experiment, the filter contained a white powder, which on further inspection with a light microscope showed that it was composed of two materials of different morphologies. There were long needles and short rods without many intermediates. The sizes ranged between 2-4μm wide and 15-30μm length.

Example 6

The method used in Example 1 was repeated using a solution containing 5% each of adipic acid and L-(+)-ascorbic acid in methanol. The filter held a white powder, which on further inspection with a light microscope was found to contain two distinct types of crystalline particles with differing optical properties. Some particles rotated polarised light, as one would expect of L-(+)-ascorbic acid, while the rest did not.

Example 7

The method of Example 1 was repeated using a solution of 2.5% w/v each of adipic acid and copper (II) sulphate in methanol. At the end of the experiment the filter was found to contain pale blue product, which on further inspection with a light microscope appeared to be made up from two particle types showing distinct morphologies. 1μm spheres were observed with thin needles from 5μm-20μm in length.

Example 8

5% solution of adipic acid was prepared in iso-propanol. The experimental procedure described in example 1 was repeated with the exception that HFC236 was used instead of HFC134a. HFC flow was maintained at 120ml/minute and the formulation at 1ml/min. On completion of the experiment white crystalline material was isolated from the filter device. Examination by optical microscope showed that the product comprised well defined rods of about 2μm wide and 20μm long.

Example 9

The procedure of Example 7 was repeated HFC227 instead of HFC236. The HFC flow was maintained at 90ml/min and the formulation at 1ml/min. On completion of the experiment white crystalline material was isolated from the filter device. Examination by optical microscope showed that the product comprised well defined rods of about 1-2μm wide and 10μm long.

An alternative, second mixing device 10b for use as a mixer 10 in apparatus 2 is shown in figures 4 and 5. The

device includes a first stainless steel body part 50 and a second stainless steel body part 52 which engages therewith.

The first body part 50 includes a main chamber 54 which has a circular cross-section cylindrical upper portion 56 and, continuous therewith, a downwardly tapering conical position 58 which communicates with a first elongate axial flow channel 60 which, in turn, communicate with an exit port 62.

The body part 50 includes opposing HFC inlet portions 64, 66 which are arranged to communicate via narrow flow channels 68 (only one of which is shown in figure 4). The flow channels 68 extend tangentially to cylindrical upper portion 56, on opposite sides of a diameter thereof, and are arranged to deliver two streams of fluid in opposing directions into the upper end of the upper portion 56.

The body part 50 also includes a stepped region 70 which is arranged to cooperate with a corresponding step (not shown) provided in lower face 72 of second body part 52 for facilitating cooperation and securement of the first and second body parts 50, 52 together.

The second body part 52 includes a downwardly extending body 74 which include a first solid circular cross-section cylindrical portion 76 and a second solid conical portion 78. The portions 76, 78 are arranged such that when the first and second body parts 50, 52 are secured together,

body 74 fits within main chamber 54, with a narrow gap being defined around the body 74 (see figure 5).

The body 74 includes a second axial flow channel 80 which opens through upper face 82 of body part 52, extends axially through body 74, and opens at its lower end 84.

The first and second body parts 50, 52 are secured together by bolts (not shown) which extend through aligned openings 84, 86 in the respective body parts.

The mixer 10b is incorporated into the arrangement of figure 1 except that immediately downstream of HFC pump 20, fluid line 27 is divided into two HFC lines one of which is connected to HFC inlet port 64 and the other of which is connected to HFC inlet port 66.

In use, liquefied HFC is pumped through inlets 64, 66 so that two HFC streams are directed tangentially into chamber 54 from opposite directions. The HFC is caused to flow in a rotating, spiralling turbulent path as it passes down the cavity formed between body 74 and the wall of chamber 54. As the diameter of the cavity decreases in the region of conical portion 78, the velocity of the liquid increases, with the maximum agitation and energy being attained at tip 90 of the chamber 54.

A liquid formulation comprising a substance to be prepared as solid particles is pumped via pump 7 into the second axial flow channel 80 and is arranged to contact the

liquid HFC at tip 90 of chamber 54. As a consequence, there is very rapid mixing of HFC and the liquid formulation and solid particles of the substance are formed and subsequently isolated as described above for the figure 1 embodiment.

Examples 8 to 15 describe the preparation of solid particles using the apparatus of figures 4 and 5.

Example 10

Liquefied 1,1,1,2 tetrafluoroethane (HFC134a) was pumped into the spiral mixer through ports 64 and 66 at a flow rate of 69 ml/min. A 3% w/v solution of a proprietary pharmaceutical compound in methanol was pumped through port 80 at a flow rate of 0.7 ml/min. Inlet port was 50µm diameter giving flow velocity of the solution of 5.94m/s. The mixture exited the mixing zone at 90 at a flow velocity of 1.46m/s. The particulate product was collected on the in-line filter and the resulting solution comprising the HFC and organic carrier solvent passed through the back pressure device 28 into the evaporation vessel 29 from which the HFC was removed by evaporation using gas compressor 34. Conditions within the mixer 10b and in-line filter 26 were maintained at temperature of 12°C and 13.25barg. This was achieved by the HFC being chilled before entering the mixer which was thermally insulated. Temperatures were monitored using thermocouples.

After a run time of 10 minutes the solution flow was terminated and the system was flushed through with fresh HFC for a few minutes before the process was stopped and

the solid product harvested. The product comprised a white powder consisting of fine needle crystals, primarily 1-8μm in length.

Example 11

A solution containing 10% w/v adipic acid in ethanol was treated as in Example 8. 1,1,1,2,tetrafluoroethane was pumped through the mixer 106 at a flow rate of 69 ml/min. The adipic acid solution was pumped into the mixer at a flow rate of 0.7ml/min through a 50μm diameter solution inlet port 80 giving an inlet velocity of 5.94m/s. Resulting solid particles were removed on the in-line filter and the HFC/ethanol solution passed through back pressure device 28 to the evaporation vessel. Conditions within the mixer 10b and in-line filter were maintained at 12°C and 13.5barg. The harvested produce comprised a white powder, mostly comprising needles of 2-15μm in length.

Example 12

5% w/v solution of adipic acid in ethanol was treated as in Example 9. Conditions within the mixer 10b/ filter 26 were maintained at 38°C and 15barg. Fine white crystalline product was isolated. Needle sizes of 5-20μm were observed.

Example 13

An almost saturated solution of ascorbic acid in methanol was prepared. HFC134a was pumped at 104 ml/min into the mixer 10b. The ascorbic acid solution was pumped at 1ml/min through a 100μm solution inlet 80 giving an inlet velocity of 2.12m/s. Conditions within the mixer 10b/ filter 26 were maintained at 19°C and 13.5 barg. The

resulting mixture exited the mixer 10b at a velocity of 2.20m/s. Rod shape crystalline white powder was collected having an average particle size of <2μm with a range of <1μm-8μm.

Example 14

A solution of 4% w/v of copper (II) sulphate in methanol was treated as described in Example 8. HFC134a was pumped at 69 ml/min and the solution at 2ml/min through a 50μm solution inlet 8 giving an inlet velocity of 17m/s. Conditions in the mixer 10b/filter 26 were maintained at 24°C and 13 barg. The resulting mixture exited the mixer at a velocity of 1.46m/s. Extremely small, uniform, amorphous spherical particles were obtained

Example 15

A solution of 1%w/v polystyrene was formed in toluene. HFC134a was pumped at 69 ml/min into the mixer 10b. The solution was injected at 2ml/min through a 50μm solution inlet giving an inlet velocity of 17m/s. Conditions in the mixer 10b/filter 26 were maintained at 24°C and 12.5barg. Conglomerates of amorphous small, fine solid particles were obtained

Example 16

A solution containing 5% w/v each of adipic acid and L-(+)-Ascorbic acid particles was prepared in methanol and treated as described in Example 8. The HFC134a was pumped at 104 ml/min and the solution at 1ml/min through a 130μm solution inlet giving an inlet velocity of 1.25m/s. Conditions in the mixer 10b/filter 26 were maintained at 24°C and 14.5barg. Fine white powder was isolated which

consisted of homogeneous rod shape crystals of <1μm-3μm in length.

Example 17

A solution containing 2.5% w/v each of adipic acid and copper (II) sulphate was prepared in methanol and treated as described in Example 8. The HFC134a was pumped at 104 ml/min and the solution at 1ml/min through a 100μm solution inlet giving an inlet velocity of 2.2m/s. Conditions in the mixer 10b/filter 26 were maintained at 19°C and 12.5barg. The product isolated from the filter was pale blue in colour and consisted of a homogeneous mixture of two distinct crystal types. These were fine needles 10μm-20μm in length, and <5μm rods.

The apparatus of figure 1 may be varied as described below with reference to figure 6 to 8.

Referring to figure 6, downstream of pump 20, line 27 is divided into two HFC streams, one of which is directed through capillary tube 90 to pre-mix with the formulation in line 31. Typically, the ratio of the volume of HFC to formulation is 1:1 to 10:1. During the pre-mixing stage, the formulation undergoes initial blending with the HFC which modifies the formulation so that it has similar physical properties to those of the HFC. The premix may then be used in mixer 10a or 10b either by being directed into inlet 46b of mixer 10a or into inlet 80 of mixer 10b. The mixer 10a, 10b may then be operated as described above. When the modified formulation is brought into contact with HFC in the mixers 10a, 10b, it will mix with the HFC more readily and more efficiently resulting in the formulation of smaller particles.

Referring to Figure 7, a similar effect to that described with reference to Figure 6 is achieved by using a first static mixer 100 in which formulation in line 31 is mixed with HFC in line 102. In this case, however, flow 102 was pumped and therefore controlled independently. The ratio of HFC to formulation may be in the range 1:1 to 10:1. Downstream of the static mixer 100 the mixture may be treated as described with reference to Figure 6.

The static mixer 100 may be of similar design to the mixer 10a. Optionally, the pre-mixing stage may be used to introduce a second (or further) formulation of a substance in an organic carrier solvent such as a second active ingredient or an excipient, coating material or the like.

Referring to Figure 8, the mixer, for example mixer 10a may be modified so as to incorporate three or more tangential flow channels allowing the mixing of HFC with two or more formulations. In figure 6, there is shown first and second HFC flows 27, 127 and first and second solution flows 31, 131 being directed into mixer 10. The substances in solutions 31, 131 may comprise multiple active ingredients or one active ingredient and one excipient, particle coating agent or the like.

An example of use of the Figure 7 embodiment, is provided below.

Example 18

A 3% w/v solution of the same proprietary pharmaceutical compound that was used in Example 1 in methanol was

prepared. HFC134a was recycled through the apparatus via the mixer 10 at a flow rate of 120ml/min. The methanolic solution (1.5ml/min) was pumped together with HFC134a (3ml/min) into the mixer via a T-piece. At the end of the run, fine white powder was collected in the filter. On inspection, it was found to consist of uniform needle shape particles with widths of approximately 0.5-1.0μm, and lengths between 3-6μm.

Attention is directed to all papers and documents which are filed concurrently with or previous to this specification in connection with this application and which are open to public inspection with this specification, and the contents of all such papers and documents are incorporated herein by reference.

All of the features disclosed in this specification (including any accompanying claims, abstract and drawings), and/or all of the steps of any method or process so disclosed, may be combined in any combination, except combinations where at least some of such features and/or steps are mutually exclusive.

Each feature disclosed in this specification (including any accompanying claims, abstract and drawings) may be replaced by alternative features serving the same, equivalent or similar purpose, unless expressly stated otherwise. Thus, unless expressly stated otherwise, each feature disclosed is one example only of a generic series of equivalent or similar features.

The invention is not restricted to the details of the foregoing embodiment(s). The invention extends to any

novel one, or any novel combination, of the features disclosed in this specification (including any accompanying claims, abstract and drawings), or to any novel one, or any novel combination, of the steps of any method or process so disclosed.

CLAIMS

1. A process for preparing particles of a substance comprising:

(a) selecting a first formulation including a first substance or a precursor of a first substance;

(b) selecting a second formulation which includes a fluorocarbon;

(c) directing said first or said second formulation into a mixing device which is arranged to cause fluid directed into it to travel about an axis;

(d) contacting said formulation directed into the mixing device with the other one of either said first or said second formulation, wherein particles comprising said first substance form after contact of the first and second formulations.

2. A process according to claim 1, wherein said mixing device is arranged to defined a first travel path for the formulation directed into it in step (c), said first travel path including a curved component, downstream of an inlet of the travel path, which is arranged to cause fluid directed into the first travel path to travel about a said axis.

3. A process according to claim 2, wherein a part of said first travel path extends transversely to said axis.

4. A process according to claims 2 or 3, wherein said curved component of said first travel path is defined by a chamber which comprises an outer wall which includes a curved cross-section which includes a curved region which extends around the entirety of said axis of said travel path.

5. A process according to any of claims 2 to 4, wherein said first travel path includes a constriction which defines a part of an outlet travel path via which fluid can exit the mixing device.

6. A process according to any preceding claim, wherein fluid is arranged to travel about the said axis in step (c) and also to travel in the direction of said axis.

7. A process according to any preceding claim, wherein the ratio of the sum of the cross-sectional area(s) of each inlet of the mixing device to the sum of the cross-sectional area(s) of each outlet of the device is in the range 1:2 to 10:1.

8. A process according to any preceding claim, wherein in step (c) said second formulation is directed into the mixing device and caused to travel about said axis.

9. A process according to any preceding claim, wherein said mixing device is arranged to define a second travel path for a second stream of solvent formulation directed into it in step (c).

10. A process according to any preceding claim, wherein said mixing device comprises a first body and a second body which are releasably securable to one another, said first body including a first fluid inlet which extends from one side of the body to an opposite side thereof and wherein, in the method, said first formulation is directed through said first fluid inlet in step (d).

11. A process according to claim 10, wherein said first body includes a first face which is arranged to cooperate with said second body to define, in part, a fluid travel path of the mixing device.

12. A process according to any preceding claim, wherein the mixing device includes a first body which includes a said first fluid inlet and a second inlet, wherein said inlets extend substantially parallel to one another from one side of the body to an opposite side thereof and wherein said first and second inlets are arranged to receive the first and second formulations respectively; said second body defining at least a part of a first travel path and a second travel path, wherein said first and second travel paths extend transversely to a chamber of said mixing device and are arranged to direct fluids flowing in the first and second travel paths into one another in step (d).

13. A process according to claim 12, wherein the mixing device includes a third body which is releasably securable to the second body and which includes an outlet of the device.

14. A process according to any preceding claim, wherein said first or second formulation is caused to travel about said axis and the other one of said first or second formulation is initially contacted with the formulation travelling about said axis at a position downstream of a position at which travel of said fluid about said axis has been initiated.

15. A process according to claim 14, wherein the mixing device comprises a chamber into which said first or second formulation is arranged to be directed, the chamber being arranged to cause fluid directed into it in step (c) to rotate about a said axis, said mixing device including a first conduit means for delivering fluid into the chamber at a position towards a first end thereof and a second conduit means for delivering fluid into the chamber at a position towards a second end thereof, the arrangement being such that fluid passing into the chamber via said second conduit means contacts fluid in the chamber which has been delivered into the chamber upstream of said second conduit means and which has passed through the chamber and been caused to rotate about said axis as it moves towards said second end.

16. A process according to claim 15, wherein said chamber tapers inwardly on moving from said first end to said second end.

17. A process according to any preceding claim, wherein said first formulation and said second formulation are in a non-supercritical state.

18. A process according to any preceding claim, wherein a said fluorocarbon solvent used in the preparation of said particles is selected from a C_{1-4} fluorinated hydrocarbon, a perfluorocarbon and a C_{1-4} hydrofluorocarbon ether.

19. A process according to any preceding claim, wherein said fluorocarbon comprises one or more carbon, fluorine and hydrogen atoms only.

20. A process according to any preceding claim, wherein said fluorocarbon is a C_{2-3} fluorinated hydrocarbon.

21. A process according to any preceding claim, wherein said fluorocarbon is selected from iodotrifluoromethane, 1,1,1,2,3,3,3-heptafluoropropane (R-227 EA), 1,1,1,2,2,3,3-heptafluoropropane (R-227CA) and 1,1,1,2-tetrafluoroethane.

22. A process according to any preceding claim, wherein the first formulation comprising the first substance or precursor is a solution.

23. A process according to any preceding claim, wherein the first substance is an active ingredient selected from flavours, fragrances, plastics, polymers, bio-polymers, pigments, dyes, and biologically active compounds.

24. A process according to any preceding claim, wherein the temperature of the first and second formulations selected in steps (a) and (b) are each

independently greater than or equal to -20°C and are each independently less than or equal to 75°C.

25. A process for preparing particles of a substance comprising:

(a) selecting a first formulation including a first substance or a precursor of a first substance;

(b) selecting a second formulation;

(c) directing said first or said second formulation into a mixing device which is arranged to cause fluid directed into it to travel about an axis;

(d) contacting the formulation travelling about said axis at a position downstream of a position at which travel of said fluid about said axis has been initiated, wherein particles of said first substance form after contact of the first and second formulations.

26. A process according to claim 25, wherein said mixing device comprises a chamber which includes a first end and a second end, a first conduit means being provided for delivering fluid into the chamber at a position towards said first end and a second conduit means being provided for delivering fluid into the chamber at a position towards said second end, the arrangement being such that fluid passing into the chamber via said second conduit means contacts fluid which has been delivered into the chamber via said first conduit means, from a position upstream of said second conduit means, and has been caused to rotate about said axis as it moves towards said second end, and

particles of said first substance form after contact of the first and second formulations.

27. A process for preparing particles of a substance comprising:

(a) selecting a first formulation including a first substance or a precursor of a first substance;

(b) selecting a second formulation;

(c) directing said first or said second formulations into a mixing device which is arranged to cause fluid directed into it to rotate about an axis within an annular cavity and to pass axially along the cavity;

(d) contacting the formulation rotating about said axis with the other one of either said first or second formulation, wherein particles of said first substance form after contact of the first and second formulations.

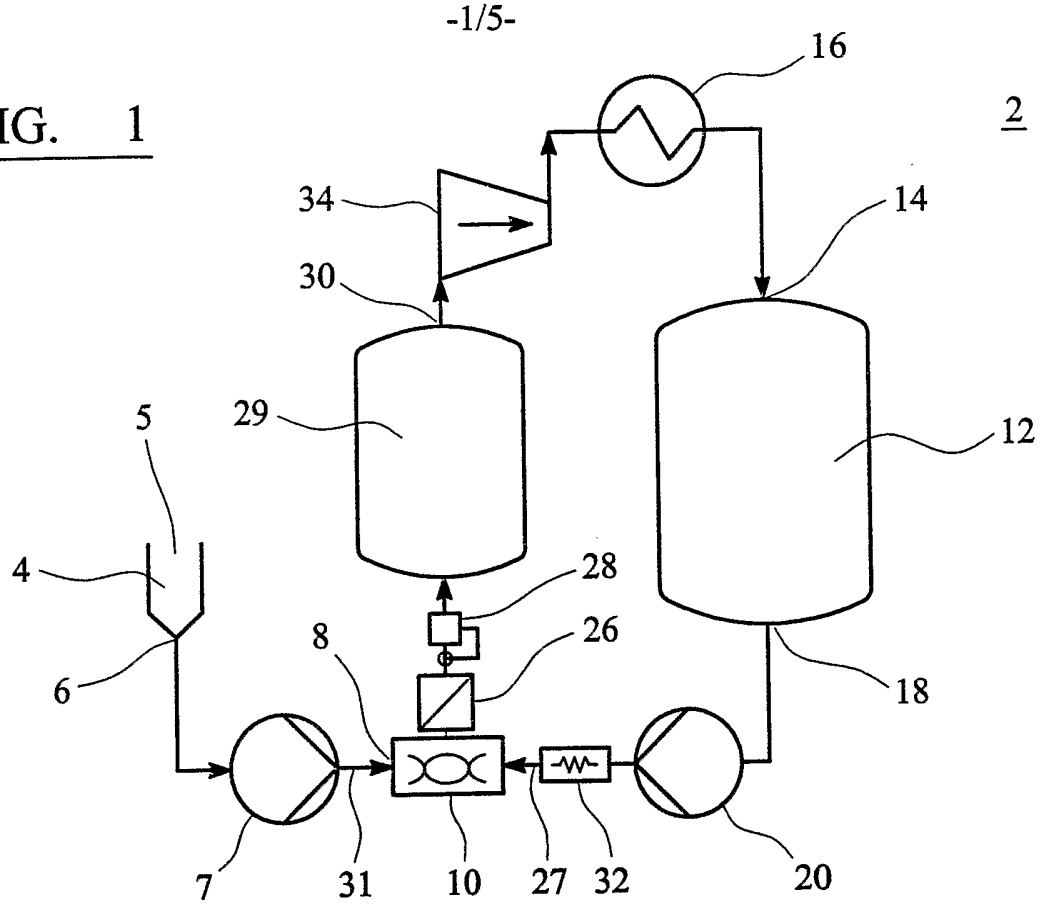
28. A mixing device comprising:

(a) a chamber which includes a first end and a second end;

(b) a first conduit means for delivering fluid into the chamber at a position towards said first end wherein said chamber is arranged to cause fluid directed into it via said first conduit means to rotate about an axis and move towards said second end;

(c) a second conduit means for delivering fluid into the chamber at a position toward said second end wherein said chamber is arranged to cause fluid directed into it via said second conduit means to contact fluid directed into said chamber via said first conduit means.

FIG. 1


16
2
34
14
30
29
12
5
4
28
26
8
6
18
7
31
10
27
32
20

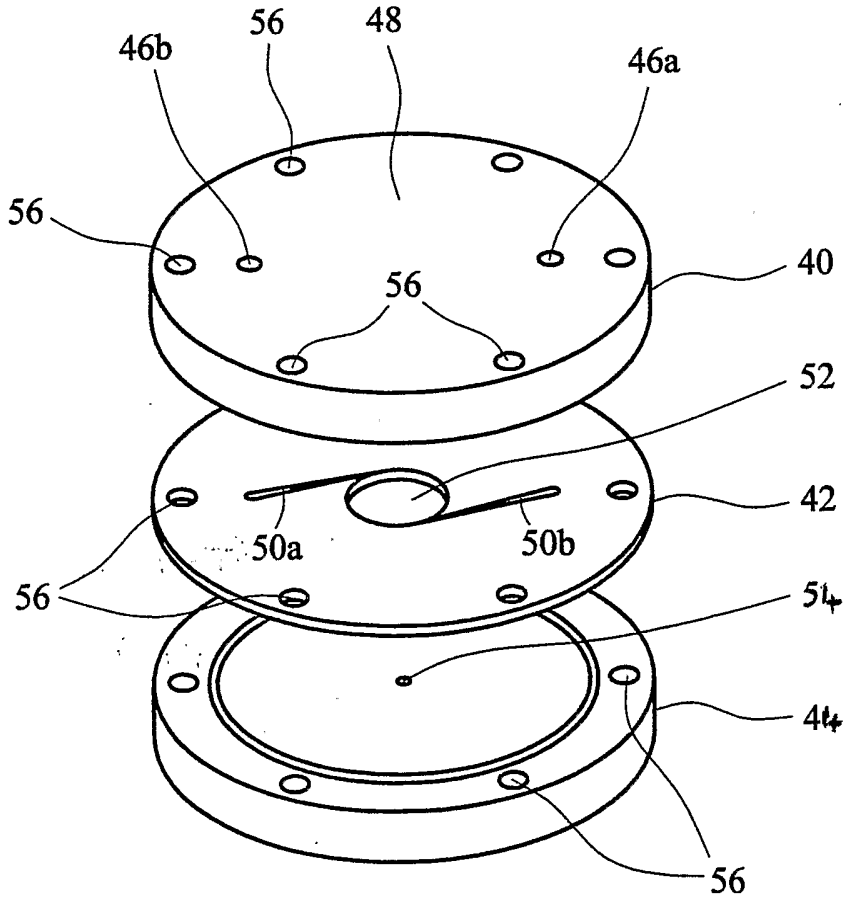

46b
56
48
46a
56
40
56
52
42
50a
50b
56
54
44
56

FIG. 2

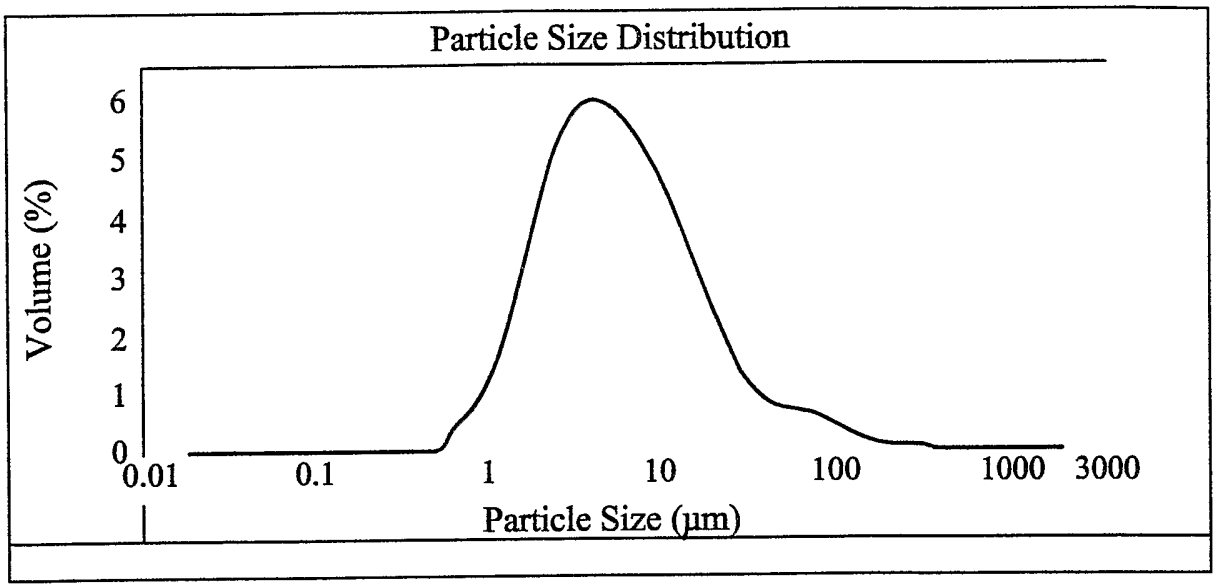

Particle Size Distribution
Volume (%)
0
1
2
3
4
5
6
0.01
0.1
1
10
100
1000
3000
Particle Size (µm)

FIG. 3

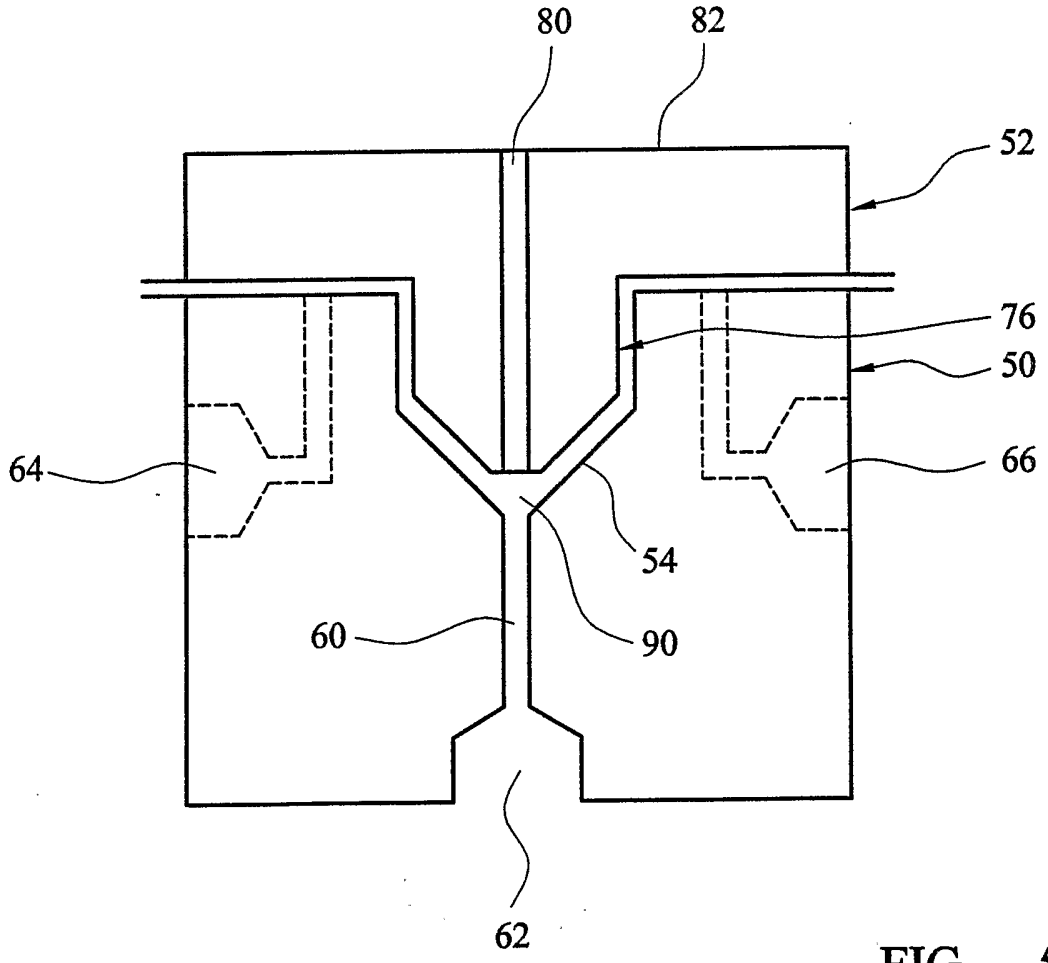

80
82
52
76
50
64
66
54
60
90
62

FIG. 5

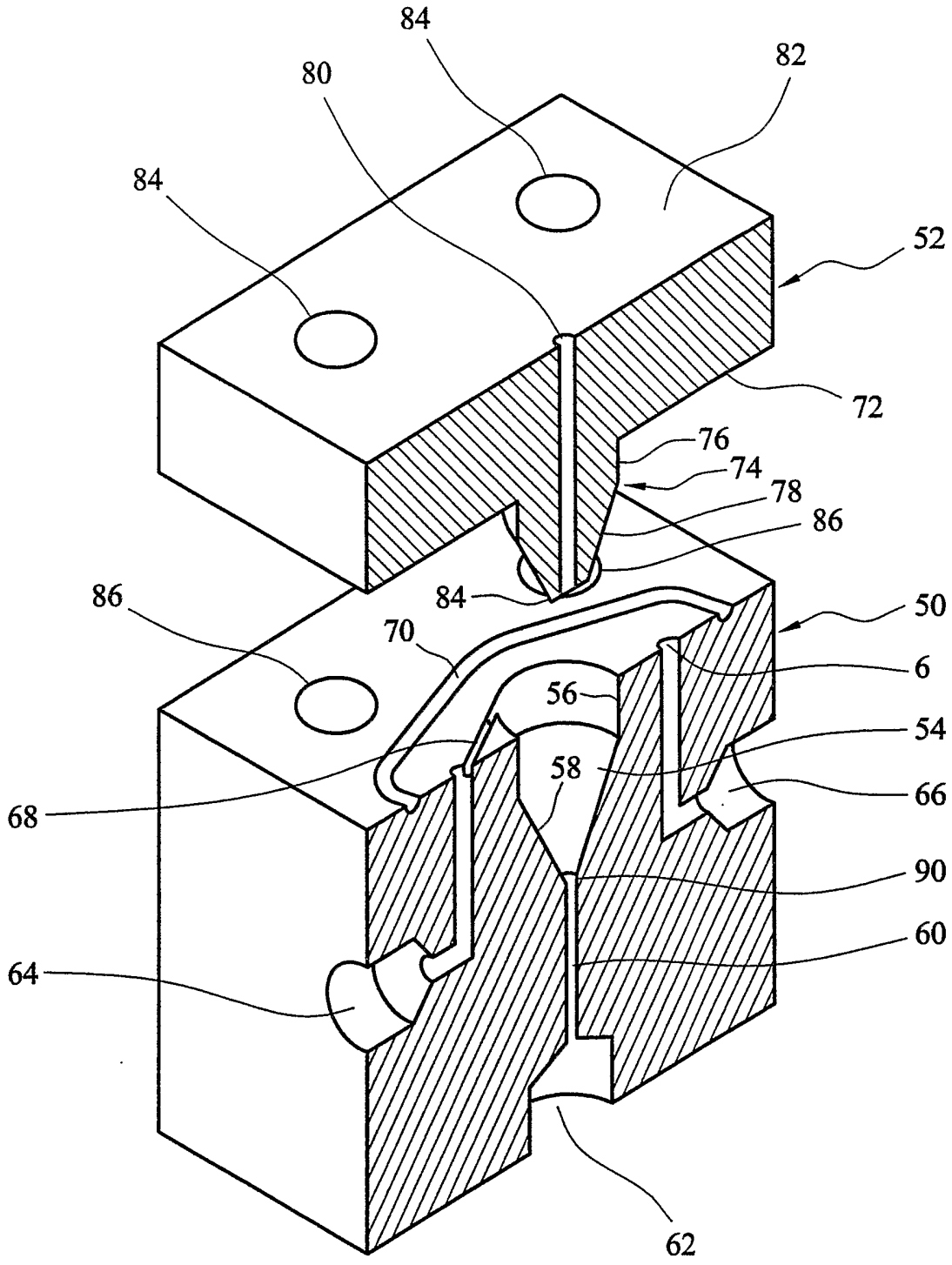


FIG. 4

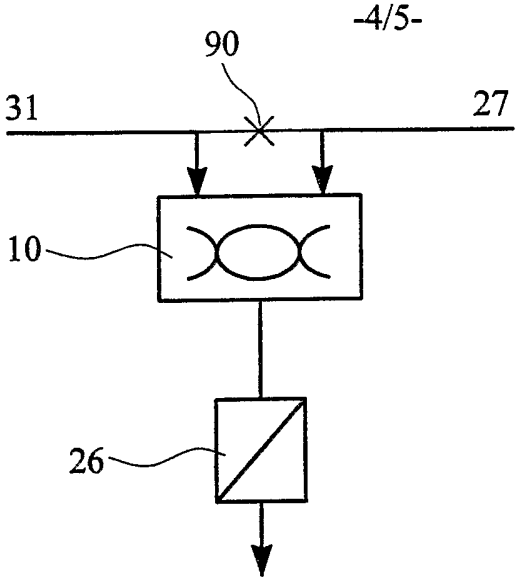


FIG. 6

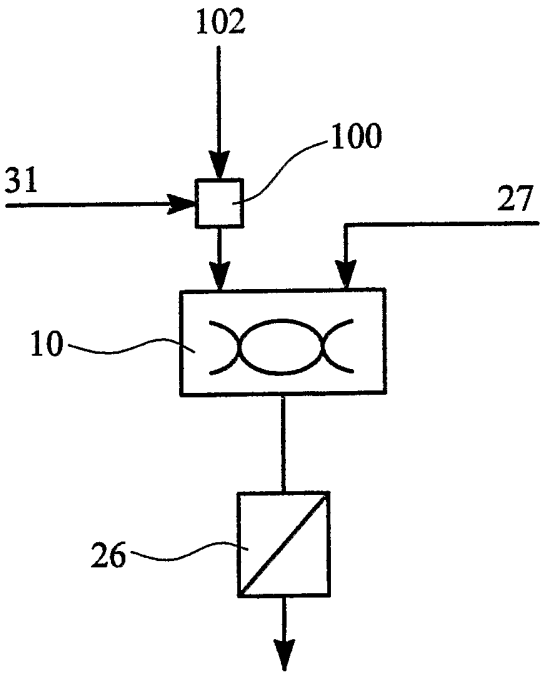


FIG. 7

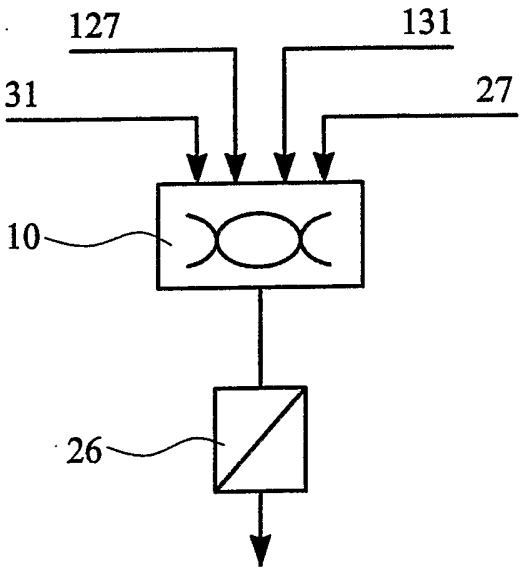
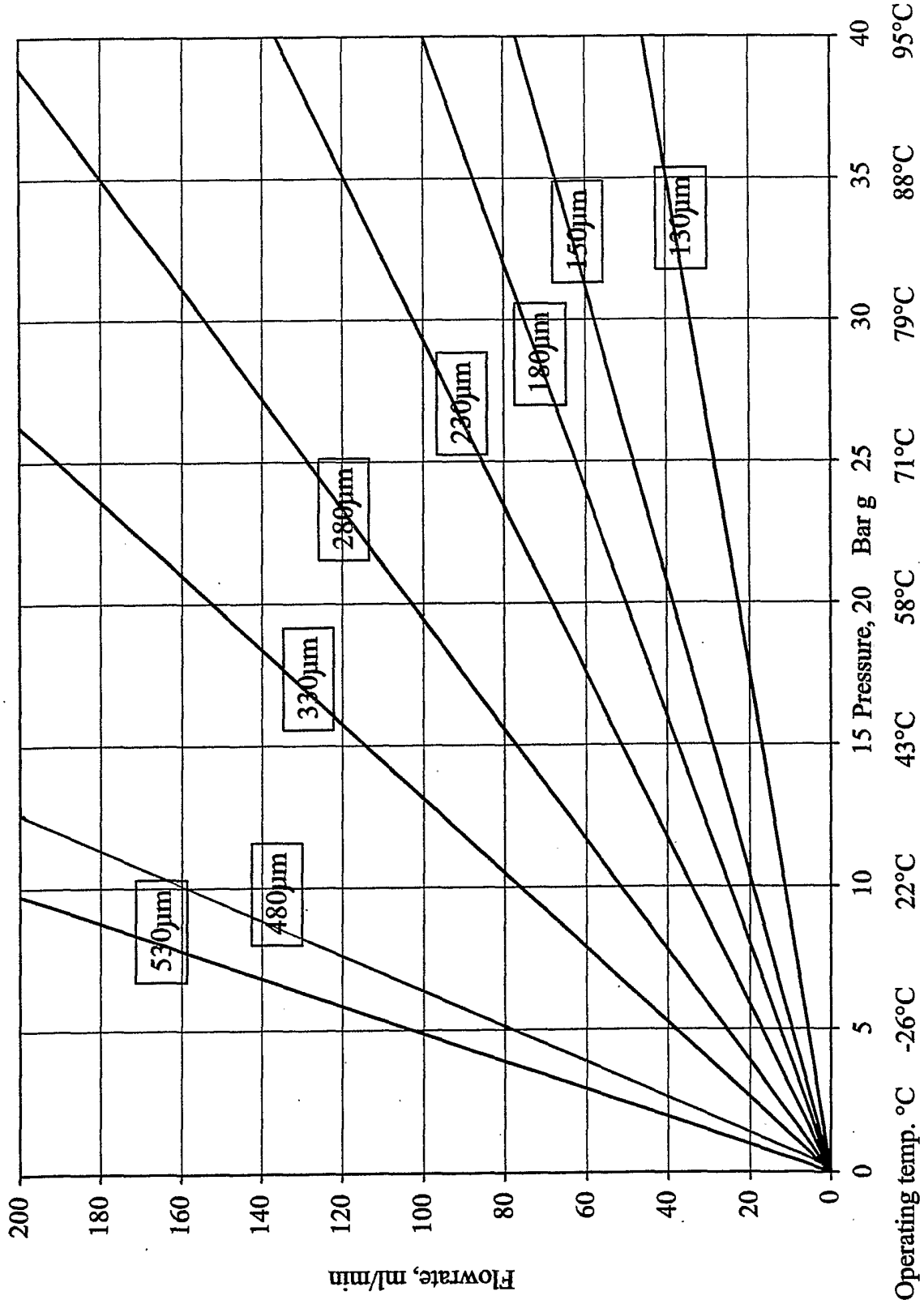


FIG. 8

FIG. 9


Flowrate, ml/min
200
180
160
140
120
100
80
60
40
20
0
530µm
480µm
330µm
280µm
230µm
180µm
150µm
130µm
Operating temp. °C -26°C 22°C 43°C 58°C 71°C 79°C 88°C 95°C
0 5 10 15 Pressure, 20 Bar g 25 30 35 40

INTERNATIONAL SEARCH REPORT

Inte al Application No
PCT/GB2005/003231

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C08J3/12 B01J2/02 B01D1/18 B01F3/08 B01F5/06

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)
IPC 7 C08J B01J B01D B01F

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

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Y	pages 37-43; figures 1-5	2-5,27
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Y	page 4, line 53 - page 6, line 1; figures 2-5	2-5,27
X	US 5 887 977 A (MORIKAWA ET AL) 30 March 1999 (1999-03-30) figures 1,2,4	28

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in 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
26 October 2005	07/11/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gruber, M

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INTERNATIONAL SEARCH REPORT

Int[illegible]al Application No
PCT/GB2005/003231

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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		DE 60001944 D1	08-05-2003
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