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(54) Title: COLLECTION DEVICE AND METHODS FOR USE

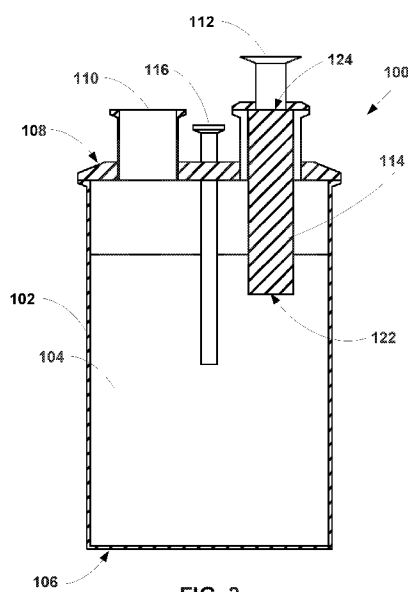


FIG. 3

(57) Abstract: The present disclosure provides an apparatus and methods of use for collecting particles. An example collection device includes (a) a vessel defining a chamber, wherein the vessel includes a distal end and a proximal end, (b) an inlet port extending from the proximal end of the vessel, wherein the inlet port is in fluid communication with the chamber, and (c) an outlet port extending from the proximal end of the vessel, wherein the inlet port is in fluid communication with the chamber, and wherein the outlet port includes a porous material positioned between the chamber and the outlet port.



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Collection Device and Methods for Use

5 Cross Reference

This application claims priority to U.S. Provisional Patent Application 62/171,008, U.S. Provisional Patent Application 62/171,001, and U.S. Provisional Patent Application 62/171,060, each filed June 4, 2015, each of which are incorporated by reference herein in their entirety.

10

Background

A need exists for apparatuses and methods capable of producing sub-micron and nano-sized particles. The need is particularly pronounced in the field of pharmaceuticals. Conventional techniques for particle-size reduction currently practiced suffer from many disadvantages. As such, a need remains for improved equipment and processes for the preparation, harvesting and collection of small particles.

Summary of the Invention

In one aspect, the invention comprises a collection device, including (a) a vessel defining a chamber, wherein the vessel includes a distal end and a proximal end, (b) an inlet port extending from the proximal end of the vessel, wherein the inlet port is in fluid communication with the chamber, and (c) an outlet port extending from the proximal end of the vessel, wherein the outlet port is in fluid communication with the chamber, and wherein the outlet port includes a porous material positioned between the chamber and the outlet port.

25 In a second aspect, the invention includes a method for isolating particles comprising (a) providing a collection device including (i) a vessel defining a chamber, (ii) an inlet port in fluid communication with the chamber, (iii) an outlet port in fluid communication with the chamber, wherein the outlet port includes a porous material positioned between the chamber and the outlet port, and (iv) a sampling tube having a distal end and a proximal end, wherein the proximal end of the sampling tube extends from the proximal end of the vessel, and wherein the distal end of the sampling tube extends into the chamber, (b) receiving a plurality of particles through the inlet port of the particle collection device, (c) collecting the plurality of particles in the chamber of the vessel, (d) receiving a gas through the inlet port, and (e) venting the gas through the porous material and out of the outlet port.

These as well as other aspects, advantages, and alternatives, will become apparent to those of ordinary skill in the art by reading the following detailed description, with reference where appropriate to the accompanying drawings.

5 **Brief Description of the Figures**

FIGURE 1 illustrates a perspective view of a particle collection device, according to an example embodiment.

FIGURE 2 illustrates a top view of the particle collection device, according to an example embodiment.

10 FIGURE 3 illustrates a cross-section view of the particle collection device, according to an example embodiment.

FIGURE 4 illustrates another cross-section view of the particle collection device, according to an example embodiment.

15 FIGURE 5 illustrates another cross-section view of the particle collection device, according to an example embodiment.

FIGURE 6 illustrates a perspective view of a support frame, according to an example embodiment.

FIGURE 7 is a block diagram of a method, according to an example embodiment.

20 **Detailed Description of the Invention**

All references cited are herein incorporated by reference in their entirety. As used herein, the singular forms "a", "an" and "the" include plural referents unless the context clearly dictates otherwise. "And" as used herein is interchangeably used with "or" unless expressly stated otherwise. All embodiments of any aspect of the invention can be used in
25 combination, unless the context clearly dictates otherwise.

As used herein, "about" means +/- 5% of the recited value.

In one aspect, the present invention comprises a collection device, including (a) a vessel defining a chamber, wherein the vessel includes a distal end and a proximal end, (b) an inlet port extending from the proximal end of the vessel, wherein the inlet port is in fluid
30 communication with the chamber, and (c) an outlet port extending from the proximal end of the vessel, wherein the outlet port is in fluid communication with the chamber, and wherein the outlet port includes a porous material positioned between the chamber and the outlet port.

With reference to the Figures, as shown in Figure 1, the invention comprises a collection device 100 including a vessel 102 defining a chamber 104. The vessel 102

includes a distal end 106 and a proximal end 108. The outer diameter of the vessel 102 may range from about 152.4 mm to about 914.4 mm. The collection device 100 further includes an inlet port 110 extending from the proximal end 108 of the vessel 102. The inlet port 110 is in fluid communication with the chamber 104. The inlet port 110 may have an outer diameter ranging from about 12.7 mm to about 101.6 mm. Further, the collection device 100 includes an outlet port 112 extending from the proximal end 108 of the vessel 102. As shown in Figures 3 and 4, the outlet port 112 is in fluid communication with the chamber 104, and the outlet port 112 includes a porous material 114 positioned between the chamber 104 and the outlet port 112. The outer diameter of the outlet port may range from about 12.7 mm to about 50.8 mm.

As shown in Figures 1-4, the collection device 100 may further include a sampling tube 116 having a distal end 118 and a proximal end 120. The outer diameter of the sampling tube 116 may range from about 6.35 mm to about 25.4 mm. As shown in Figures 3 and 4, the proximal end 120 of the sampling tube 116 extends from the proximal end 108 of the vessel 102, and the distal end 118 of the sampling tube 116 extends into the chamber 104. The sampling tube 116 may be configured to remove a small sample of particles from the chamber 104 during a particle production run in which additional particles are being formed. In particular, the sampling tube 116 may include a sample thief that enables an operator to remove a small sample of particles without opening the chamber 104 or removing the sampling tube 116 from the rest of the collection device 100 during processing. This enables an operator to test a small sample of particles to ensure that the product is within specifications as the process continues to run. For example, particle size or residual solvent analysis may be performed on the sample. If the measured specifications do not match the desired specifications, the operating parameters of the particle formation process may be suitably adjusted to correct the situation before an entire batch of product with undesirable characteristics is created.

The porous material 114 positioned between the chamber 104 and the outlet port 112 may take a variety of forms. In one example, the porous material 114 is selected from the group consisting of a frit, a mesh, a cloth. As one specific example, the porous material 114 may comprise a high-efficiency particulate arrestance (HEPA) filter. An example HEPA filter may include a mat of randomly arranged fibers, the fibers composed of fiberglass and possessing diameters between about 0.5 micrometers and about 2.0 micrometers. In another example, the porous material 114 comprises a sintered filter having a distal end 122 and a proximal end 124. In such an example, the proximal end 124 of the sintered filter extends

from the proximal end 108 of the vessel 102 and is coupled to the outlet port 112, and the distal end 122 of the sintered filter extends into the chamber 104. Such a sintered filter may include a porous stainless steel filter cartridge, as an example. Other porous materials are possible as well.

5 The inlet port 110 may include a coupling mechanism connecting an outlet of a particle filtration system to the inlet port 110. In one example, the coupling mechanism comprises one or more sanitary fittings. In another example, the coupling mechanism comprises a threaded connection between the outlet of the particle filtration system to the inlet port 110. In yet another example, the coupling mechanism comprises one or more
10 compression fittings. Other example coupling mechanisms are possible as well.

Further, as shown in Figure 5, the collection device 100 may further include a collection insert 126 positioned within the chamber 104 of the vessel 102, and a support frame 128 positioned between an interior wall 130 of the chamber 104 and the collection insert 126. The collection insert 126 may be a plastic bag, as an example. As shown in
5 Figure 6, the support frame 128 may include a distal ring 132, a proximal ring 134, one or more support legs 136 connecting the distal ring 132 to the proximal ring 134, and a gasket 138 positioned adjacent to the proximal ring 134. In one example, the gasket 138 may comprise a neoprene gasket. The vessel 102 may include a removable lid 140 that can be removed to access the collection insert 126 once particle collection is completed. In such an
10 example, the collection insert 126 may be positioned within the chamber 104 of the vessel 102 such that top edge of the collection insert 126 folds over the top of the support frame 128 and is sealed between the gasket 138 and the removable lid 140 when the lid is in the closed position. Other arrangements are possible as well.

Further still, the components of the collection device 100 may be a part of a larger
15 particle production system. Such a particle production system may include one or more nozzle assemblies, a sonic energy source positioned adjacent to the orifice of each nozzle, one or more particle filtration systems in communication with one or more nozzle assemblies, and one or more particle collection devices, such as those described above, each in communication with the one or more particle filtration systems. In one example, the one or
20 more particle filtration systems comprise a tandem particle filtration system including at least one high pressure harvesting filter system and at least one low pressure collection filter system in tandem and downstream to the harvesting filter. In such an example, the particle production system may include at least two particle harvesting filters, two particle collection filters and two collection devices.

25 In one example, the nozzle assembly includes (a) a vessel defining a pressurizable chamber, wherein the vessel includes a distal end and a proximal end, (b) an inlet of the pressurizable chamber at the proximal end of the vessel, (c) a nozzle positioned within the pressurizable chamber, wherein the nozzle includes an inlet tube in fluid communication with the inlet of the pressurizable chamber, wherein the nozzle includes an outlet aperture,
30 wherein the nozzle is adjustable to alter a distance between the proximal end of the vessel and the outlet aperture of the nozzle, and wherein the nozzle is adjustable to alter an angle between a longitudinal axis of the vessel and a longitudinal axis of the nozzle, and (d) an outlet of the pressurizable chamber at the distal end of the vessel. In such an example, the

inlet port 110 of the collection device 100 may be coupled to the outlet of the pressurizable chamber of the nozzle assembly.

In various embodiments, the one or more particle formation systems comprise one or more high pressure supercritical fluid (SCF) particle formation systems. In such an example, the one or more high pressure SCF particle formation systems may include a pressurizable precipitation chamber including a SCF inlet, a process fluid inlet, and a fluid outlet, and a process fluid disperser to disperse process fluid into the precipitation chamber. Any suitable pressurizable chamber may be used, including but not limited to those disclosed in U.S. Patent Nos. 5,833,891 and 5,874,029.

In another example, the particle production system comprises at least one of a) two particle harvesting filters, two particle collection filters and two collection devices; b) two particle harvesting filters, one particle collection filter and one or more collection devices; c) two particle harvesting filters, two particle collection filters and one or more collection devices; d) two particle harvesting filters, one particle collection filter and one or more collection devices; e) two tandem filter particle harvesting and collection devices arranged in parallel; f) two or more particle harvesting filters arranged in parallel, one particle collection filter and two or more collection devices arranged in parallel; g) two or more precipitation chambers; h) at least two tandem filter particle filtration systems; i) at least two collection devices; or j) a combination thereof.

In another aspect, the invention provides methods for isolating particles comprising (a) providing a collection device including (i) a vessel defining a chamber, (ii) an inlet port in fluid communication with the chamber, (iii) an outlet port in fluid communication with the chamber, wherein the outlet port includes a porous material positioned between the chamber and the outlet port, and (iv) a sampling tube having a distal end and a proximal end, wherein the proximal end of the sampling tube extends from the proximal end of the vessel, and wherein the distal end of the sampling tube extends into the chamber, (b) receiving a plurality of particles through the inlet port of the particle collection device, (c) collecting the plurality of particles in the chamber of the vessel, (d) receiving a gas through the inlet port, and (e) venting the gas through the porous material and out of the outlet port.

Figure 7 is a block diagram of a method 200, according to an example embodiment. Method 200 shown in Figure 7 presents an embodiment of a method that could be used with the collection device 100 of Figures 1-6, for example. Method 200 may include one or more operations, functions, or actions as illustrated by one or more of blocks 202-210. Although the blocks are illustrated in a sequential order, these blocks may in some instances be

performed in parallel, and/or in a different order than those described herein. Also, the various blocks may be combined into fewer blocks, divided into additional blocks, and/or removed based upon the desired implementation.

In addition, for the method 200 and other processes and methods disclosed herein, the flowchart shows functionality and operation of one possible implementation of present embodiments. In this regard, each block may represent a module, a segment, a portion of a manufacturing or operation process, or a portion of program code, which includes one or more instructions executable by a processor for implementing specific logical functions or steps in the process. The program code may be stored on any type of computer readable medium, for example, such as a storage device including a disk or hard drive. The computer readable medium may include non-transitory computer readable medium, for example, such as computer-readable media that stores data for short periods of time like register memory, processor cache and Random Access Memory (RAM). The computer readable medium may also include non-transitory media, such as secondary or persistent long term storage, like read only memory (ROM), optical or magnetic disks, compact-disc read only memory (CD-ROM), for example. The computer readable media may also be any other volatile or non-volatile storage systems. The computer readable medium may be considered a computer readable storage medium, for example, or a tangible storage device.

In addition, for the method 200 and other processes and methods disclosed herein, each block in Figure 2 may represent circuitry that is wired to perform the specific logical functions in the process.

At block 202, the method 200 includes providing a collection device including (i) a vessel defining a chamber, (ii) an inlet port in fluid communication with the chamber, (iii) an outlet port in fluid communication with the chamber, wherein the outlet port includes a porous material positioned between the chamber and the outlet port, and (iv) a sampling tube having a distal end and a proximal end, wherein the proximal end of the sampling tube extends from the proximal end of the vessel, and wherein the distal end of the sampling tube extends into the chamber.

At block 204, the method 200 includes receiving a plurality of particles through the inlet port of the particle collection device. At block 206, the method 200 includes collecting the plurality of particles in the chamber of the vessel. At block 208, the method 200 includes receiving a gas through the inlet port. At block 210, the method 200 includes venting the gas through the porous material and out of the outlet port. Venting the gas through the porous

material and out of the outlet port enables the separation of the produced particles from the gases, such as gaseous CO₂.

In one embodiment, the method 200 further includes the steps of removing the plurality of particles from the chamber of the vessel. In yet another embodiment, the method further includes the steps of sampling one or more particles from the sampling tube, and
5 adjusting one or more parameters of the particle formation system in response to the sampled one or more particles.

10 Examples

Materials and Methods

Raw paclitaxel and docetaxel were purchased from Phyton Biotech (British Columbia, Canada), lot number FP2-15004 and DT7-14025, respectively. Both were
15 characterized in their raw form. The milling of both drugs was accomplished using a Deco-PBM-V-0.41 mill (Deco). The milling conditions for both compounds were as follows:

Ball size = 5 mm

RPM = 600

Processing time = 60 min

20 Room temperature.

Preparation of paclitaxel particles

A solution of 65 mg/ml of paclitaxel was prepared in acetone. A BETE MicroWhirl® fog nozzle (BETE Fog Nozzle, Inc) and a sonic probe (Qsonica, model number Q700) were
25 positioned in the crystallization chamber approximately 8 mm apart. A stainless steel mesh filter with approximately 100 nm holes was attached to the crystallization chamber to collect the precipitated paclitaxel nanoparticles. The supercritical carbon dioxide was placed in the crystallization chamber of the manufacturing equipment and brought to approximately 1200 psi at about 38 °C and a flow rate of 24 kg/hour. The sonic probe was adjusted to 60% of
30 total output power at a frequency of 20 kHz. The acetone solution containing the paclitaxel was pumped through the nozzle at a flow rate of 4.5 mL/minute for approximately 36 hours. Paclitaxel nanoparticles produced had an average number-weighted mean size of 0.81 µm with an average standard deviation of 0.74 µm over three separate runs.

Preparation of docetaxel particles

A solution of 79.32 mg/ml of docetaxel was prepared in ethanol. The nozzle and a sonic probe were positioned in the pressurizable chamber approximately 9 mm (apart. A stainless steel mesh filter with approximately 100 nm holes was attached to the pressurizable chamber to collect the precipitated docetaxel nanoparticles. The supercritical carbon dioxide was placed in the pressurizable chamber of the manufacturing equipment and brought to approximately 1200 psi at about 38 °C and a flow rate of 68 slpm. The sonic probe was adjusted to 60% of total output power at a frequency of 20 kHz. The ethanol solution containing the docetaxel was pumped through the nozzle at a flow rate of 2 mL/minute for approximately 95 minutes). The precipitated docetaxel agglomerates and particles were then collected from the supercritical carbon dioxide as the mixture is pumped through the stainless steel mesh filter. The filter containing the nanoparticles of docetaxel was opened and the resulting product was collected from the filter.

Docetaxel nanoparticles produced had an average number-weighted mean size of 0.82 μm with an average standard deviation of 0.66 μm over three separate ethanol runs.

Particle Size Analysis

Particle size was analyzed by both light obscuration and laser diffraction methods. An Particle Sizing Systems AccuSizer 780 SIS system was used for the light obscuration method and Shimadzu SALD-7101 was used for the laser diffraction method. Paclitaxel nanoparticles were analyzed using 0.10% (w/v) sodium dodecyl sulfate (SDS) in water as the dispersant. Docetaxel nanoparticles were analyzed using isopar G as the dispersant.

Paclitaxel suspensions were prepared by adding approximately 7 mL of filtered dispersant to a glass vial containing approximately 4 mg of paclitaxel particles. The vials were vortexed for approximately 10 seconds and then sonicated in a sonic bath approximately 1 minute. If the sample was already suspended, 1:1 solution of paclitaxel suspension to 0.1% SDS solution was made, vortexed for 10 seconds, and sonicated in the sonic bath for 1 minute.

Docetaxel suspensions were prepared by adding approximately 7 mL of filtered dispersant to a plastic vial containing approximately 4 mg of docetaxel particles. The vial was vortexed for approximately 10 seconds and then sonicated in a sonic bath for approximately 2 minutes. This suspension was used for laser diffraction analysis. Unused suspension was poured into a 125mL particle-free plastic bottle, which was then filled to approximately 100 mL with filtered dispersant. The suspension was vortex for

approximately 10 seconds and then sonicated in the sonic bath for approximately 2 minutes. This diluted suspension was used for light obscuration analysis.

A background test was first performed prior to analyzing particles on the AccuSizer 780 SIS. A new particle-free plastic bottle was filled with blank suspension solution by pumping from a reservoir, using a peristaltic pump, through a 0.22 μm Millipore filter and into the bottle. A background analysis was run to ensure the particle/mL count was below 100 particles/mL. A small amount of paclitaxel suspension, 5-100 μL , depending upon concentration of solution, was pipetted into the plastic bottle in place from the background test and was filled with ~ 100 mL dispersant and the analysis was started. Counts were monitored and paclitaxel solution added to reach and/or maintain 6000-8000 particle counts/mL during the entire analysis. Once the analysis was completed, the background data was removed and any measurement with less than four counts was removed.

To analyze particles on SALD-7101 using a batch cell, the analysis was started by choosing Manual Measurement. The refractive index was set as 1.5 to 1.7. The batch cell was filled with filtered dispersant just past the etched line. The blank measurement was run. A small amount of API (paclitaxel or docetaxel) suspension was pipetted, generally < 1 mL, depending upon concentration of solution as low as 100 μL , into the batch cell as needed to achieve an acceptable absorbance between 0.15 and 0.2 absorbance units. The measurements were executed, and the resulting graph with the highest level of confidence was selected; background was automatically accounted for.

BET Analysis

A known mass between 200 and 300 mg of the analyte was added to a 30 mL sample tube. The loaded tube was then mounted to a Porous Materials Inc. SORPTOMETER[®], model BET-202A. The automated test was then carried out using the BETWIN[®] software package and the surface area of each sample was subsequently calculated.

Bulk density analyte

Paclitaxel or docetaxel particle preparations were added to a 10 mL tared graduated cylinder through a plastic weigh funnel at room temperature. The mass of the drug was measured to a nearest 0.1 mg, the volume was determined to the nearest 0.1 mL and the density calculated.

*Dissolution studies*Paclitaxel

5 Approximately 50 mg of material (i.e.: raw paclitaxel, milled paclitaxel, or paclitaxel particles) were coated on approximately 1.5 grams of 1 mm glass beads by tumbling the material and beads in a vial for approximately 1 hour. Beads were transferred to a stainless steel mesh container and placed in the dissolution bath containing methanol/water 50/50 (v/v) media at 37°C, pH 7, and a USP Apparatus II (Paddle), operating at 75 rpm. At 10, 20, 30,
10 60, and 90 minutes, a 5 mL aliquot was removed, filtered through a 0.22 µm filter and analyzed on a U(V/V)is spectrophotometer at 227 nm. Absorbance values of the samples were compared to those of standard solutions prepared in dissolution media to determine the amount of material dissolved.

15 Docetaxel

 Approximately 50 mg of material (i.e.: raw docetaxel, milled docetaxel, or docetaxel particles) was placed directly in the dissolution bath containing methanol/water 15/85 (v/v) media at 37°C, pH 7, and a USP Apparatus II (Paddle), operating at 75 rpm. At 5, 15, 30,
20 60, 120 and 225 minutes, a 5 mL aliquot was removed, filtered through a 0.22 µm filter, and analyzed on a UV/VIS spectrophotometer at 232 nm. Absorbance values of the samples were compared to those of standard solutions prepared in dissolution media to determine the amount of material dissolved.

Results

25 The BET surface area of particles produced using the above protocol and variations thereof (i.e.: modifying nozzles, filters, sonic energy sources, flow rates, etc.) ranged between 22 and 39 m²/g. **Figure 1** shows exemplary particles produced using the methods of the invention. By comparison, the BET surface area of raw paclitaxel was measured at 7.25 m²/g(Figure 2), while paclitaxel particles made according to the methods of US patents
30 5833891 and 5874029 ranged from 11.3 to 15.58 m²/g . Exemplary particle sizes produced using the methods of the invention are shown in Table 1.

Table 1

	Surface area m ² /g	Mean Size		St Dev	
		μm		μm	
		Number	Volume	Number	Volume
1	38.52	0.848	1.600	0.667	0.587
2	33.82	0.754	0.988	0.536	0.486
3	35.90	0.777	1.259	0.483	0.554
4	31.70	0.736	0.953	0.470	0.466
5	32.59	0.675	0.843	0.290	0.381
6	38.22	0.666	0.649	0.344	0.325
7	30.02	0.670	0.588	0.339	0.315
8	31.16	0.672	0.862	0.217	0.459
9	23.90	0.857	1.560	0.494	0.541
10	22.27	0.857	1.560	0.494	0.541
11	26.19	0.861	1.561	0.465	0.546

- 5 Comparative studies on bulk density, SSA, and dissolution rates (carried out as noted above) for raw drug, milled drug particles, and drug particles produced by the methods of the present invention are provided in Tables 2 and 3 below. The full dissolution time course for the paclitaxel and docetaxel materials are provided in Tables 4 and 5, respectively.

Table 2**Compound: Paclitaxel**

Characteristic	Raw Material	Particles			
		Batch 1	Batch 2	Mean	Milled
Number Mean (um)	1.16	0.83	0.67	0.75	0.89
Volume Mean (um)	1.29	1.42	0.57	1.00	1.35
Bulk Density (g/cm³)	0.26	0.060	0.11	0.085	0.31
Surface Area (m²/g)	10.4	35.6	39.8	37.7	15.0
Dissolution (30 min)	18%	42%	52%	47%	32%

Table 3**Compound: Docetaxel**

Characteristic	Raw Material	Particles			
		Batch 1	Batch II	Mean	Milled
Number Mean (um)	1.58	0.92	0.80	0.86	1.11
Volume Mean (um)	5.05	4.88	4.03	4.46	3.73
Bulk Density (g/cm³)	0.24	0.062	0.096	0.079	0.44
Surface Area (m²/g)	15.9	43.0	45.4	44.2	15.2
Dissolution (30 min)	11%	27%	27%	27%	9%

Table 4: Paclitaxel Dissolution time course

Timepoint (minutes)	Paclitaxel Raw Material	Paclitaxel Particles	Milled Paclitaxel
0	0.0%	0.0%	0.0%
10	14.0%	40.2%	23.0%
20	17.8%	47.6%	30.0%
30	18.4%	51.9%	32.3%
60	23.9%	58.3%	38.6%
90	28.6%	62.9%	43.5%

Table 5: Docetaxel Dissolution time course

Timepoint (minutes)	Docetaxel Raw Material	Docetaxel Particles	Milled Docetaxel
0	0.0%	0.0%	0.0%
5	3.2%	12.1%	3.2%
15	6.9%	21.7%	5.9%
30	11.2%	27.2%	9.3%
60	16.4%	32.9%	12.2%
120	22.4%	38.9%	13.6%
225	26.8%	43.1%	16.0%

It should be understood that arrangements described herein are for purposes of example only. As such, those skilled in the art will appreciate that other arrangements and other elements (e.g. machines, interfaces, functions, orders, and groupings of functions, etc.) can be used instead, and some elements may be omitted altogether according to the desired results. Further, many of the elements that are described are functional entities that may be implemented as discrete or distributed components or in conjunction with other components, in any suitable combination and location, or other structural elements described as independent structures may be combined.

While various aspects and embodiments have been disclosed herein, other aspects and embodiments will be apparent to those skilled in the art. The various aspects and embodiments disclosed herein are for purposes of illustration and are not intended to be limiting, with the true scope being indicated by the following claims, along with the full scope of equivalents to which such claims are entitled. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

Since many modifications, variations, and changes in detail can be made to the described example, it is intended that all matters in the preceding description and shown in the accompanying figures be interpreted as illustrative and not in a limiting sense. Further, it is intended to be understood that the following clauses (and any combination of the clauses)

5 further describe aspects of the present description.

Claims

We claim:

1. A particle collection device, comprising:
a vessel defining a chamber, wherein the vessel includes a distal end and a proximal
5 end;
an inlet port extending from the proximal end of the vessel, wherein the inlet port is in
fluid communication with the chamber; and
an outlet port extending from the proximal end of the vessel, wherein the outlet port is
in fluid communication with the chamber, and wherein the outlet port includes a porous
10 material positioned between the chamber and the outlet port.
2. The particle collection device of claim 1, further comprising:
a sampling tube having a distal end and a proximal end, wherein the proximal end of
the sampling tube extends from the proximal end of the vessel, and wherein the distal end of
15 the sampling tube extends into the chamber.
3. The particle collection device of any one of claims 1 or 2, further comprising:
a collection insert positioned substantially within the chamber; and
a support frame positioned between an interior wall of the chamber and the collection
20 insert.
4. The particle collection device of claim 3, wherein the collection insert
comprises a plastic bag.
- 25 5. The particle collection device of any one of claims 3 or 4, wherein the support
frame comprises:
a distal ring;
a proximal ring;
one or more support legs connecting the distal ring to the proximal ring; and
30 a gasket positioned adjacent to the proximal ring.
6. The particle collection device of claim 5, wherein the gasket comprises a
neoprene gasket.

7. The particle collection device of any one of claims 1-6, wherein the porous material is selected from the group consisting of a frit, a mesh, and a cloth.

8. The particle collection device of any one of claims 1-7, wherein the porous material comprises a sintered filter having a distal end and a proximal end, wherein the proximal end of the sintered filter extends from the proximal end of the vessel and is coupled to the outlet port, and wherein the distal end of the sintered filter extends into the chamber.

9. The particle collection device of any one of claims 1-8, wherein an outer diameter of the inlet port has a range from about 12.7 mm to about 101.6 mm.

10. The particle collection device of any one of claims 1-9, wherein an outer diameter of the outlet port has a range from about 12.7 mm to about 20.8 mm.

11. The particle collection device of any one of claims 1-10, wherein an outer diameter of the sampling tube has a range from about 6.35 mm to about 25.4 mm.

12. The particle collection device of any one of claims 1-11, wherein an outer diameter of the vessel has a range from about 152.4 mm to about 914.4 mm.

13. The particle collection device of any one of claims 1-12, wherein the inlet port includes a coupling mechanism to connect an outlet of a particle filtration system to the inlet port.

14. The particle collection device of claim 13, wherein the coupling mechanism comprises one or more sanitary fittings.

15. The particle collection device of claim 13, wherein the coupling mechanism comprises one or more compression fittings.

16. A particle collection system, comprising:
one or more particle formation systems;
one or more particle filtration systems in communication with one or more particle formation systems; and

one or more particle collection devices of any one of claims 1-15 in communication with the one or more particle filtration systems.

17. The system of claim 16, wherein the one or more particle formation systems
5 comprise one or more high pressure supercritical fluid (SCF) particle formation systems.

18. The system of claim 17, wherein the one or more high pressure SCF particle formation systems include:

a pressurizable precipitation chamber including a SCF inlet, a process fluid inlet, and
10 a fluid outlet; and
a process fluid disperser to disperse process fluid into the precipitation chamber.

19. The particle collection system of any one of claims 16-18, wherein the one or more particle filtration systems comprise a tandem particle filtration system including at least
15 one high pressure harvesting filter system and at least one low pressure collection device in tandem and downstream of the harvesting filter.

20. The particle collection system of claim 19, further comprising at least one of:

a) two particle harvesting filters, two particle collection filters and two collection
20 devices; b) two particle harvesting filters, one particle collection filter and one or more collection devices; c) two particle harvesting filters, two particle collection filters and one or more collection devices; d) two particle harvesting filters, one particle collection filter and one or more collection devices; e) two tandem filter particle harvesting and collection devices arranged in parallel; f) two or more particle harvesting filters arranged in parallel, one particle
25 collection filter and two or more collection devices arranged in parallel; g) two or more precipitation chambers; h) at least two tandem filter particle filtration systems; i) at least two collection devices; or j) a combination thereof.

21. A method for isolating particles, the method comprising:

30 providing a collection device including (i) a vessel defining a chamber, (ii) an inlet port in fluid communication with the chamber, (iii) an outlet port in fluid communication with the chamber, wherein the outlet port includes a porous material positioned between the chamber and the outlet port, and (iv) a sampling tube having a distal end and a proximal end,

wherein the proximal end of the sampling tube extends from the proximal end of the vessel,
and wherein the distal end of the sampling tube extends into the chamber;

receiving a plurality of particles through the inlet port of the particle collection
device;

- 5 collecting the plurality of particles in the chamber of the vessel;
receiving a fluid through the inlet port; and
venting the fluid through the porous material and out of the outlet port.

22. The method of claim 21, further comprising:
10 removing the plurality of particles from the chamber of the vessel.

23. A non-transitory computer readable medium having stored thereon
instructions, that when executed by one or more processors, causes the collection device of
claim 1 to:

- 15 receive a plurality of particles through the inlet port of the particle collection device;
collect the plurality of particles in the chamber of the vessel;
receive a gas through the inlet port; and
vent the gas through the porous material and out of the outlet port.

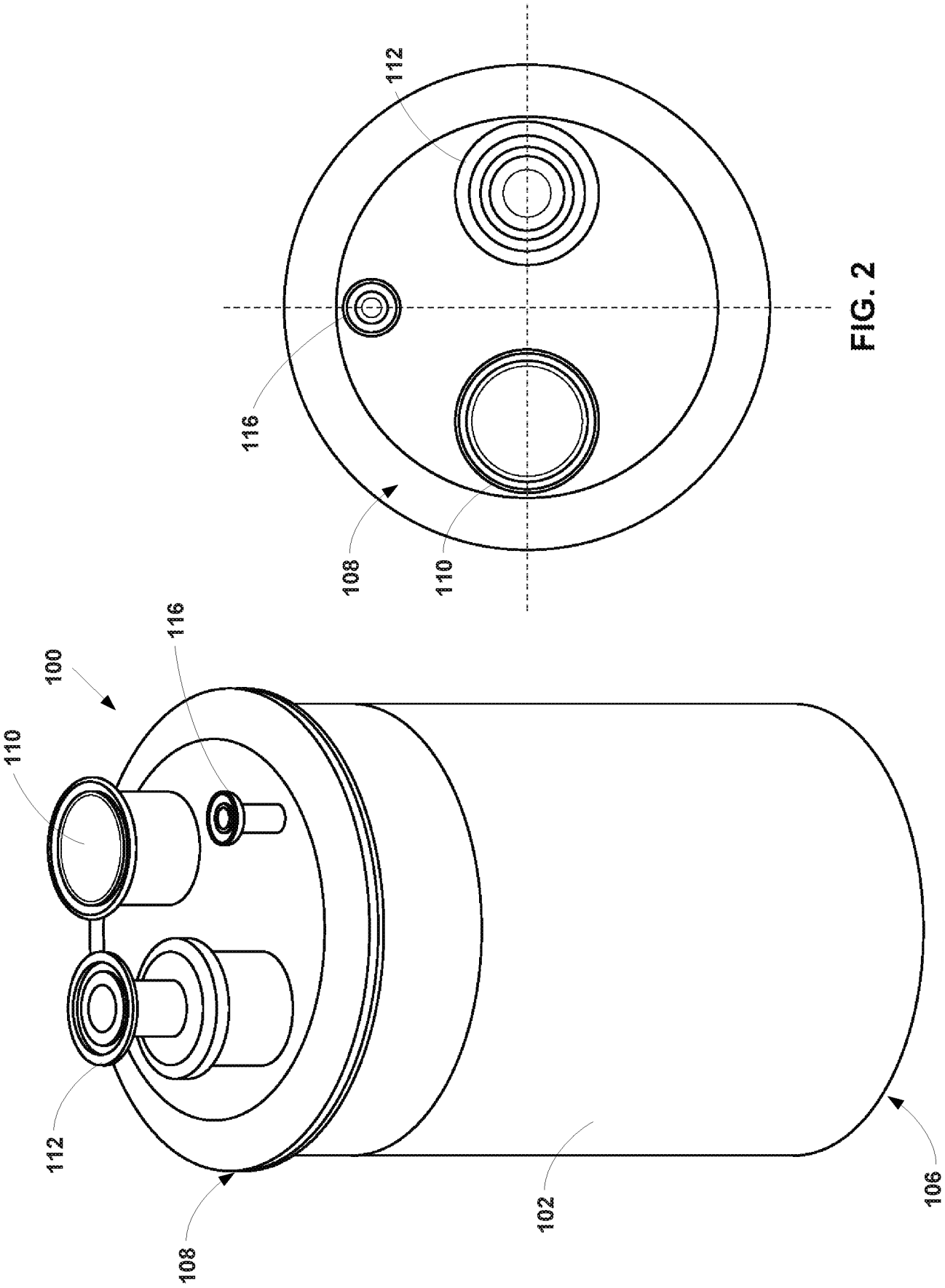


FIG. 1

FIG. 2

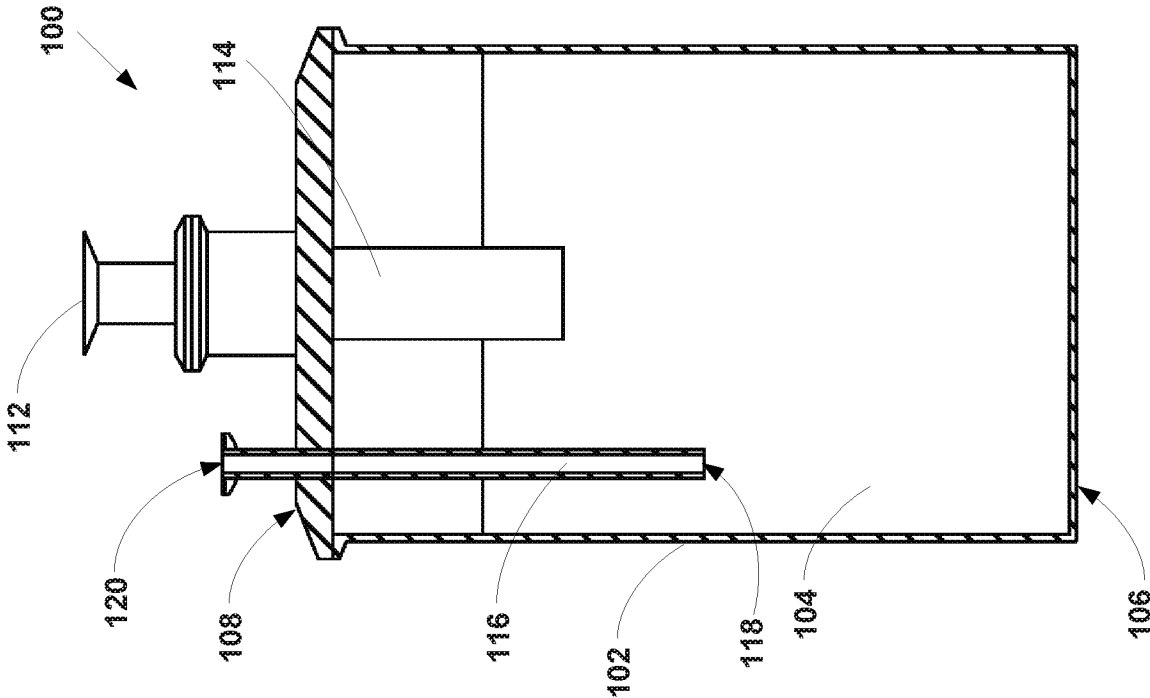


FIG. 4

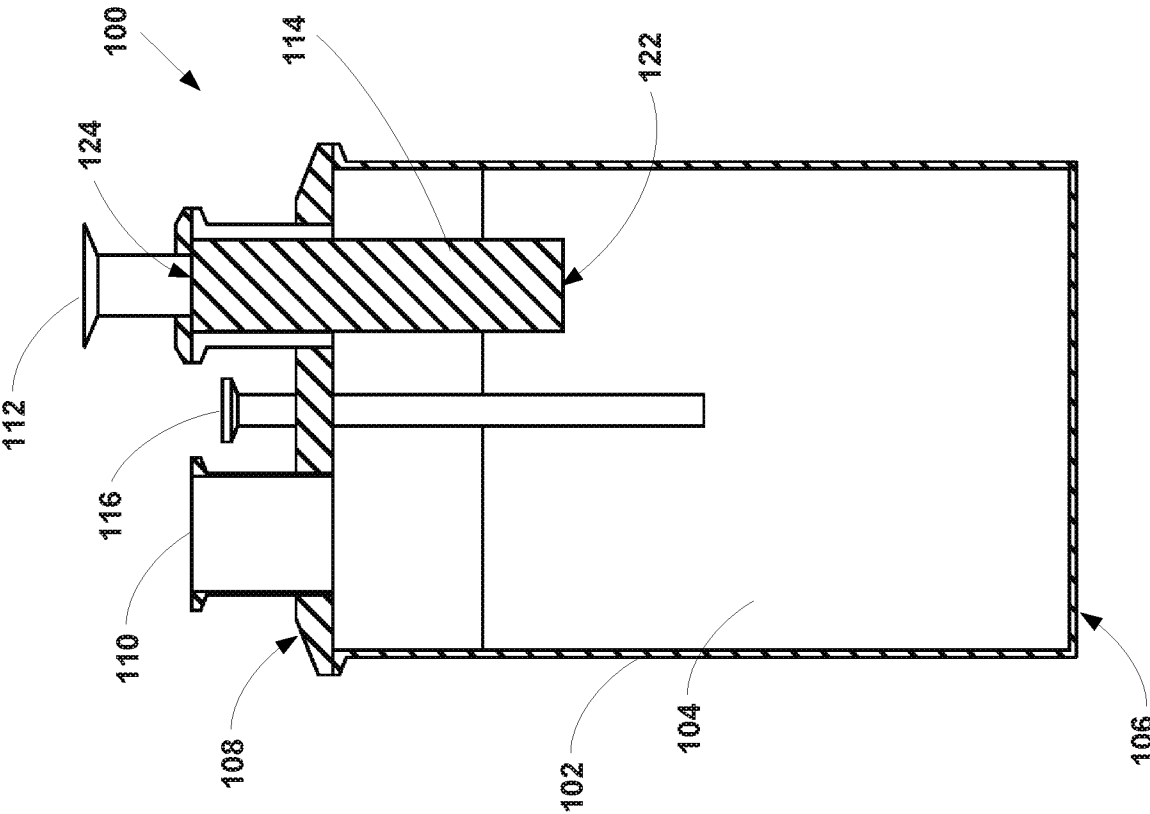


FIG. 3

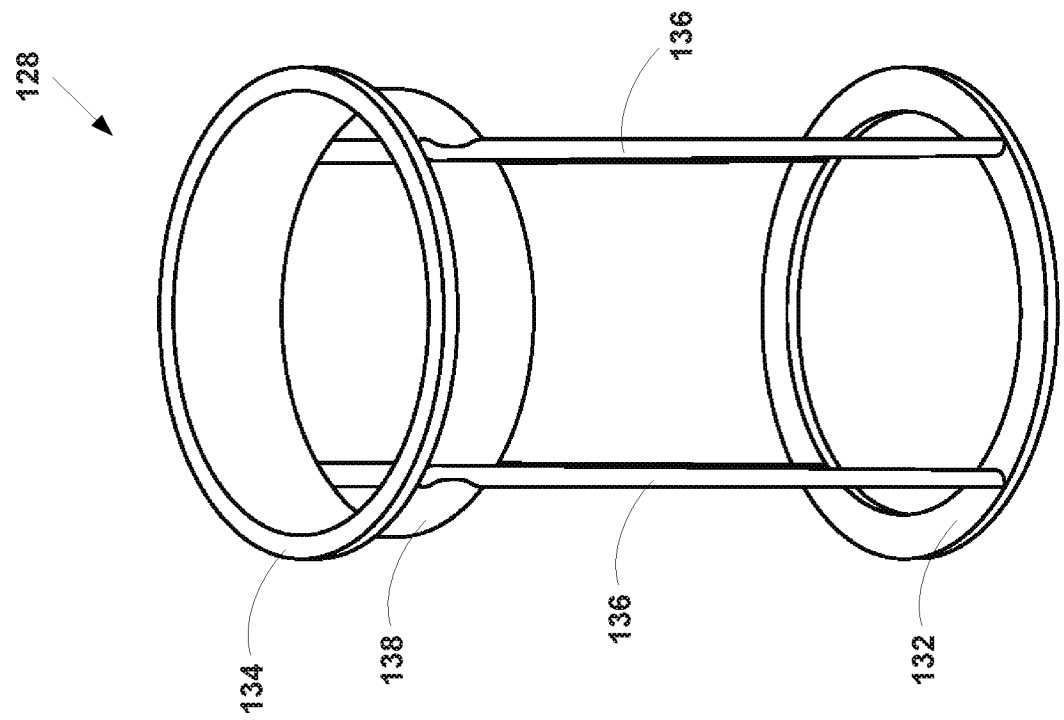


FIG. 6

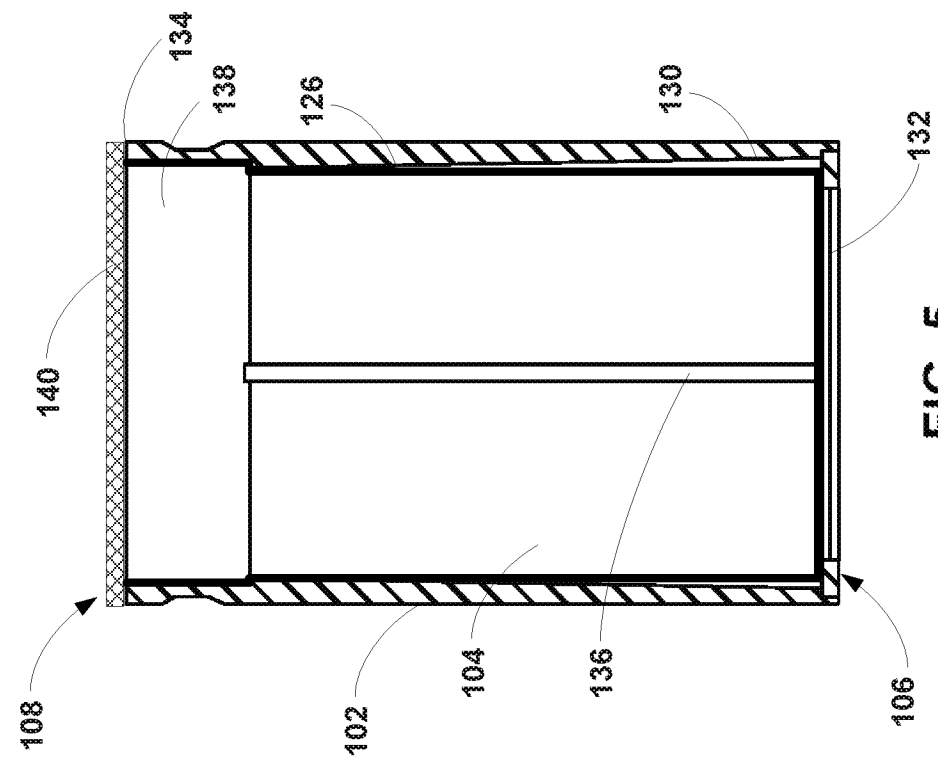
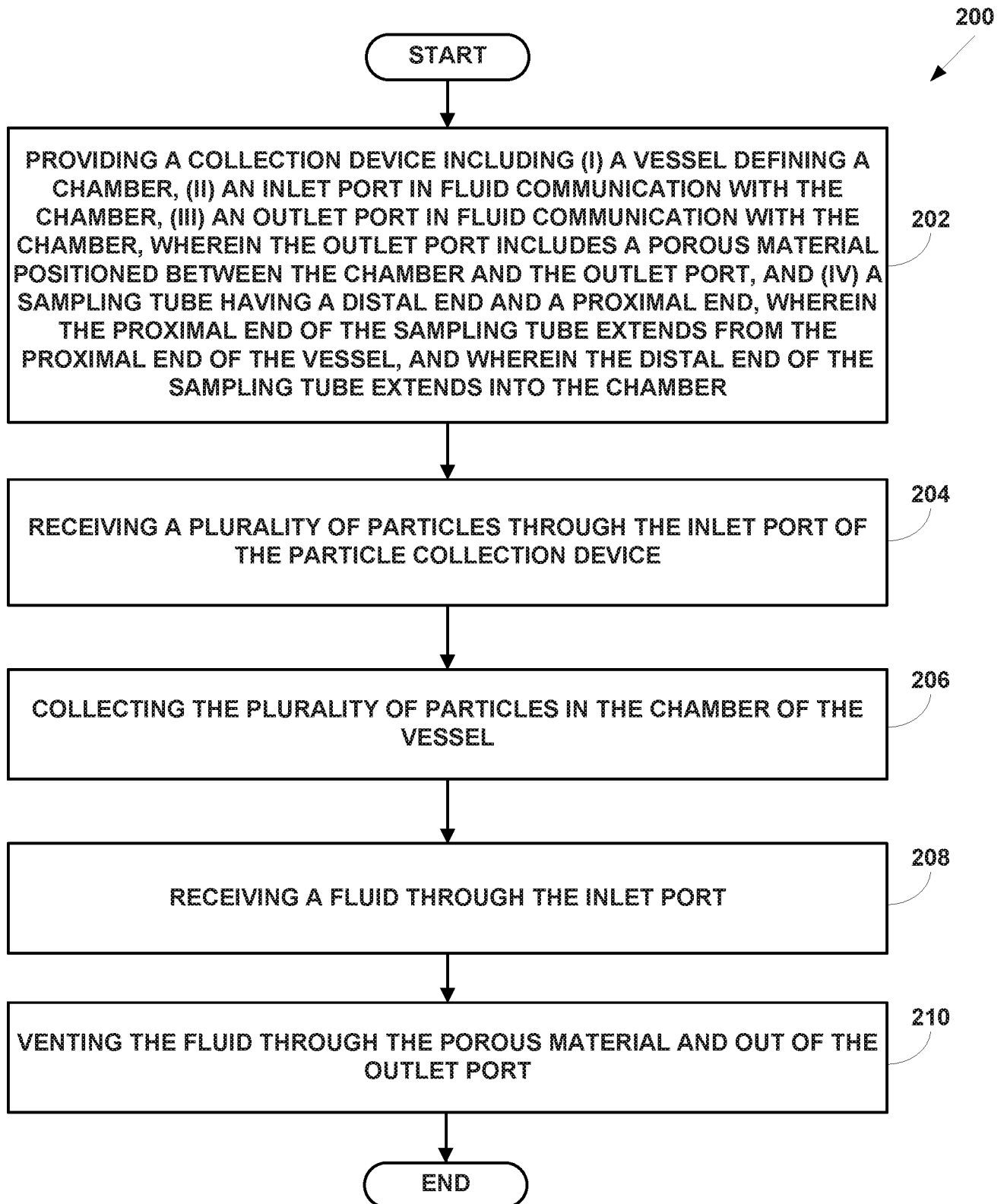


FIG. 5

**Fig. 7**

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 15-424-PCT	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2016/036013	International filing date (<i>day/month/year</i>) 6 June 2016 (06-06-2016)	(Earliest) Priority Date (<i>day/month/year</i>) 4 June 2015 (04-06-2015)
Applicant CRITITECH, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☒

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of:

☒

the international application in the language in which it was filed

☐

a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐

This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6**bis**(a)).

c. ☐

With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐

Certain claims were found unsearchable (See Box No. II)

3. ☐

Unity of invention is lacking (see Box No III)

4. With regard to the **title**,

☒

the text is approved as submitted by the applicant

☐

the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒

the text is approved as submitted by the applicant

☐

the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,

a. the figure of the **drawings** to be published with the abstract is Figure No. 3

☐

as suggested by the applicant

☒

as selected by this Authority, because the applicant failed to suggest a figure

☐

as selected by this Authority, because this figure better characterizes the invention

b. ☐

none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/036013

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K9/00 B01J3/00 B01D46/00 B01J2/04
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K B01J B01D B05D

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 8 778 181 B1 (JOHNSON GREG S [US] ET AL) 15 July 2014 (2014-07-15) column 7, lines 5-50; figures 1,8 column 9, lines 22-30 column 12, lines 9-18	1,7,13, 16-23
X	----- WO 2005/054130 A1 (DEGUSSA [DE]; ADLER PETER [DE]; PIRZL WOLFGANG [DE]; SONNENSCHNEIN RAYM) 16 June 2005 (2005-06-16) figure 1	1,7,8
A	----- WO 95/01221 A1 (UNIV BRADFORD [GB]; HANNA MAZEN [GB]; YORK PETER [GB]) 12 January 1995 (1995-01-12) page 26; figure 2B ----- -/-	1-23



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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"E" earlier application or patent but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

30 August 2016

Date of mailing of the international search report

07/09/2016

Name and mailing address of the ISA/

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Authorized officer

Veronesi, Sergio

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/036013

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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Information on patent family members

International application No

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