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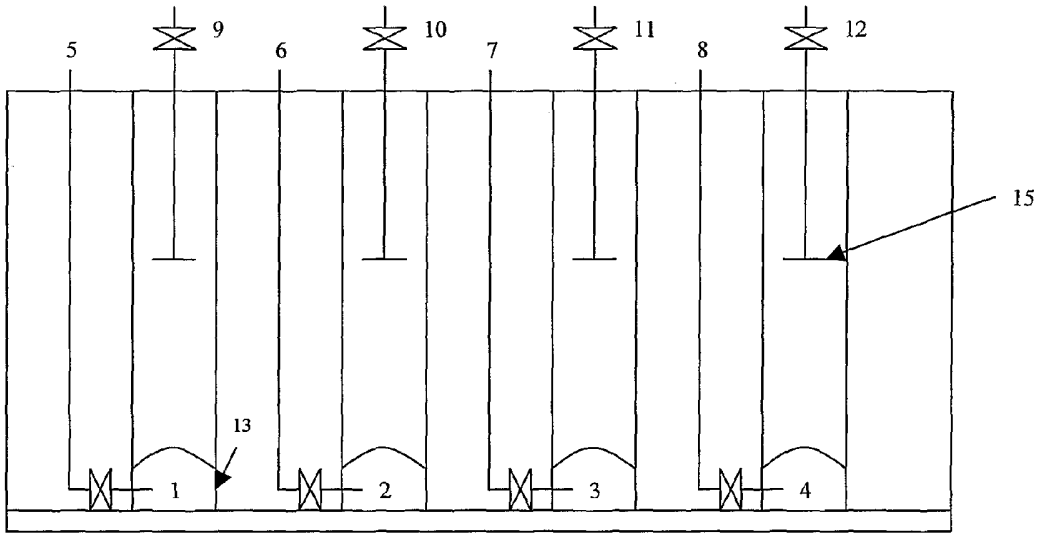
(54) **Title:** METHOD AND APPARATUS OF SCREENING POLYMORPHS OF A SUBSTANCE



(57) **Abstract:** The present invention provides a method and apparatus for screening polymorphs of a desired substance providing a plurality of enclosed spaces. The temperature and pressure of the enclosed spaces can be controlled. Various crystal identification means can be used to identify the polymorphic form of the solidified substance. The present invention uses an antisolvent technique for crystallizing a droplet or a cluster of droplets to form various polymorphs.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

TITLE

METHOD AND APPARATUS OF SCREENING POLYMORPHS OF A SUBSTANCE

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CROSS-REFERENCE TO RELATED APPLICATION

[0001] This patent application claims priority from the United States patent application of the same title, which was filed on May 3, 2004 and assigned United States patent application serial number 10/837876 and United States provisional patent application, which was filed on April 6, 2004 and assigned United States patent application serial number 60/559896, teachings of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0002] High-throughput screening is a technique used in a variety of fields including drug discovery. It is a process in which a large number of compounds are tested at one time for interaction with a specific target. Examples of interactions include various types of binding and biological activity against a target. Sophisticated systems can screen over 100,000 compounds per day, allowing for a fast way to eliminate compounds that are not potential drug candidates. Similar high throughput techniques are used in systems

where an experimental design can be performed to evaluate the effects of the variables on one or more specific characteristics.

[0003] In many instances, the same chemical compound can possess multiple crystalline structures. The term polymorphism is used to refer to this phenomenon and has been found to be increasingly important in catalytic, cosmetic, pharmaceutical and other applications. Drug research and development greatly depends on which polymorph of a drug substance is being used in the process because polymorphs of a substance can exhibit varying physical properties. Such varying properties may include:

1. Solubility
2. Melting point
3. Dissolution rate
4. Chemical Stability
5. Physical Stability
6. Powder flowability
7. Compaction
8. Particle Morphology
9. Hygroscopic behavior

[0004] Polymorph screening has been previously demonstrated and can be accomplished by altering parameters such as temperature, crystallization agent and solvent concentrations. However, these screening processes also need to be efficient, especially when the compounds involved are pharmaceutical in nature. Drug compounds can be very costly and synthesizing large quantities of early development compounds is often fraught with difficulties. Therefore, keeping quantities for screening experiments small

is critical. Multi-well plates can be employed in order to enable screening of a large number of crystallization conditions with minimal quantities of a desired drug substance.

[0005] Recently, several research groups have published results for the high-throughput screening of various compounds, namely proteins. Juárez-Martínez et al. (2002) *Anal. Chem.* 74:3505-3510 designed a micromachined miniaturized array of chambers for protein crystallization screening using hen egg white lysozyme as a model. The resulting crystals were analyzed using X-ray diffraction. Karain et al. (2002) *Acta Cryst.* D58:1519-1522 reported a system which was automated to screen protein crystals via X-ray diffraction. A semi-automatic system for protein crystallization was also described by Watanabe et al. *Acta Cryst.* D58:1527-1530. Finally, Heinemann et al. *Acc. Chem. Res.* 36:157-163 discussed the facilities and methods used for the high-throughput crystal structure analysis of human proteins. Proteins were first purified using affinity chromatography and then a robotic high-throughput screening system was built with the capacity to handle 960,000 experiments simultaneously. X-ray diffraction was used to analyze the crystals.

[0006] In addition to the aforementioned published journal articles, several patents and patent applications have also addressed this issue. In 1995, WO 95/01221 disclosed a method and apparatus for the formation of particles using an antisolvent process in which different polymorphs could be selectively formed. For example, when the antisolvent (carbon dioxide) was at 250 bar and 90°C, one polymorph was formed. However, at 300 bar and 45°C, a completely different polymorph resulted. This patent was thus able to demonstrate that variation of experimental parameters could indeed produce

various polymorphs. WO 02/20538 also teaches an unexpected finding of a way to produce a polymorph with a high level of purity by controlling the amount of water in the solvent.

[0007] Edwards et al (2001) *J. Pharm. Sci*, 90(8), 1115, Kordikowski et al. (2001) *Pharm. Res*,18(5), 682, Beach et al. *Org. Proc. Res. Dev* (1999) 3,370, Tong et al. (2001) *Pharm. Res.* 18(6) 852 and Hong et al. *Pharm. Res.* (2002) 19(5) 640 describe the background for the present invention where several polymorphs were obtained by changing certain conditions.

[0008] Various methods for the high-throughput screening of crystalline materials have been discussed in patent literature. Notable examples are WO 02/082047, WO 99/59716, WO 00/67872, WO 02/42731, US 2002/0177167, and US 2003/0061687. WO 01/82659 specifically discloses a system and method for the high-throughput screening of polymorphs. The system is comprised of an X-ray source which can emit a beam. An automatic sample changer allows for each sample to be positioned in the path of the beam. Once the sample is irradiated, a detector is used so the sample can be analyzed further. The automatic sample changer then removes the sample and inserts a new one in the path of the beam.

[0009] High-throughput crystallization and screening of biomolecules are discussed in WO 02/066713 and US 2002/0191048. These patents disclose a method in which fluid drops are ejected acoustically and subsequently from arrays that can be crystallized. The method can allow for the formation of combinatorial libraries of biomolecules, such as proteins. Additionally, small volumes of fluid are employed so the process can proceed more efficiently. Similarly, US 2003/0059522 also discloses the preparation of arrays of

peptides using acoustic energy. The fluids that can be used for this invention include a wide array of compounds, such as organic solvents, lipidic liquids, and supercritical fluids, provided that they can solubilize the given compound. The present invention differs from these in the way fluids are used: the present invention uses an antisolvent technique for crystallizing a droplet or a cluster of droplets to form various polymorphs.

[0010] The screening of polymorph libraries via X-ray diffraction is disclosed in US 6,507,636. Multi-well plates are used to create arrays that can be subjected to analysis for the potential discovery of new crystalline structures. Crystallization is performed in the wells of the plate, followed by the removal of a base plate. An X-ray beam is then scanned over the base plate and the crystals can then be analyzed. Automation in supercritical fluid extraction has been disclosed in US 5,866,004, the teachings of which set the background for the engineering structures needed for certain embodiments of the present invention.

BRIEF SUMMARY OF THE INVENTION

[0011] One embodiment of the present invention provides a method for screening polymorphs of a desired substance. The steps of this method embodiment comprise: (i) providing a plurality of enclosed spaces; (ii) transferring the dispersions of the desired substance in at least one solvent into different enclosed spaces; and (iii) applying a compressed antisolvent to the enclosed spaces to solidify the desired substance.

[0012] Another embodiment of the present invention provides an apparatus for the screening of polymorphs of a desired substance. The steps of

this apparatus embodiment comprise: (i) a plurality of enclosed spaces; (ii) a means for transferring dispersions of the desired substance in at least one solvent into different enclosed spaces; and (iii) a means for applying a compressed antisolvent to the enclosed spaces to solidify the desired substance.

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BRIEF DESCRIPTION OF THE DRAWINGS

[0013] **FIG.1** is a schematic representation of one embodiment of the present invention;

[0014] **FIG.2** illustrates the bottom cap of the battery of enclosed spaces 10 referred to in the present invention;

[0015] **FIG.3** illustrates the same element referred to in FIG.2 with a series of enclosed spaces;

[0016] **FIG.4** illustrates another embodiment of the present invention with enclosed spaces taking any shape or form;

15 [0017] **FIG.5** illustrates an embodiment of the present invention with antisolvent directly injected into the dispersion phase;

[0018] **FIG. 6** is a schematic representation of one embodiment of the polymorph screening system which uses a compressed antisolvent;

[0019] **FIG. 7** is a schematic representation of one embodiment of the 20 polymorph screening system which uses a compressed antisolvent and a co-antisolvent;

[0020] **FIG. 8** is a schematic representation of one embodiment of the polymorph screening system which uses a compressed antisolvent and a separate pump for the solution to enter the chamber; and

[0021] **FIG. 9** is a schematic representation of one embodiment of the polymorph screening system which uses a compressed antisolvent and a co-antisolvent and a separate pump for the solution to enter the chamber.

DETAILED DESCRIPTION OF THE INVENTION

Definitions:

[0022] "Polymorph" means

Different crystalline or non-crystalline structures of a solid material. It includes the amorphous form and various solvate, hydrate forms commonly referred to as pseudo polymorphs. Different polymorphs have different free energies associated with them.

[0023] "Metastable polymorph" means

A polymorph that is not stable at a specific environmental condition and may transform into another form in a period of time.

[0024] "Polymorph screening" means

Producing and identifying various polymorphs of a material.

[0025] "Desired substance" means

The material comprised of one or more substances of interest.

[0026] "Enclosed Space" means

A space enclosed by a metal or any other material.

[0027] "Antisolvent" means

A fluid that acts as a nonsolvent to a substance and crystallizes the substance.

[0028] "Compressed antisolvent" means

An antisolvent at a compressed state, i.e. at a higher pressure than atmospheric pressure.

[0029] "Crystal identification means" means

Techniques used to identify different crystal forms, structures or lack thereof. The present invention is not restricted by the type of the identification means. Any technique developed in the future can be used to practice the embodiments of the present invention. Typically, X-ray diffraction, differential scanning calorimetry, Raman spectroscopy, infrared or near infrared spectroscopy, thermal microscopy and others can be used for crystal identification.

[0030] "Crystal identification means transparent material" means

A material that is amorphous or single crystalline so that it does not affect the crystal structure identification of another substance present in the containers made of the material. It may be an amorphous or single crystalline material where its effects can be accounted for in crystal structure identification of the substance present in the container made of the material.

[0031] "Dispersion" means

A homogeneous or heterogeneous mixture of the desired substance in one or more suitable solvents with or without dispersants.

Description

[0032] The present invention provides a method and apparatus for screening polymorphs of a variety of substances in a reasonably rapid way. It should be noted that the term "screening" is used herein to mean "producing" and "producing and identifying" polymorphs of a variety of substances. It uses supercritical fluid technology as the basis for screening polymorphs. In the present invention, dispersions of a desired substance in various suitable solvents at various concentrations are prepared and transferred into several enclosed spaces which are capable of holding high pressures. A compressed

antisolvent is added to the enclosed space either directly into the dispersion phase or near the dispersion phase at a controlled rate. In another embodiment of the present invention, the enclosed space already contains the compressed antisolvent prior to the transfer of the dispersion of the desired substance into the enclosed space. Depending on the solvent, temperature, concentration of the dispersion, rate of addition of antisolvent to the enclosed space and pressure inside the enclosed space, solidification of the desired substance can be varied. It will be obvious to one skilled in the art that the term "solidification" includes crystallization or precipitation of the desired substance. By controlling crystallization, different polymorphs are formed. The temperature of the enclosed spaces can be controlled by devices including, but not limited to, electric heaters, zone heaters or magnetic heaters.

[0033] Techniques such as infrared and raman spectroscopy, X-ray diffraction, rate of dissolution, atomic force microscopy, near or infrared spectroscopy, attenuated total reflected FTIR and differential scanning calorimetry (DSC) can be used to identify different crystalline forms. Once various polymorphs are generated, any of these methods can be subsequently used as an analytical tool. Crystal structure identification may be performed while the dispersion is being solidified, after the dispersion is solidified, after the enclosed space is depressurized, or after the solidified desired substance is removed from the enclosed space. In one embodiment of the present invention, at least one side of the enclosed space is made of crystal structure identification means transparent material. This allows for a crystal structure identification means to be coupled to the apparatus for subsequent analysis of the solidified desired substance.

[0034] The volume of the enclosed spaces is chosen such that a given rate of addition of antisolvent can be achieved for a given amount of solution. **Fig. 1** illustrates an embodiment of the present invention. For representative reasons, four enclosed spaces are illustrated. It does not signify any limitation on the present invention. It can be 4, 8, 12, 96, 384, 864, 1536, or as many spaces as possible in any design. Typically, it can be defined by the automation available in crystal structure identification means and its ability to handle as many samples in an automated fashion. Enclosed spaces **1**, **2**, **3**, **4** are capable of holding pressures up to 30,000 psi. Antisolvent inlets **5**, **6**, **7**, **8** are provided with a one way check valve to ensure no fluid is moved out of the enclosed space in those inlet lines. Outlets **9**, **10**, **11** and **12** are provided for the antisolvent/solvent mixture to exit the enclosed space. Filtering element **15** provides a way to retain the crystallized material in the enclosed space. **Fig. 2** illustrates how bottom cap **14** and enclosed space wall **13** are attached and sealed using a high pressure seal **15**. A high pressure seal is optional if the bottom cap is pressure fitted to the vessel. **Fig. 3** illustrates the same in a configuration with four enclosed spaces.

[0035] **Fig. 4** illustrates an embodiment of the present invention in which the enclosed space can be in any shape. In a preferred embodiment, it is shown to be close to a spherical or spheroidal shape **1** with two split half spheres or spheroids pressed together with an optional high pressure seal. Crystallized material can be transferred either to a well plate designed for crystal structure identification means or a well plate designed to fit in the bottom half of the spheroids. In another embodiment of the present invention, the material can be crystallized directly onto the well plate. A crystal structure

identification means that is coupled to the apparatus can then be used to analyze the material. The spheroids are connected together forming a structure that can be described in layman's terms similar to a carton of eggs. Dispersion droplet **2** can be placed in the well plates prior to closing the spheroidal enclosed space by several dispensing means. Commercially available dispensers like ROBBINS® HYDRA® dispenser from Robbins Scientific Corporation, Sunnyvale, California can be used. The volume of the fluid can vary from fempto liter ($1x10^{-15}$) quantities to milliliter quantities based on the dispensing means used and the availability of the dispersion. Certain solutes, such as new drug candidates, are very expensive and difficult to synthesize in large quantities. As a result, very small quantities need to be used. In such situations, a dispensing means capable of dispensing fempto liter ($1x10^{-15}$), pico liter ($1x10^{-12}$) or nanoliter ($1x10^{-9}$) quantities will be chosen. Antisolvent inlet **3** can add antisolvent directly into the dispersion droplet or just into the enclosed space. It has a check valve to ensure no reverse flow of any fluid. A high pressure seal **5** seals the two spheroids or spheroids and the well plate element to ensure no fluid leaks out. Exit **4** is fitted with a filtering element to retain the crystallized material inside the enclosed spaces. **Fig. 5** illustrates an embodiment similar to the one in **Fig. 4** except that the compressed antisolvent is added directly into the dispersion phase.

[0036] In another embodiment of the present invention, after the dispersion is dispensed onto the bottom half-spheroids or well plates, the enclosed spaces are closed and sealed. Compressed antisolvent is added at a controlled rate either into the enclosed space or directly inside the dispersion phase. Typically, slow additions increase the pressure inside the enclosed

space slowly leading to slow saturation. At a pressure close to the cloud point of the system, crystallization starts and the pressure is further increased to a point where almost all the material is crystallized as per the thermodynamics and kinetics of crystallization. After that, a valve in the exit line is opened and using a valve or a back pressure regulator, the pressure is maintained at the same value while antisolvent is continuously added to and removed from the enclosed spaces. The antisolvent extracts the solvent from the droplet while simultaneously dissolving in the droplet, thus expanding it and crystallizing the desired substance. The solvent/antisolvent mixture exits the enclosed space through exit **4** while the crystallized material is retained in the enclosed spaces.

[0037] In another embodiment of the present invention, the pressure of the enclosed spaces can be varied. The pressure can be varied before or during the application of the compressed antisolvent. Adding pressure at different times can also vary the crystallization parameters and therefore lead to obtaining different polymorphs.

[0038] In another embodiment of the present invention, provisions are provided for introducing external agents that can enhance or induce the crystallization of the dispersion droplets in the enclosed space. The amount of the enhancing agent or inducing agents can be varied depending on the nature of the system. The rate of addition of such agents can also be varied to vary the crystallization rate and obtain different polymorphs. Similarly, a small amount of a desired polymorph can be seeded around the time the dispersion starts crystallizing in the enclosed space. Such addition of a solid to a pressurized enclosed space may require some solid addition means.

[0039] Another embodiment of the present invention is shown in **FIG. 6.** The system comprises high pressure pump **1** for pumping a compressed antisolvent. A plunger **3** is in fluidic communication with the compressed antisolvent. A plurality of enclosed spaces is provided in a circular carousel **2.** The plurality of enclosed spaces can also be in the form of a well plate, high pressure vessels or any other from capable of enhanced throughput. An enclosed space **13** presented to the plunger **3** can be pushed from the carousel **2** by the plunger **3** into the chamber **4.** The enclosed space **13** contains a filter with a check valve **5** at the inlet and another filter **6** at the outlet. The check valve **5** ensures no dispersion flow back into the compressed antisolvent addition line. Inside each enclosed space **13** will be a dispersion of a desired substance dissolved in a suitable solvent at a desired concentration. Once the enclosed space **13** is in chamber **4**, compressed antisolvent is added to the enclosed space **13** in a controlled manner increasing the pressure in the enclosed space **13** slowly. This results in crystallization of the dispersion in the enclosed space **13**. Experimental conditions, such as dispersion concentration, pressure, temperature and compressed antisolvent addition rate will be varied in each enclosed space **13**. Depending on the experimental conditions, different polymorphs can be formed. Once the polymorphs are formed as per the embodiments of the present invention in chamber **4**, the compressed antisolvent with the solvent will be carried out of the chamber **4** through a back pressure regulator (BPR) **7** into a separator **8** in which the compressed antisolvent will be vented off through the top **9** and the solvent will be removed at the bottom **10**. The enclosed space **13** that is inside of the chamber **4** will be returned to its designated place in the carousel **2** and the carousel **2** will then

rotate so as to allow another enclosed space **13** to be pushed into the chamber **4** by the plunger **3**. The individual enclosed space **13** can then be removed from the carousel **2**. The contents of enclosed space **13** can be transferred to a crystal structure identification means. Such transfer can be accomplished after all the enclosed spaces were processed in chamber **4**.

[0040] Another embodiment of the present invention is shown in **FIG. 7.** The system comprises high pressure pump **1** for pumping a compressed antisolvent. Another high pressure pump **11** to pump a co-antisolvent is also provided. A mixing tee **14** is provided so as to completely mix the compressed antisolvent and the co-antisolvent. A plunger **3** is in fluidic communication with the compressed antisolvent/co-antisolvent mixture. A plurality of enclosed spaces is provided in a circular carousel **2**. The plurality of enclosed spaces can also be in the form of a well plate, high pressure vessels or any other from capable of enhanced throughput. An enclosed space **13** presented to the plunger **3** can be pushed from the carousel **2** by the plunger **3** into chamber **4.** The enclosed space **13** contains a filter with a check valve **5** at the inlet and another filter **6** at the outlet. The check valve **5** ensures no dispersion flow back into the compressed antisolvent addition line. Inside each enclosed space **13** will be a dispersion of a desired substance dissolved in a suitable solvent at a desired concentration. Once the enclosed space **13** is in chamber **4**, compressed antisolvent is added to the enclosed space **13** in a controlled manner increasing the pressure in the enclosed space **13** slowly. This results in crystallization of the dispersion in the enclosed space **13**. Experimental conditions, such as dispersion concentration, pressure, temperature and compressed antisolvent addition rate will be varied in each enclosed space **13**.

Depending on the experimental conditions, different polymorphs can be formed. Once the polymorphs are formed as per the embodiments of the present invention in chamber **4**, the compressed antisolvent, with the solvent and co-antisolvent will be carried out of the chamber **4**, through a back pressure regulator (BPR) **7** into a separator **8** in which the compressed antisolvent will be vented off through the top **9** and the solvent will be removed at the bottom **10**. The enclosed space **13** that is inside of the chamber **4** will be returned to its designated place in the carousel **2** and the carousel **2** will then rotate so as to allow another enclosed space **13** to be pushed into the chamber **4** by the plunger **3**. The individual enclosed space **13** can then be removed from the carousel **2**. The contents of **13** can be transferred to a crystal structure identification means. Such transfer can be accomplished after all the enclosed spaces were processed in chamber **4**.

[0041] Another embodiment of the present invention is shown in **FIG. 8.** The system comprises a high pressure pump **1** for pumping a compressed antisolvent. A plunger **3** is in fluidic communication with the compressed antisolvent. An enclosed space **13** presented to the plunger **3** can be pushed from the carousel **2** by the plunger **3** into chamber **4.** The enclosed space **13** contains a filter with a check valve **5** at the inlet and another filter **6** at the outlet. The check valve ensures no dispersion flow back into the compressed antisolvent addition line. Once the enclosed space **13** is in chamber **4**, compressed antisolvent is added to the enclosed space at a constant rate and the pressure of the enclosed space **13** is maintained at a constant pressure with the use of the back pressure regulator **7**. Once the pressure and temperature are stabilized at the desired values, a dispensing means **12** transfers the

dispersion containing the desired substance in a suitable solvent directly into the enclosed space **13** which is inside chamber **4**. Appropriate fluidic connections are provided to accomplish this transfer. An optional dispersing means **16** may be provided for dispersing the dispersion into the enclosed space **13**. This can be accomplished by any suitable dispersing means, including but not limited to a nozzle. This example is meant to illustrate a suitable dispersing means, but is not intended to limit the scope of this invention. It will be obvious to one skilled in the art that a multitude of suitable dispersing means exist and all are encompassed by the scope of the present invention. A dispersing means is not mandatory to practice the present invention. However, it may provide for an increased crystallization rate, allowing some embodiments of the present invention to be practiced more easily. Mass transfer can also be enhanced by a vibrating surface. This can be accomplished by any suitable means for surface vibration, including but not limited to ultrasound and magnetorestrictive means. The frequency of the vibrating surface includes, but is not limited to, the gigahertz range. This is meant to illustrate a suitable means for surface vibration, but is not intended to limit the scope of this invention. It will be obvious to one skilled in the art that a multitude of suitable surface vibration means exist and all are encompassed by the scope of the present invention. The dispensing means **12** has the ability to vary properties such as dispersion concentration, dispersion addition rate and solvent type. The substance in the dispersion is crystallized and such crystals are retained inside the enclosed space **13** by the provided filters at the outlet end. The compressed antisolvent, with the solvent will be carried out of the chamber **4**, through the back pressure regulator (BPR) **7** into a separator **8** in which the

compressed antisolvent will be vented off through the top **9** and the solvent will be removed at the bottom **10**. The enclosed space **13** that is inside of the chamber **4** will be returned to its designated place in the carousel **2** and the carousel **2** will then rotate so as to allow another enclosed space **13** to be pushed into the chamber **4** by the plunger **3**. The individual enclosed space **13** can then be removed from the carousel **2**. The contents of enclosed space **13** can be transferred to a crystal structure identification means. Such transfer can be accomplished after all the enclosed spaces were processed in chamber **4**.

[0042] Another embodiment of the present invention is shown in **FIG. 9.** The system comprises a high pressure pump **1** for pumping a compressed antisolvent. Another high pressure pump **11** for pumping a co-antisolvent is also provided. A mixing tee **14** is provided so as to completely mix the compressed antisolvent and the co-antisolvent. A plunger **3** is in fluidic communication with the compressed antisolvent/co-antisolvent mixture. An enclosed space **13** presented to the plunger **3** can be pushed from the carousel **2** by the plunger **3** into chamber **4**. The enclosed space **13** contains a filter with a check valve **5** at the inlet and another filter **6** at the outlet. The check valve ensures no dispersion flow back into the compressed antisolvent addition line. Once the enclosed space **13** is in chamber **4**, compressed antisolvent is added to the enclosed space at a constant rate and the pressure of the enclosed space **13** is maintained at a constant pressure with the use of back pressure regulator (BPR) **7**. Once the pressure and temperature are stabilized at the desired values, a dispensing means **12** transfers the dispersion containing desired substance in a suitable solvent directly into the enclosed space **13** which is inside the chamber **4**. Appropriate fluidic connections are provided to

accomplish this transfer. An optional dispersing means **16** may be provided for dispersing the dispersion into the enclosed space **13**. This can be accomplished by any suitable dispersing means, including but not limited to a nozzle. This example is meant to illustrate a suitable dispersing means, but is not intended to limit the scope of this invention. It will be obvious to one skilled in the art that a multitude of suitable dispersing means exist and all are encompassed by the scope of the present invention. A dispersing means is not mandatory to practice the present invention. However, such dispersing means may provide for increased crystallization rate, allowing some embodiments of the present invention to be practiced more easily. Mass transfer can also be enhanced by a vibrating surface. This can be accomplished by any suitable means for surface vibration, including but not limited to ultrasound and magnetorestrictive means. The frequency of the vibrating surface includes, but is not limited to, the gigahertz range. This is meant to illustrate a suitable means for surface vibration, but is not intended to limit the scope of this invention. It will be obvious to one skilled in the art that a multitude of suitable surface vibration means exist and all are encompassed by the scope of the present invention. The dispensing means **12** has the ability to vary properties such as dispersion concentration, dispersion addition rate and solvent type. The substance in the dispersion is crystallized and such crystals are retained inside the enclosed space **13** by the provided filters at the outlet end. The compressed antisolvent with the solvent will be carried out of chamber **4** through back pressure regulator (BPR) **7** into a separator **8,** where the compressed antisolvent will be vented off through the top **9** and the solvent will be removed at the bottom **10**. The enclosed space **13** that is inside of the chamber **4** will be returned to its

designated place in the carousel **2** and the carousel **2** will then rotate so as to allow another enclosed space **13** to be pushed into the chamber **4** by the plunger **3**. The individual enclosed space **13** can then be removed from the carousel **2**. The contents of **13** can be transferred to a crystal structure identification means. Such transfer can be accomplished after all the enclosed spaces were processed in chamber **4**.

[0043] In another embodiment of the present invention, instead of a carousel **2** allowing for rotation of each extraction vessel **13**, the carousel **2** may remain stationary and the chamber **4** will have the ability to rotate to each enclosed space **13**. In another embodiment of the present invention, referring to **Fig. 6** through **Fig. 9**, a collecting plate **15**, can be placed beneath the carousel **2** in order to collect the polymorphs that are formed from each enclosed space **13** present in the carousel **2**. Once all polymorphs are collected on the collecting plate **15**, the collecting plate **15** can be transferred to a crystal structure identification means.

[0044] The embodiments shown in **Fig. 7** and **Fig. 9** provide for co-antisolvent mixed with antisolvent. Such schemes are used when the solvent used is not directly substantially miscible with the antisolvent. For example, when water or any other polar solvents are used, a co-antisolvent such as ethanol or methanol can be used with carbon dioxide as the antisolvent. Other antisolvents include, but are not limited to, methanol, ethanol, dimethylsulfoxide, tetrahydrofuran, N,N dimethylformamide, toluene, dichloromethane, ethyl ether, heptane, hexane, methylethylketone, methylisobutylketone, acetone, chloroform, fluoroform, carbon tetrachloride, cyclohexane, ethyl acetate, ethyl formate, isbutyl acetate, isopropyl acetate, 2-

methyl-1 propanol, pentane, 1-pentanol, 1-propanol, and 2-propanol, ethane, propane, carbon dioxide, nitrous oxide, butane, isobutene, sulfur hexafluoride, a hydrofluorocarbon, a chlorofluorocarbon, or a combination thereof. This is applicable to a large category of water soluble medicaments including, but not limited to, proteins, peptides and water soluble salt forms such as albuterol sulfate. Typically, if an organic solvent is used, it may affect the secondary and tertiary structures of proteins. Such issues will be completely eliminated when water is used as per the embodiments of the present invention.

[0045] Crystal structure identification means may be broadly classified into visual analysis, microscopic analysis, thermal analysis, diffraction analysis and spectroscopic analysis.

[0046] Any one or more than one of these techniques can be used to identify a crystal structure or a lack thereof. Visual analysis includes, but is not limited to, observing it under different light sources. Microscopic analysis includes, but is not limited to, scanning or tunneling electron microscopy, atomic force microscopy, thermal microscopy, or optical microscopy. Thermal analysis includes, but is not limited to, thermo gravimetric analysis and differential scanning calorimetry. Diffraction analysis includes, but is not limited to, X-ray diffraction, laser diffraction or dynamic laser diffraction. Spectroscopic techniques include, but are not limited to, near infrared spectroscopy, fourier transform infrared spectroscopy, attenuated total reflectance fourier tranform infrared spectroscopy, and nuclear magnetic resonance spectroscopy.

[0047] In another embodiment of the present invention, the portion of the dispersion inside the enclosed spaces can be pre-pressurized before the end

anti-solvent is applied. In an additional embodiment, such a pre-pressurized system can be maintained at a constant pressure while the compressed anti-solvent is being added by increasing the volume simultaneously. This allows crystallization to take place at a constant pressure.

[0048] Various elements of the present invention can be practiced individually or in any combination thereof without any limitation. All elements disclosed in the present disclosure can be practiced within the context of various industries including but not limited to, fine chemicals, pharmaceuticals, nutraceuticals, coatings, and petro-chemical industries.

[0049] The following example clearly illustrates the present invention:

Example 1. Searching for and generating polymorphs of sulfathiazole.

Carbon dioxide was used as the antisolvent and testing was carried out in an antisolvent system manufactured by Thar Technologies, Inc. This design of experiments utilized only one pressure, 100 bar, but pressure may be varied as a process parameter. Table 1 summarizes the temperatures and solvents used in this design of experiments.

Table 1: Solvents and Temperatures Used for Sulfathiazole Polymorph Generation

Experiment	Temp (C)	Solvent	Solution Conc. (mg/ml)
1	35	MeOH	10
2	35	Acetone	15
3	61	MeOH	10
4	60	MeOH	10
5	35	EtOH	20
6	36	EtOH	10
7	49	EtOH	10
8	35.8	EtOH	10

9	36.2	EtOH/H20	40
10	36.3	2-Propanol	5.5
11	88.1	2-Propanol	5.5
12	36.3	2-Propanol/EtOH	10

The analysis was conducted by RJ Group (Monroeville, PA). A portion of each sample was loaded onto a zero background XRD holder for analysis. The samples were run using standard run parameters on a PANalytical X'Pert Pro XRD unit equipped with a copper radiation source. The following table presents those results.

Table 2: Results of XRD Analysis for Sulfathiazole Polymorph Generation

Experiment	Polymorph
1	III Major, IV Major
2	III, Minor, IV Major
3	III Major
4	I Major, III Minor
5	I Trace, IV Major
6	II Trace, IV Major
7	II Minor, IV Major
8	I Major, III Minor, IV Minor
9	III Major, IV Minor
10	III Major, I Minor
11	I Major, IV Minor
12	I Minor, IV Major

[0050] The above-provided discussion of various embodiments of the present invention is intended to be an illustrative, but not exhaustive, list of possible embodiments. It will be obvious to one skilled in the art that other embodiments are possible and are included within the scope of this invention.

Claims:

1. A method for screening polymorphs of a desired substance comprising the steps of:

    a. Providing a plurality of enclosed spaces

    b. Transferring dispersions of said desired substance in at least one solvent into different enclosed spaces; and

    c. Applying a compressed antisolvent to said enclosed spaces to solidify said desired substance

2. The method of claim 1 wherein the temperature of said enclosed spaces is controlled.
3. The method of claim 1 wherein identification of the polymorphic form of said solidified desired substance is accomplished using a crystal structure identification means.
4. The method of claim 1 wherein said dispersion is atomized into said enclosed spaces.
5. The method of any one of claims 1 through 4 wherein said transfer of dispersion and application of antisolvent are carried out simultaneously.
6. The method of claim 1 wherein said solvents are aqueous-based.
7. The method of claim 1 wherein said solvents are organic-based.
8. The method of claim 1 wherein said solvents are a combination of organic and aqueous-based.
9. The method of claim 1 wherein said plurality of enclosed spaces is selected from the group consisting of at least one well plate, a carousel, high pressure vessels, and a combination thereof.

10. The method of claim 2 wherein said temperature is controlled from the group consisting of electric heaters, magnetic heaters, zone heaters, and a combination thereof.

11. The method of claim 1 wherein a means for controlling the rate of application of said compressed antisolvent is provided.

12. The method of claim 1 wherein said compressed antisolvent is added directly into said dispersion phase.

13. The method of claim 1 wherein the pressure of said enclosed spaces can be varied.

14. The method of claim 13 wherein said pressure can be varied before applying said compressed antisolvent.

15. The method of claim 13 wherein said pressure can be varied while applying said compressed antisolvent.

16. The method of claim 1 wherein said compressed antisolvent is selected from the group consisting of methanol, ethanol, dimethylsulfoxide, tetrahydrofuran, N,N dimethylformamide, toluene, dichloromethane, ethyl ether, heptane, hexane, methylethylketone, methylisobutylketone, acetone, chloroform, fluoroform, carbon tetrachloride, cyclohexane, ethyl acetate, ethyl formate, isbutyl acetate, isopropyl acetate, 2-methyl-1 propanol, pentane, 1-pentanol, 1-propanol, and 2-propanol, ethane, propane, carbon dioxide, nitrous oxide, butane, isobutene, sulfur hexafluoride, a hydrofluorocarbon, a chlorofluorocarbon, and a combination thereof.

17. The method of claim 3 wherein said crystal structure identification means is selected from the group consisting of X-ray diffractometry,

thermomicroscopy, solid state nuclear magnetic resonance spectroscopy, infrared spectroscopy, near infrared spectroscopy, differential scanning calorimetry, raman spectroscopy, and a combination thereof.

18. The method of claim 1 wherein the bottom of said enclosed space holds said solidified desired substance.

19. The method of claim 1 wherein at least one side of said enclosed spaces is made of crystal identification means transparent material.

20. The method of claim 3 wherein said crystal structure identification is performed while said dispersion is being solidified.

21. The method of claim 3 wherein said crystal structure identification is performed after said dispersion is solidified.

22. The method of claim 3 wherein said crystal structure identification is performed after said enclosed space is depressurized.

23. The method of claim 3 wherein said crystal structure identification is performed after said solidified desired substance is removed from said enclosed space.

24. The method of claim 1 wherein transfer of said dispersion is accomplished through a dispensing means.

25. The method of claim 24 wherein said dispensing means can handle femptoliter quantities or greater.

26. The method of claim 1 wherein said enclosed spaces contain said compressed antisolvent prior to transfer of said dispersions of said desired substance in at least one solvent.

27. The method of claim 26 wherein transferring said dispersions of said desired substance in at least one solvent into different enclosed spaces

that already contain said compressed antisolvent is accomplished through a dispersing means.

28. The method of claim 27 wherein the dispersing means is a nozzle.

29. The method of claim 27 wherein mass transfer can be enhanced by a vibrating surface.

30. The method of claim 1 wherein external agents are introduced to enhance or induce the crystallization of the dispersion droplets in the enclosed space.

31. An apparatus for screening polymorphs of a desired substance comprising:

a. A plurality of enclosed spaces;

b. A means for transferring dispersions of said desired substance in at least one solvent into different enclosed spaces; and

c. A means for applying a compressed antisolvent to said enclosed spaces to solidify said desired substance.

32. The apparatus of claim 31 wherein the temperature of said enclosed spaces is controlled.

33. The apparatus of claim 31 wherein identification of the polymorphic form of said solidified desired substance is accomplished using a crystal structure identification means.

34. The apparatus of claim 31 wherein said dispersion is atomized into said enclosed spaces.

35. The apparatus of any one of claims 31 through 34 wherein said transfer of dispersion and application of antisolvent are carried out simultaneously.

36. The apparatus of claim 31 wherein said plurality of enclosed spaces is selected from the group consisting of at least one well plate, a carousel, high pressure vessels, and a combination thereof.

37. The apparatus of claim 32 wherein said temperature is controlled from the group consisting of electric heaters, magnetic heaters, zone heaters, and a combination thereof.

38. The apparatus of claim 31 wherein a means for controlling the rate of application of compressed antisolvent is provided.

39. The apparatus of claim 31 wherein said compressed antisolvent is added directly into said dispersion phase.

40. The apparatus of claim 31 wherein the pressure of said enclosed spaces can be varied.

41. The apparatus of claim 40 wherein said pressure can be varied before applying said compressed antisolvent.

42. The apparatus of claim 40 wherein said pressure can be varied while applying said compressed antisolvent.

43. The apparatus of claim 33 wherein said crystal structure identification means is selected from the group consisting of X-ray diffractometry, thermomicroscopy, solid state nuclear magnetic resonance spectroscopy, infrared spectroscopy, near infrared spectroscopy, differential scanning calorimetry, raman spectroscopy, and a combination thereof.

44. The apparatus of claim 31 wherein the bottom of said enclosed space holds said solidified desired substance.

45. The apparatus of claim 31 wherein at least one side of said enclosed spaces is made of crystal identification means transparent material.

46. The apparatus of claim 33 wherein said crystal structure identification is performed while said dispersion is being solidified.

47. The apparatus of claim 33 wherein said crystal structure identification is performed after said dispersion is solidified.

48. The apparatus of claim 33 wherein said crystal structure identification is performed after said enclosed space is depressurized.

49. The apparatus of claim 33 wherein said crystal structure identification is performed after said solidified desired substance is removed from said enclosed space.

50. The apparatus of claim 31 wherein transfer of said dispersion is accomplished through a dispensing means.

51. The apparatus of claim 50 wherein said dispensing means can handle femptoliter quantities or greater.

52. The apparatus of claim 31 wherein said enclosed spaces contain said compressed antisolvent prior to transfer of said dispersions of said desired substance in at least one solvent

53. The apparatus of claim 52 wherein transferring said dispersions of said desired substance in at least one solvent into different enclosed spaces is accomplished through a dispersing means.

54. The apparatus of claim 53 wherein the dispersing means is a nozzle.

55. The apparatus of claim 53 wherein mass transfer can be enhanced by a vibrating surface.

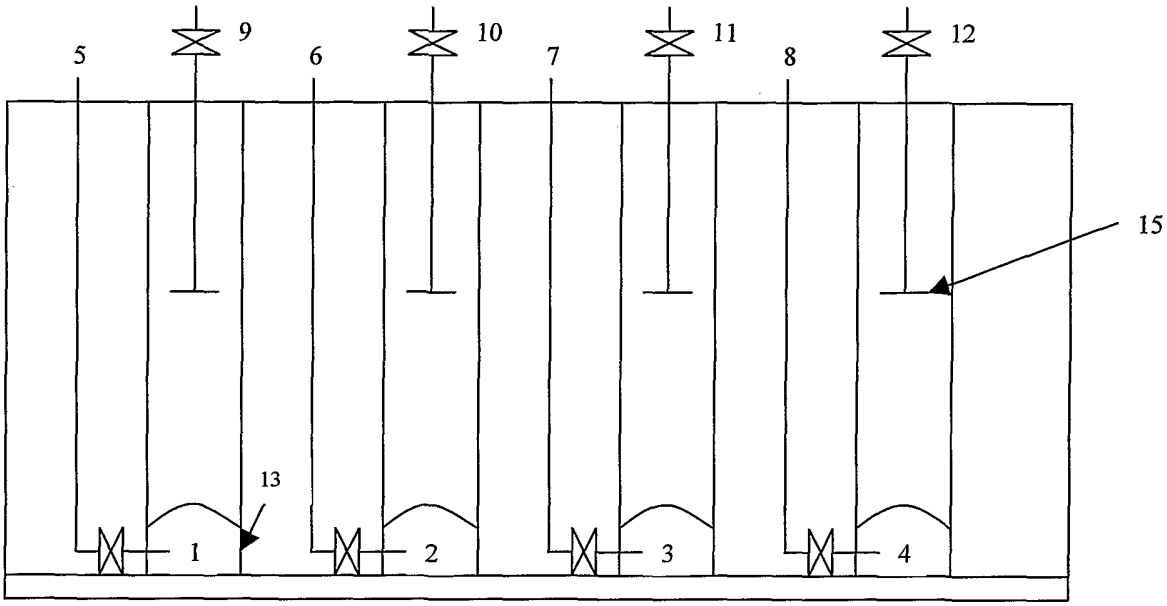


Figure 1

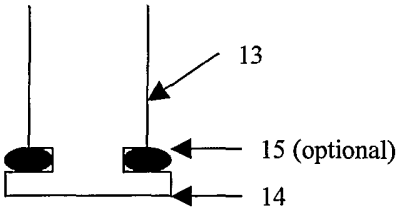
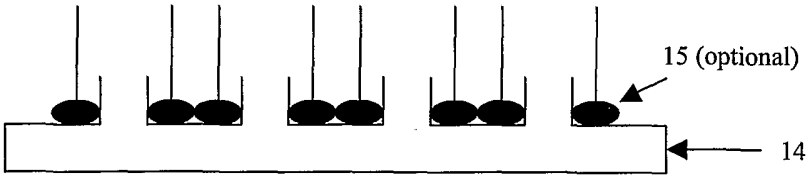


Figure 2



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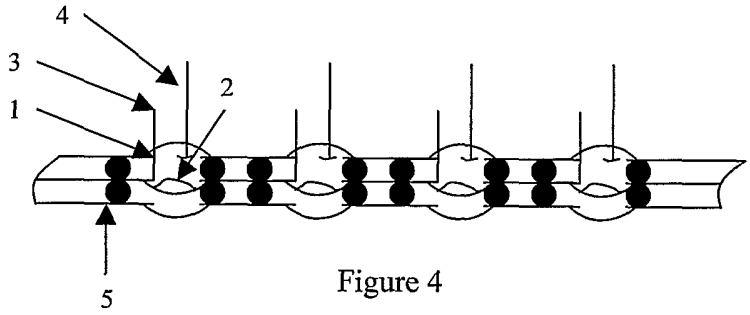

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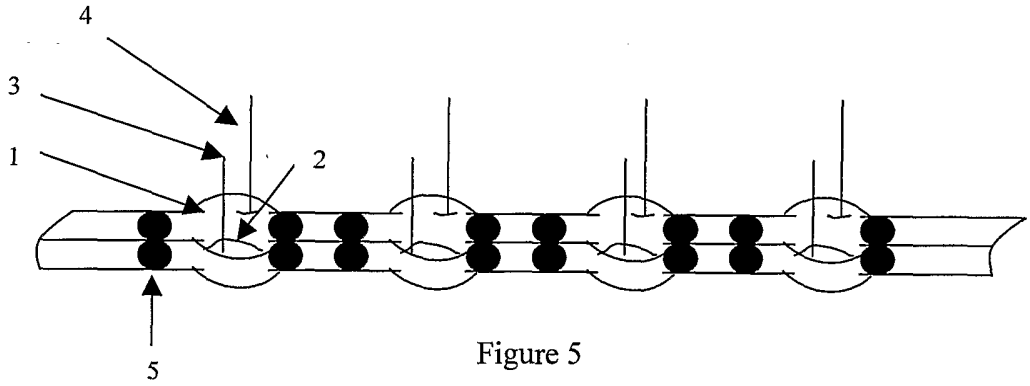

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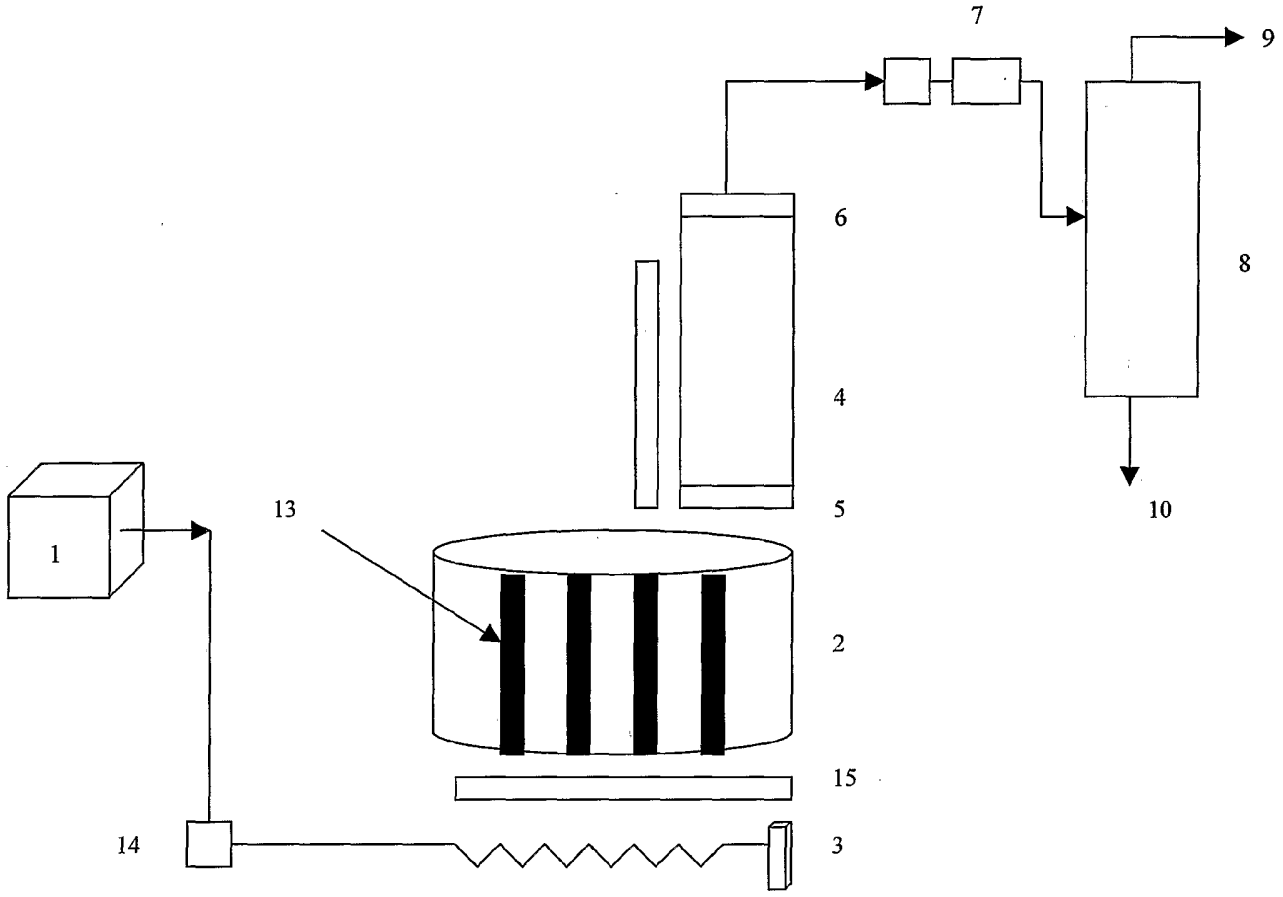

Figure 6

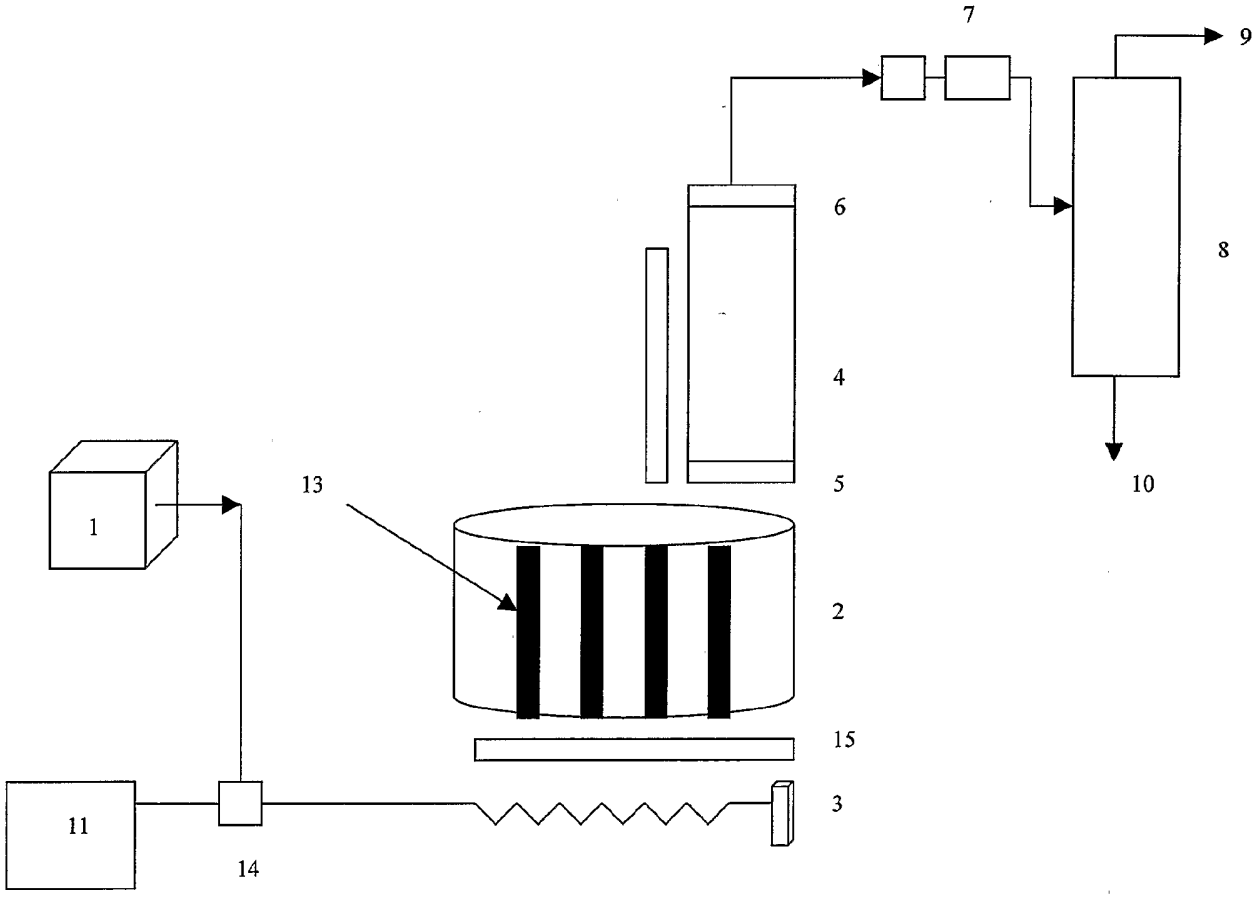

Figure 7

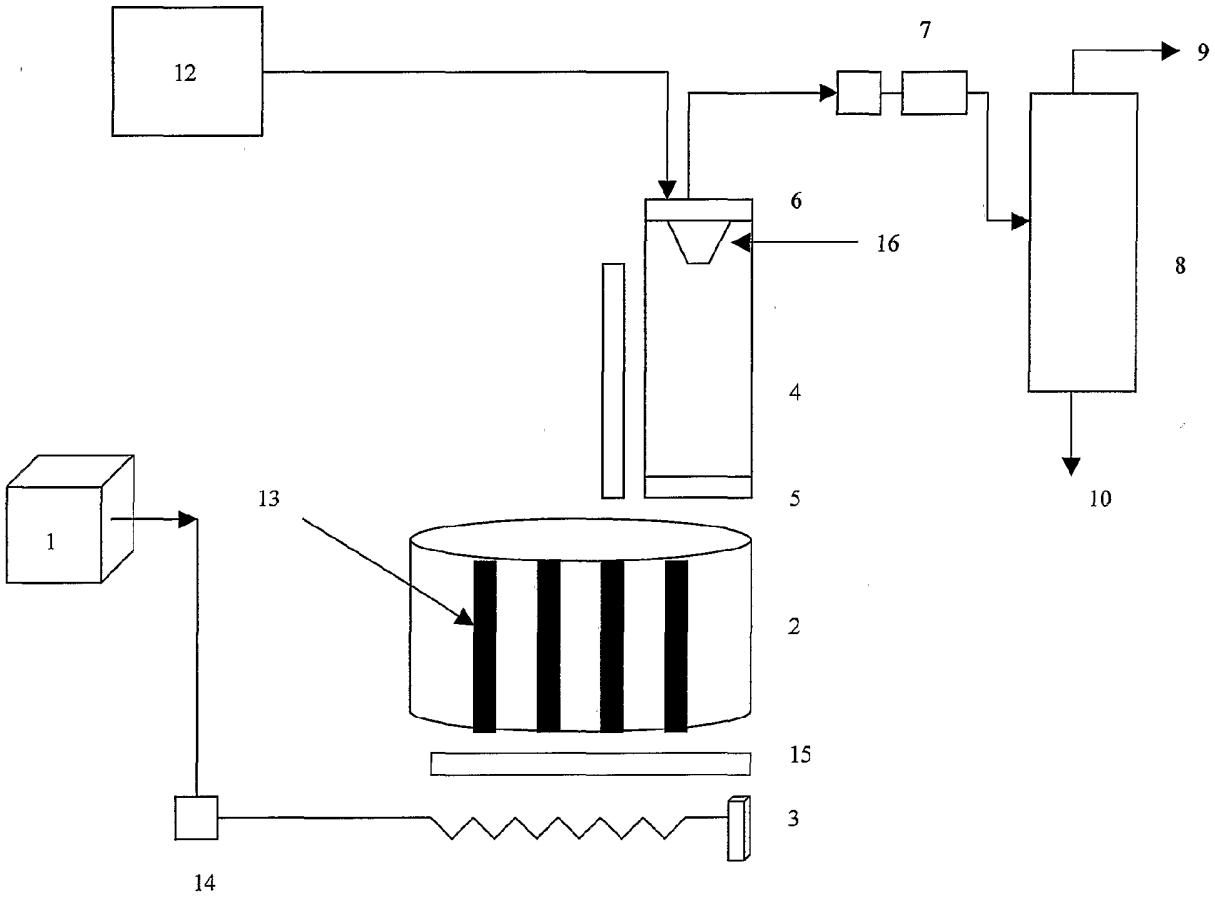

Figure 8

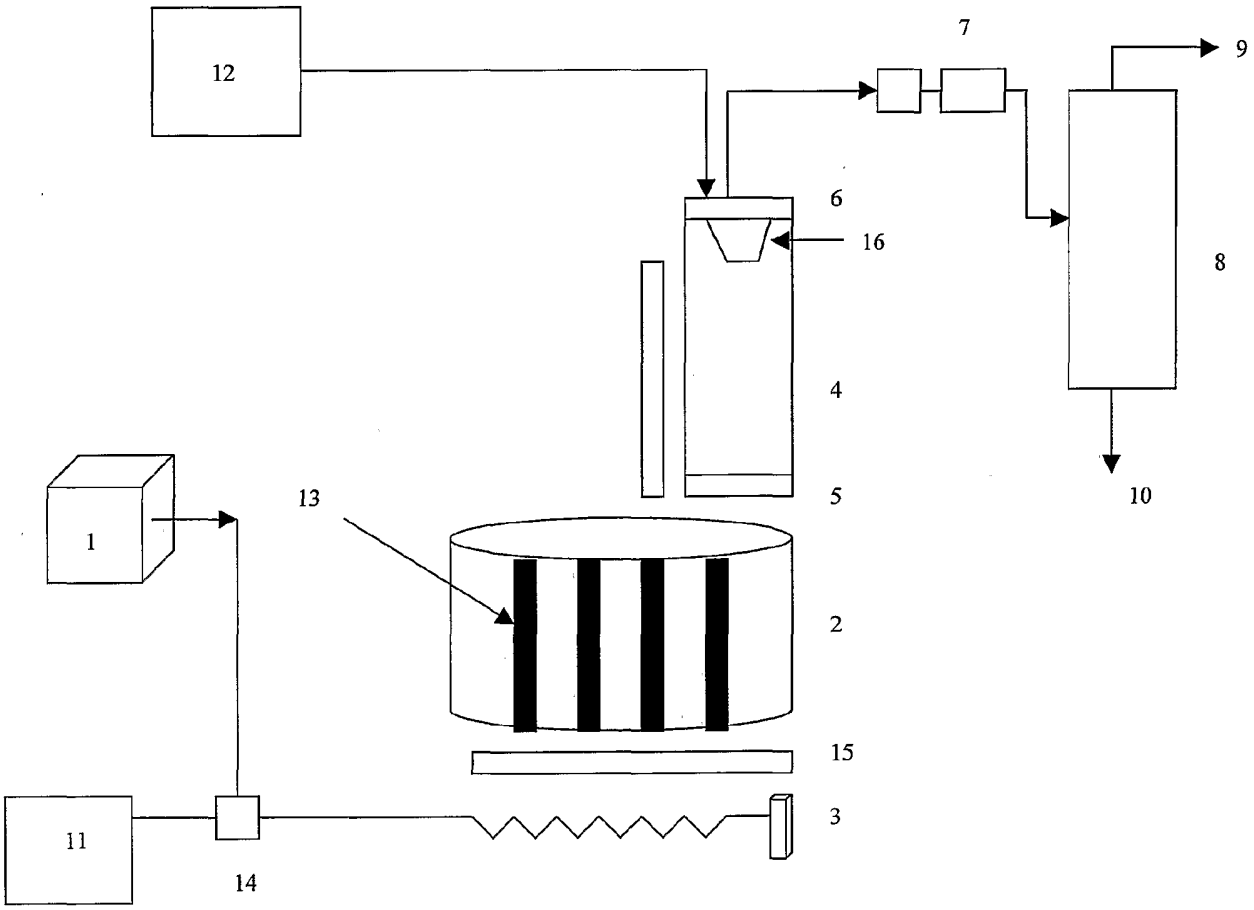

Figure 9

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/011508

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 B01J19/00 G01N31/02

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 G01N B01J

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, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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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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Date of the actual completion of the international search	Date of mailing of the international search report
20 July 2005	22/08/2005

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	Wulveryck, J-M

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/011508

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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