(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 December 2012 (20.12.2012)

WIPO | PCT

(10) International Publication Number
WO 2012/174437 A1

(51) International Patent Classification:
B01D 15/08 (2006.01)

(21) International Application Number:
PCT/US2012/042755

(22) International Filing Date:
15 June 2012 (15.06.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/498,458 17 June 2011 (17.06.2011) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

(54) **Title**: METHODS AND DEVICES FOR OPEN-BED ATMOSPHERIC COLLECTION FOR SUPERCRITICAL FLUID CHROMATOGRAPHY

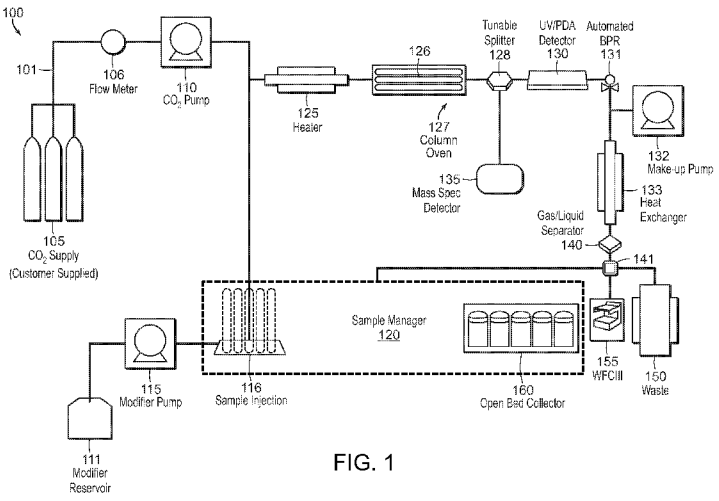

FIG. 1

(57) **Abstract**: A supercritical fluid chromatography system comprises a first pump for pumping a first flow stream comprising a compressible fluid and a second pump for pumping a second flow stream comprising a modifier fluid. The second pump is in parallel with the first pump. A column is located in a combined flow stream. The column is located downstream of the first and second pumps. The combined flow stream comprises the first flow stream, the second flow stream, and a sample. A detector is located downstream of the column. A gas-liquid separator is located downstream of the detector. The gas-liquid separator is configured to vent a majority of the compressible fluid while maintaining a majority of the sample, thus preventing aerosolization of the flow stream and minimizing sample loss as well as cross contamination. An open bed collector is located after the gas-liquid separator.

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METHODS AND DEVICES FOR OPEN-BED ATMOSPHERIC COLLECTION FOR SUPERCRITICAL FLUID CHROMATOGRAPHY

RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 61/498,458, filed on June 17, 2011, the entire contents of which are hereby incorporated by reference.

TECHNICAL FIELD

[0002] The present technology relates generally to methods and devices for open-bed atmospheric collection for supercritical fluid chromatography ("SFC"), and in particular to methods and devices for open-bed atmospheric collection with an XY type fraction collector (e.g., a collector arm with no Z-movement) for SFC.

BACKGROUND

[0003] Open bed type fraction collectors, for example, XY type fraction collectors, have been widely used in preparative liquid chromatography instruments for their flexibility, simplicity, efficiency, wide applicability, reliability and economy. The prior art collectors can include a platform that can accommodate various sizes of containers and configurations of rack adapters to hold tubes, bottles, vessels, pass-through/funnel-type connections as well as larger size containers for fraction collections. The collector can also have electrical components for automated control either through front panel or via direct control by sophisticated software communication protocols.

[0004] The actual collection of chromatography fractions is realized through liquid plumbing connections from chromatography instruments. After the fractions are separated from the column/cartridges in the chromatography system, they are transferred via connecting tubing to an XY type collector, flowing through a robotic arm collector tip, and are collected in containers underneath the robotic arm collector tip. The type of containers can be, for example, glass tubes, bottles, vessels, and/or pass-thru adapters, which can allow the fractions to be collected in larger size containers such as carboys. During the collection process, the robotic collector arm can move along the containers

based on preset methodologies by the operator to realize the separation and collection of different fractions into their corresponding containers.

[0005] The XY type collector has wide applicability and can be used in various chromatographic systems, ranging from flash chromatography ("Flash"), low to mid-level pressure chromatography ("LPLC" and "MPLC," respectively) to high performance liquid chromatography ("HPLC"). The XY type collector can be controlled either manually, by using a preset method from the front panel or from programmed control via software for full automation of the chromatography system. XY type collectors, as their name implies, have adapter arms that can travel only in two dimensions, i.e. no Z-movement. Typically, the arm is disposed above a grid-formation of open collection vessels, for example test tubes in which the sample is collected. In the case of many chromatography setups such as "Flash," "LPLC," "MPLC," and "HPLC," there is no need for the adapter arm to move in the Z dimension because the eluent exiting the column can easily be directed to drip down into the open collection vessels under the action of gravity alone, i.e the eluent is in liquid phase or liquid-solid phase. Thus the advantages of the XY type collector include but are not limited to ease of use, reliability, economy, and flexibility.

[0006] Supercritical Fluid Chromatography ("SFC") is a high-pressure, high performance chromatographic tool that can be used instead of liquid chromatography systems. Typically, today's SFC systems employ compressible fluids (e.g., carbon dioxide) at conditions above its supercritical point as a mobile phase, along with modifying solvents in most cases, to perform the chromatographic separation and purification processes. In general, SFC possesses higher efficiency, higher capacity and faster process times than other chromatography systems, for example, HPLC. SFC can significantly process more crude cleanup and separation/purification in less unit of measure, with significant reduction of toxic organic solvent waste by the use of carbon dioxide. It is therefore considered a green technique with high productivity and great economic impact.

[0007] SFC uses supercritical fluids such as carbon dioxide as the main flow solvents. The supercritical CO_2 is under controlled pressure while it is flowing in the SFC chromatography system. A pressure regulator, for example a back pressure regulator ("BPR") can be used to control the pressure of the CO_2 throughout the SFC

system. The BPR is typically placed in the back end of the plumbing of the chromatography system. Once the fluids pass through the BPR and are transferred to collectors, the fluid is depressurized and supercritical CO_2 (as well as other compressible fluids) can be converted to gaseous vapor and vented. This leaves the sample fraction in minimal liquid volume to be collected. It is, therefore, a natural phenomenon that aerosols of liquids can be generated along with this depressurization process. The generated aerosols can carry the sample of interest from the separation process. Uncontrolled aerosols generated from this depressurization process can result in sample loss and cross contamination during collection after separation and detection, among other issues and risks, because the eluent does not simply drip straight down into a single open collection vessel, i.e. the eluent is at least partially aerosolized.

[0008] Due to the depressurization process that occurs when compressible fluids are used in an SFC system, existing collection designs for SFC chromatography use well-controlled collectors. For example, the location of the collection of the sample is enclosed inside a container that can control any resulting aerosol via means of pressure and dimensional measures. Therefore, the prior art designs typically put the location of the collection of sample inside a sealed vessel so that there is physically no chance for the aerosols to be released to the atmosphere under normal process conditions. The vessel can be made of, for example, stainless steel metal that can withstand the high pressures within an SFC process, or of glass/polymeric material with reduced pressure control (e.g., venting) at a reduced over-pressure risk level. The prior art designs can require dedicated designs with significant investment in hardware and software. This can prevent wider applicability and robustness of the collection system, among other impacts.

[0009] For several reasons, XY type collectors have not been used in SFC systems. For example, XY type collectors comprise a collector arm that is disposed above the containers, which means the location of the collection cannot be encapsulated into the sealed collection vessel. In addition, the collection arm does not have vertical movement (Z-movement, relative to X-Y plane/horizontal movement) to lower its tip down into the containers to confine the aerosols. This makes the integration of SFC instruments with XY type collectors problematic by their own design, even though there are numerous significant advantages for such integration (e.g., the combination of the

high productivity of an SFC system with the flexibility, simplicity, efficiency, wide applicability, reliability and economy of an XY type collector).

SUMMARY OF THE TECHNOLOGY

[0010] The present technology is directed to a system and process for SFC that can incorporate a standard XY type collector (i.e. no Z movement) suitable for other types of chromatography such as HPLC, MPLC, LPLC and Flash chromatography. It is also directed to an SFC system that can be coupled to an open bed atmospheric XY type collector without the loss of sample and without cross contamination when the supercritical fluid reaches atmospheric conditions.

[0011] The technology enables the use of standard XY type fraction collectors in SFC. Such fraction collectors are known in the art for use with other chromatography systems, and may incorporate a robotic collector arm that can move along the containers based on preset methodologies by the operator to realize the separation and collection of different fractions into their corresponding containers. The technology also enables use of open-bed type collectors that do not require specialized collection vessels. For example, this technology obviates the need for sealed vessels made of stainless steel or some polymer or glass that can withstand high pressure.

[0012] In one aspect, the technology features a supercritical fluid chromatography system. The system comprises a first pump for pumping a first flow stream comprising a compressible fluid (e.g. CO_2) and a second pump for pumping a second flow stream comprising a modifier fluid (e.g. methanol). Typically, the modifier fluid is an incompressible fluid. The second pump is in parallel with the first pump. A column is located in a combined flow stream. The column is located downstream of the first and second pumps. The combined flow stream comprises the first flow stream, the second flow stream, and a sample. A detector is located downstream of the column. A gas-liquid separator is located downstream of the detector. The gas-liquid separator is configured to vent a majority of the compressible fluid while maintaining a majority of the sample to avoid sample loss and cross-contamination. An open bed XY type collector is located after the gas-liquid separator.

[0013] A compressible fluid is one in which the fluid density changes significantly when it is subjected to high pressure. The key difference, in the context of

SFC, between compressible and incompressible fluids is the way the different fluids behave when pressure is applied to them. In the case of incompressible fluids, e.g. water or methanol, application of a pressure at one point immediately creates identical pressure at all other points in the system.

[0014] In the case of a compressible fluid, e.g. supercritical CO_2, the imposition of a force at one point within a system does not result in an immediate increase in pressure elsewhere the system. Instead, the fluid compresses near where the force was applied; that is, its density increases locally in response to the force. This compressed fluid subsequently expands against neighboring fluid particles causing the neighboring fluid itself to compress. In many cases, the net result is the generation of pressure waves as the locally dense fluid moves throughout the system.

[0015] In one or more embodiments of the above aspect, sample loss and cross contamination are reduced by the incorporation of one or more devices that limit aerosolization, for example the GLS. In one or more embodiments, the supercritical fluid chromatography system can also include a collector arm located downstream of the gas-liquid separator. In some embodiments, the supercritical fluid chromatography system includes a collector arm adapter coupled to the collector arm. The collector arm adapter can be configured to further reduce aerosols when the combined flow stream is at atmospheric conditions. In some embodiments the container rack is adjustable.

[0016] In some embodiments, the gas-liquid separator is made from stainless steel, an appropriate polymer, or glass. In some embodiments, a back pressure regulator can be located upstream of the gas-liquid separator. In some embodiments, the compressible fluid is carbon dioxide (CO_2).

[0017] The current technology also features a method for collecting multiple samples in supercritical fluid chromatography (SFC). The method includes pumping a first flow stream comprising a compressible fluid and pumping a second flow stream comprising an incompressible fluid. The method further includes injecting a sample into the second flow stream and combining the first and second flow streams to form a combined flow stream, then subjecting the flow stream to SFC conditions. The method further includes flowing the combined flow stream through a chromatography column and removing at least a portion of the compressible fluid from the combined flow stream

followed by collecting the sample in an open bed XY type collector.

[0018] In some embodiments, the compressible fluid used in the method is CO_2. In some embodiments, aerosolization of the sample is prevented during collection of the sample in the open-bed XY collector.

[0019] The exemplary methods and devices of the present disclosure provide numerous advantages. For example, this technology significantly improves and expands the scope of SFC technology for use in a variety of settings, including the chemical industry and academic research laboratories. By eliminating technical concerns such as cross contamination, sample loss, and unsafe venting of compressed fluids, the technology makes SFC a more robust and reliable process. Additionally, the technology makes SFC a more convenient process because it allows the use of standard, open bed atmospheric XY type fraction collectors already in use with other types of chromatography and familiar to one of ordinary skill in the art.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] The foregoing and other features and advantages provided by the present disclosure may be better understood by referring to the following description taken in conjunction with the accompanying drawings. The drawings are not necessarily to scale, emphasis instead generally being placed upon illustrating the principles of the technology.

[0021] FIG. **1** is a diagram of an SFC system with an open-bed XY type collector, according to an illustrative embodiment of the technology.

[0022] FIG. **2** shows the installations of Waters Fraction Collector III ("WFCIII"), an XY type collector installed with both a collector arm adapter and a rack adapter for SFC instrumentation, according to an illustrative embodiment of the technology.

[0023] FIG. **3A** shows the collector arm adapter design on a WFCIII, according to an illustrative embodiment of the technology.

[0024] FIG. **3B** shows a schematic representation of the collector arm adapter, according to an illustrative embodiment of the technology.

[0025] FIG. **4** shows one embodiment of a rack adapter design on WFCIII that is compatible with SFC instrumentation, according to an illustrative embodiment of the technology.

[0026] FIG. **5** is a top view of a rack adapter design on WFCIII that is compatible with SFC instrumentation, according to an illustrative embodiment of the technology.

[0027] FIG. **6** is a diagram of an embodiment of the gas-liquid separator used in the technology.

[0028] FIG. **7** shows diagrams of an embodiment of a dripper of the gas-liquid separator used in the technology.

[0029] FIG. 8 shows another embodiment of the gas-liquid separator used in the technology.

[0030] FIG. 9 shows a schematic embodiment of the open bed atmospheric collection system.

DETAILED DESCRIPTION

[0031] In order to prevent sample loss and cross-contamination when collecting fractions for SFC, the technology takes advantage of a gas-liquid separator (GLS) installed into a flow stream after a BPR, of which the purpose is to vent the majority of gaseous carbon dioxide (CO_2), or any supercritical fluids used in the process, while maintaining the incompressible modifying liquid in which the sample is dissolved. Although CO_2 may be one common supercritical fluid used for SFC, other suitable supercritical fluids may be nitrous oxide (N_2O), sulfur hexafluoride (SF_6), or chlorofluorocarbons (CFCs) such as Freon. One of ordinary skill in the art can vary the dimensions, geometry and the operational settings of the GLS to optimize the GLS so that it is suitable for flow rates ranging from approximately a few mil/min to hundreds of ml/min.

[0032] The GLS, described in International publication number WO 2010/056313, hereby incorporated by reference in its entirety, comprises a chamber in which a specially tapered tube with an increasing internal diameter is inserted. The end

of the tapered tube is angled such that as the gas-liquid mixture flows out of the tapered tube and into the larger chamber, flow is directed to impact an inner wall of the chamber at an angle tangential to the impact wall of the separator.

[0033] Because the gas-liquid flow is not straight down upon exiting the tapered tube, coalescence of the modifying liquid and sample begins inside the GLS. The impact point and angle of impact serve to direct the liquid stream into a downward spiral towards a liquid exit point. Simultaneously, compressible fluids such as CO_2 are vented upon exiting the tapered tube. Because the modifying liquid and sample coalesce in a controlled manner inside the GLS as the compressible fluid is vented, the modifying liquid and sample are able to drain towards the bottom of the GLS.

[0034] In embodiments, after passing through the GLS, the modifying liquid has been separated from the compressible fluid such as CO_2 and therefore is no longer in danger of being aerosolized. The modifying liquid now behaves just as any other mobile phase fluid common to other types of chromatography such as HPLC, MPLC, LPLC or Flash chromatography. Therefore, it can be collected using a standard open bed XY type fraction collector known to one of skill in the art without fear of sample loss or cross contamination.

[0035] Some embodiments of the technology further comprise a collector arm adapter (see e.g., FIG. **3A**) that can be attached to an XY type collector arm that can be downstream of the GLS. The function of this collector arm adapter is to curb and/or diminish the aerosols generated once the fluid flow is subject to atmospheric conditions, for example, the location where the fluid flow leaves the collector tip of the robot arm. For example, the collector arm adapter is appropriate in the event that trace residual amounts of CO_2 (e.g. 0.001%-1%, 0.01%-0.1%) remain in the flow stream after passing through the GLS. The collector arm adapter includes a cover that surrounds a tip which disperses the sample to the collector rack. The collector arm adapter creates an enclosure to trap any remaining aerosols that may be generated as a result of trace residual CO_2 left in the incompressible fluid after the combined stream has passed through the GLS. By coupling the GLS to the collector arm adapter, the aerosols can be well confined within a very limited range around the fluid flow stream between the space where the stream leaves the collector and the container underneath the collector, at a significantly reduced scale. In some embodiments, the aerosols are completely

diminished and are not observable in this design.

[0036] The process can include an adjustable container rack that can be coupled to the GLS and collector arm adapter. Corresponding dimensions and openings of receiving ports of the container rack, in addition to the adjustable height of the rack, can accommodate a wide range of fluid flow characteristics to ensure high collection efficiency of fraction flow.

[0037] The technology can also include optimum processes for hardware development for characteristic SFC instrumentation. The processes can include designs of GLS and collector arm adapters based on actual SFC flow characteristics to optimize the capability for maximum control of gas venting and aerosol diminishing. The GLS can be made of stainless steel, a polymer, glass or other types of compatible materials for the process. The geometry and dimensions of the GLS can be commensurate with the actual flow capacity to ensure proper ventilation flow while preserving most fluid flow drained down to the collector. The collector arm adapter (see, e.g., FIG. **3A** and **3B**) can include various dimensions and geometries for optimized aerosol confinement and diminished capability based on flow rate and compositions. The rack adapter (see, e.g., FIGS. **4** and **5**) can include designs for adjustable height and for accommodation and connection to various types of containers from, for example, tubes, bottles, and vessels, to carboys, to ensure maximum collection efficiency, encapsulation of liquid flow and minimum aerosol generation.

[0038] The present technology can also include optimum processes for method development. The processes can include optimization of method parameters such as pressure settings on GLS, which can range from about a few psi to 50-60 bar, combined with specific adapted geometry and dimensions for the best performance for gas-liquid separation and venting. The process can also include adjustment of the collector arm adapter in terms of its dimensions and spatial arrangement on the robot arm for best efficiency of aerosols control.

[0039] The present technology also includes various integrations of applications for the methods and devices for fraction collection purposes. Such development with an XY type collector includes, but is not limited to, routine fraction collections from high performance SFC, secondary collection in addition to conventional fraction collection in

SFC, fraction collection for high flow, high speed supercritical fluid flash chromatography, and any other type of pressurized liquid processes where there is potential risk of aerosol generation during the collections.

[0040] One such embodiment of the above mentioned technology is depicted in FIG. **1**, which shows a mass-directed preparative SFC100 (MD-SFC100) system **100**. The components of the system are interconnected via a suitable tubing **101** that is capable of withstanding the intense pressures and temperatures necessary to reach supercritical conditions without corrosion or other safety concerns. In one embodiment, the system comprises a CO_2 supply **105**, followed by a flow meter **106** to control the flow of CO_2 through the system. There is also a separate reservoir **111** which contains the modifier solvent, e.g. methanol. In some embodiments, there are pumps for both CO_2 and modifier solvents **110**, **115**, respectively. In some embodiments, there is a Waters 2767 sample manager **120** (including a sample injection **116** and an open bed collector **160**). There are also in-line heaters **125**, a separation column **126** surrounded by a column oven **127**. In some embodiments, there is a tunable splitter **128** that directs a portion of the flow to a mass spectrometry detector **135** and a remaining portion of the flow to a UV/PDA detector **130**. In some embodiments, there is an automated BPR **131** located downstream of the UV/PDA detector. There is a make-up pump **132** located downstream of the BPR, and a heat exchanger **133**. In some embodiments, the GLS **140** is used to remove the compressible fluid (e.g. 100% removal, 99.98% removal, 99.8% removal, 99% removal) from the combined flow stream and vent it without aerosolization and corresponding sample loss and cross contamination. After a junction point **141** a portion of the stream is directed to a waste receptacle **150** while the remaining flow is directed to a fraction collector **160** shown here as a Waters 2767 fraction collector and a Waters Fraction Collector (WFCIII) **155**. In this configuration the Waters Fraction Collector (WFCIII), an XY type fraction collector, is integrated as the secondary collector. WFCIII is plumbed along side with Waters 2767 fraction collector **160**, and is controlled by Waters Masslynx software that controls the whole chromatography system **100**. In one embodiment, the Waters 2767 fraction collector **160** is the primary fraction collector and is responsible for collecting the majority of fractions. In one embodiment, the WFCIII can optionally be used as a secondary fraction collector **155**. The purpose of the optional secondary collector **155** is to collect any fractions that may be missed by the primary collector **160**. For example, glitches in

software or other unforeseen circumstances may prevent the primary collector from collecting all fractions, thus the secondary collector may be present to collect any uncollected fractions. Thus in some embodiments it is possible to use only one fraction collector (e.g. Waters 2767 fraction collector **160**) whereas in some embodiments it is possible to use multiple fraction collectors.

[0041] In other embodiments, not shown, the system **100** can be used in combination with other fluids for performing SFC. That is, other compressible fluids which can be processed to form a supercritical phase for chromatography can be used in place of CO_2. For example, in one embodiment, nitrous oxide (N_2O) may be used. Alternatively, in one embodiment, other compressible fluids such as sulfur hexafluoride (SF_6) or chlorofluorocarbons (CFCs) such as Freon may be used.

[0042] FIG. **2** shows the installation of WFCIII, (e.g. part number **155** in FIG. 1) an XY type collector installed with both collector arm adapter **230** (for example, the collector arm adapter **305** of FIG. **3A**) and rack adapter **220** (for example, the rack adapter **405** in FIG. **4** and **505** in FIG. **5**) for SFC instrumentation. In this embodiment, the collectors work to collect fractions of compounds of interest based on criteria set by instrument methods from UV, Mass Spectrometer and/or Evaporative Light Scattering Detector ("ELSD") and other signals. The WFCIII collector can be fully integrated and controlled by operating software that controls the entire chromatorgraphy system. The WFCIII works with the Waters 2767 collector in either a complementary way to ensure higher collection efficiency, or the Waters 2767 collector acts as a standalone collector. WFCIII can be trigged by line of injection, peak-based signals from Mass Spec., UV, ELSD or any kind of detectors from the system, and different kinds of algorithm combinations with these signals, or it can collect fractions by time windows, peak-triggered time slicing mode, or any other manual mode controllable by preset methodologies. The configuration in this embodiment can ensure a high collection efficiency and can reduce the risk of potential sample loss from random malfunction. The configuration can also enrich versatile collection features to further extend the applicability, robustness, economy and flexibility of SFC instrumentation for more chromatography applications, such as, but not limited to, high throughput analysis and purifications, chiral analysis, flash chromatography for pharmaceutical, natural product, food analysis, environmental monitoring, petroleum analysis, and/or alternative energy

development.

[0043] The collector arm adapter **305** of FIG **3A** is an optional feature. In the event that not all of the CO_2 or compressible fluid is vented and some small portion remains, the adapter arm **305** can prevent sample loss /cross contamination by confining the space around the exit tip.

[0044] FIG. **3B** shows a schematic of the internal geometry of the collector arm adapter pictured in **3A**, i.e . adapter **305**. Fluid enters through the inlet **355**, and flows through outlet **360**. Any aerosolization resulting from this transition is collected by the enclosure portion **365**. In one embodiment, the inlet portion **355** is 8 mm in length. In one embodiment, the outlet portion **360** is 6 mm in length. In one embodiment, the enclosure element **365** is 14 mm in length.

[0045] While the collector arm adapter **305** is an optional element, which can enhance performance, the GLS is a required component. The GLS vents a significant portion (e.g. 100%, 99%) of the CO_2 from the combined flow stream.

[0046] The gas-liquid separator used in the system of FIG. **1**, e.g. GLS **140**, is shown in more detail in FIG. **6**. The separator comprises an inlet flow port **650**, a gas vent **655**, a top cap **660**, an outer vessel **670**, a bottom cap **680**, a liquid outflow port **685**, and a drain port **690**. A specially tapered tube with an increasing internal diameter, called the dripper **665**, is inserted into the separator. The mouth of the dripper **667** (through which the flow exits the dripper into the separator, the outlet) is wider than the diameter of the dripper where the flow enters the dripper **666** (inlet). The dimensions of the dripper are optimized for the system's flow rates, which assist in consolidating aerosol into a unified liquid stream. In general, the ratio of the diameter of the outlet to the diameter of the inlet is between 2-100 to one. For flow rates up to about 100 gm/minute, the ratio of the diameter of the outlet to the diameter of the inlet is between about 2-4 to one, preferably about three to one. The ratio can be adjusted to accommodate flow rates of up to 1000 gm/minute.

[0047] The dripper shown in FIG. **7**, e.g. the dripper **665** of FIG. **6**, has an angle, relative to the separator's downward pointing vertical axis, between 10 and 80 degrees. In other words, the exit of the dripper is neither straight down nor straight sideways, but rather in-between. This angle is in a vertical orientation, and is not the tangential angle.

[0048] Another embodiment of the GLS is shown in FIG. **8**. Flow is directed into the GLS via the inlet port **805**. As the fluid travels through the dripper **810**, it exits through the mouth of the dripper **815**. The incompressible fluid collects on the inner wall **820** and falls under the action of gravity towards the collecting basin **825** and finally flows through the outlet **830**. Meanwhile, the compressible fluid escapes through the gas vent **835**.

[0049] The GLS can be located anywhere downstream of the BPR and, most effectively, upstream of the fraction collectors. In one embodiment shown in FIG.**1**, the GLS is located after the heat exchanger. In another embodiment, a plurality of gas-liquid separators may be located after the junction point **141**.

[0050] FIG. 9 shows a schematic embodiment of the open bed atmospheric collection system. It shows the collector arm adapter working in combination with the rack adapter to deliver the sample to the container. Fluid flows in through the GLS **905** (i.e. the GLS **140** in FIG. **1**). After a portion of the sample is collected by the primary fraction collector **910**, i.e. the Waters 2767 fraction collector **160** from FIG. **1**, a portion of the sample passes through the collector arm adapter **920**, i.e. part **305** shown in FIG. **3A**. Any remaining traces of aerosols are collected by the rack adapter **930**, i.e. part **220** in FIG. **2**, part **405** in FIG. **4**, and part **505** in FIG. **5**. The fractions then pass into the container **940**.

[0051] The technology described above can adapt to XY type fraction collectors with no Z-movement (e.g., movement in a vertical direction) arm for preparative SFC use. The technology can modify existing XY type fraction collectors with no Z-movement so that the collector meets the requirements of both technical and safety usage in SFC systems. Safety concerns can arise when aerosols are generated outside of the SFC system. Additionally, by reducing the presence of aerosols, the technology significantly reduces sample loss and cross contamination when collecting fractions.

[0052] This technology significantly improves and expands the scope of SFC technology for use in a variety of settings, including the chemical industry and academic research laboratories. By eliminating technical concerns such as cross contamination, sample loss, and unsafe venting of compressed fluids, the technology makes SFC a more robust and reliable process. Additionally, the technology makes SFC a more convenient

process because it allows the use of standard, open bed atmospheric XY type fraction collectors already in use with other types of chromatography and familiar to one of ordinary skill in the art.

[0053] The technology can be used in any process where there is a danger of unwanted aerosols being generated. The flow conditions of the system can be optimized to diminish aerosols generated from depressurization of pressurized fluids to ensure collection efficiency and safety operation under atmospheric conditions.

[0054] Although various aspects of the disclosed apparatus and method have been shown and described, modifications may occur to those skilled in the art upon reading the specification. The present application includes such modifications.

CLAIMS

What is claimed is:

1. A supercritical fluid chromatography system comprising:

a first pump for pumping a first flow stream comprising a compressible fluid;

a second pump for pumping a second flow stream comprising a modifier fluid, the second pump in parallel with the first pump;

a column located in a combined flow stream, the column located downstream of the first and second pumps, the combined flow stream comprising the first flow stream, the second flow stream, and a sample;

a detector located downstream of the column;

a gas-liquid separator located downstream of the detector, the gas-liquid separator configured to vent a majority of the compressible fluid while maintaining a majority of the sample to avoid sample loss and cross-contamination; and

an open bed XY type collector located after the gas-liquid separator.

2. The supercritical fluid chromatography system of claim 1 further comprising a collector arm located downstream of the gas-liquid separator.

3. The supercritical fluid chromatography system of claim 2 further comprising a collector arm adapter coupled to the collector arm, the collector arm adapter configured to reduce aerosols when the combined flow stream is at atmospheric conditions.

4. The supercritical fluid chromatography system of claim 1, further comprising an adjustable container rack coupled to the XY type collector.

5. The supercritical fluid chromatography system of claim 1 wherein the gas-liquid separator is made from stainless steel, polymeric, or glass.

6. The supercritical fluid chromatography system of claim 1 further comprising a back pressure regulator located upstream of the gas-liquid separator.

7. The supercritical fluid chromatography system of claim 1 wherein the compressible fluid is carbon dioxide (CO_2).

8. A method for collecting multiple samples in supercritical fluid chromatography (SFC), the method comprising:

pumping a first flow stream comprising a compressible fluid;

pumping a second flow stream comprising an incompressible fluid;

injecting a sample into the second flow stream;

combining the first and second flow streams to form a combined flow stream;

subjecting the flow stream to SFC conditions;

flowing the combined flow stream through a chromatography column;

removing at least a portion of the compressible fluid from the combined flow stream; and

collecting the sample in an open bed XY type collector.

9. The method of claim 8, wherein the compressible fluid is CO_2.

10. The method of claim 8, wherein aerosolization of the sample is prevented during collection of the sample in the open-bed XY collector.

11. The method of claim 8, wherein removing at least a portion of the compressible fluid from the combined flow stream comprises removing at least 99% of the compressible fluid.

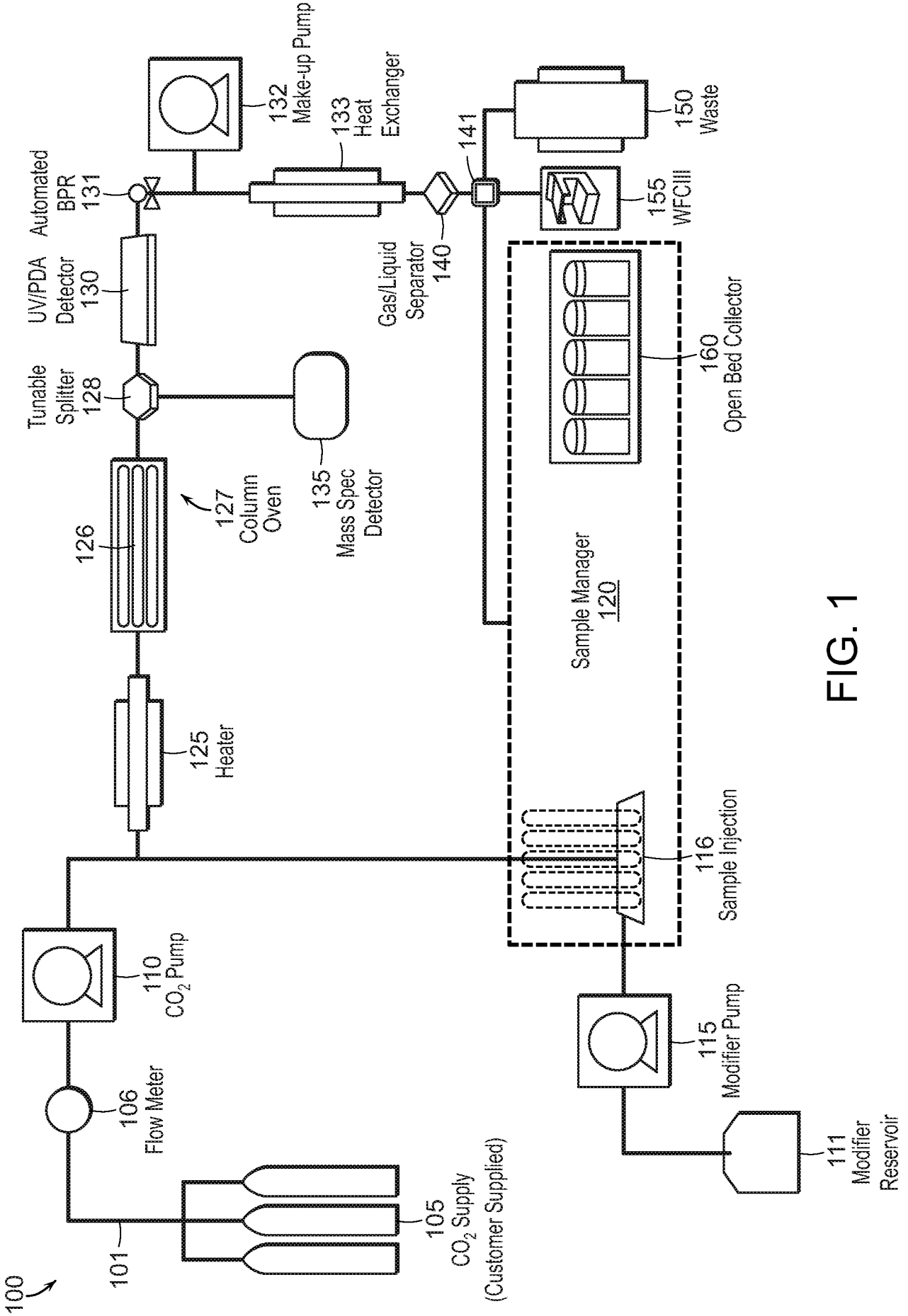
100
101
105
CO_2 Supply
(Customer Supplied)
106
Flow Meter
110
CO_2 Pump
111
Modifier
Reservoir
115
Modifier Pump
116
Sample Injection
120
Sample Manager
125
Heater
126
127
Column
Oven
128
Tunable
Splitter
130
UV/PDA
Detector
131
Automated
BPR
132
Make-up Pump
133
Heat
Exchanger
135
Mass Spec
Detector
140
Gas/Liquid
Separator
141
150
Waste
155
WFCIII
160
Open Bed Collector

FIG. 1

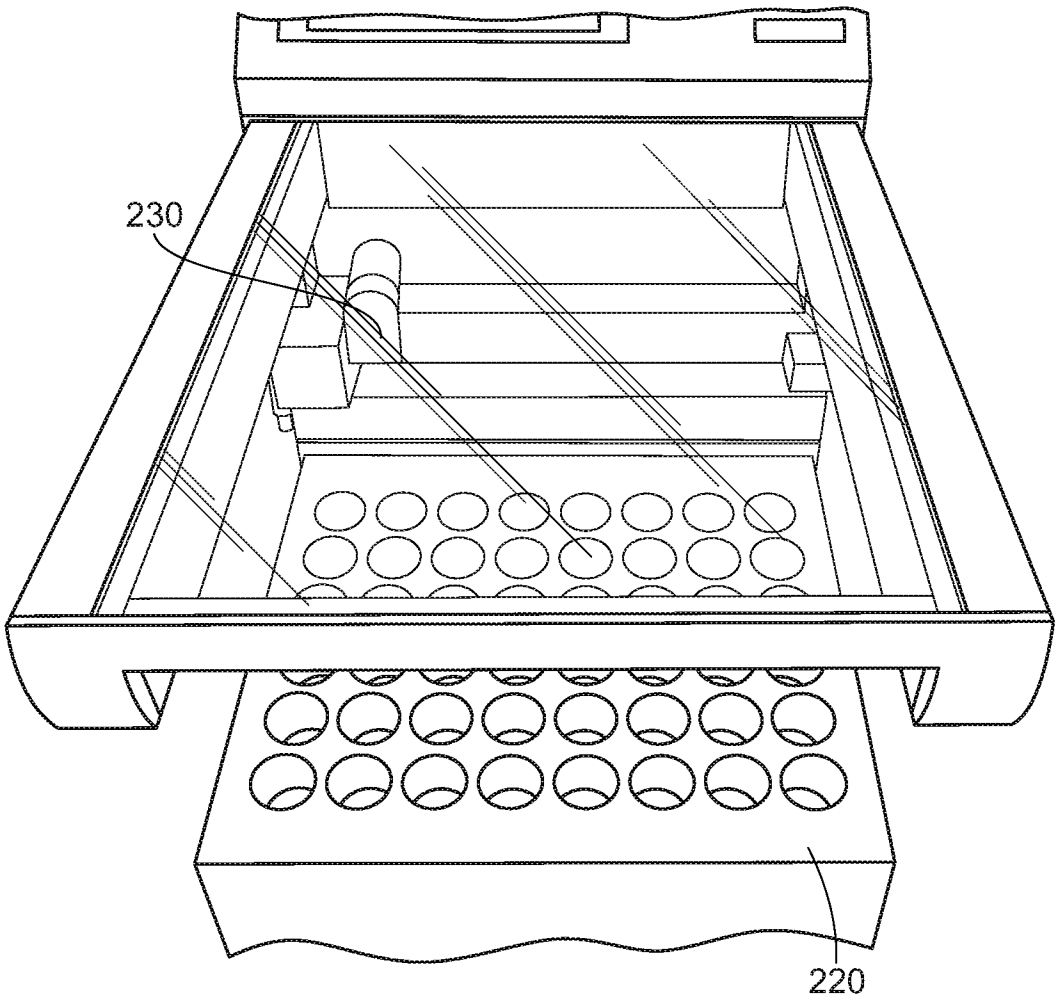

FIG. 2

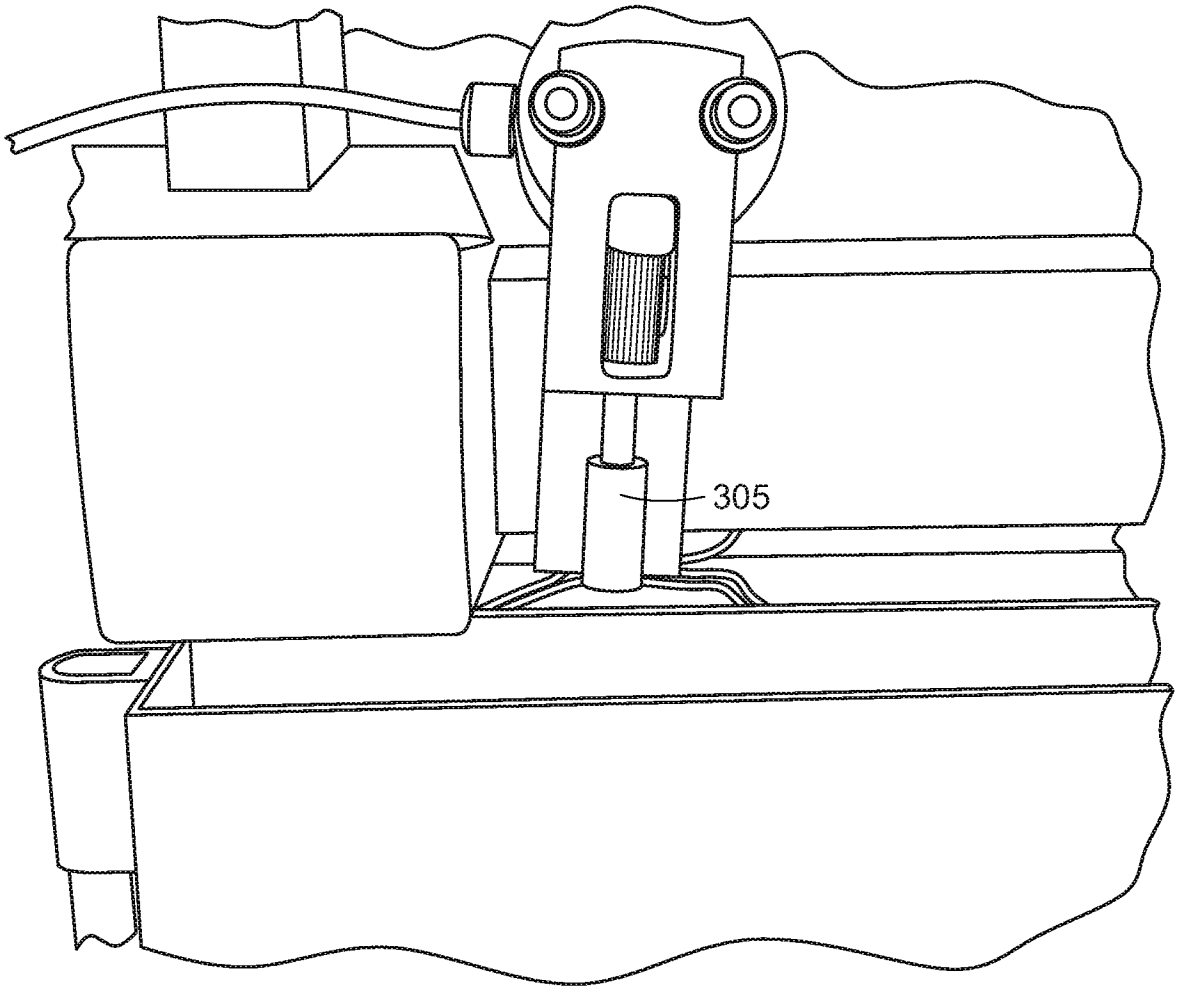

FIG. 3A

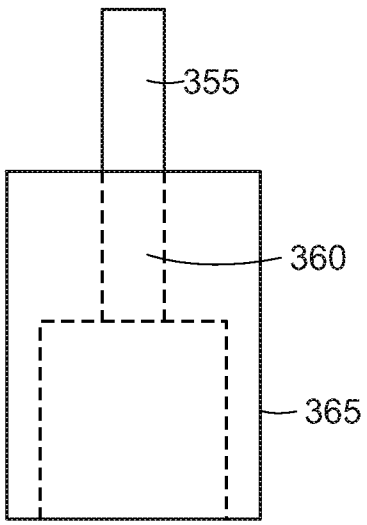

FIG. 3B

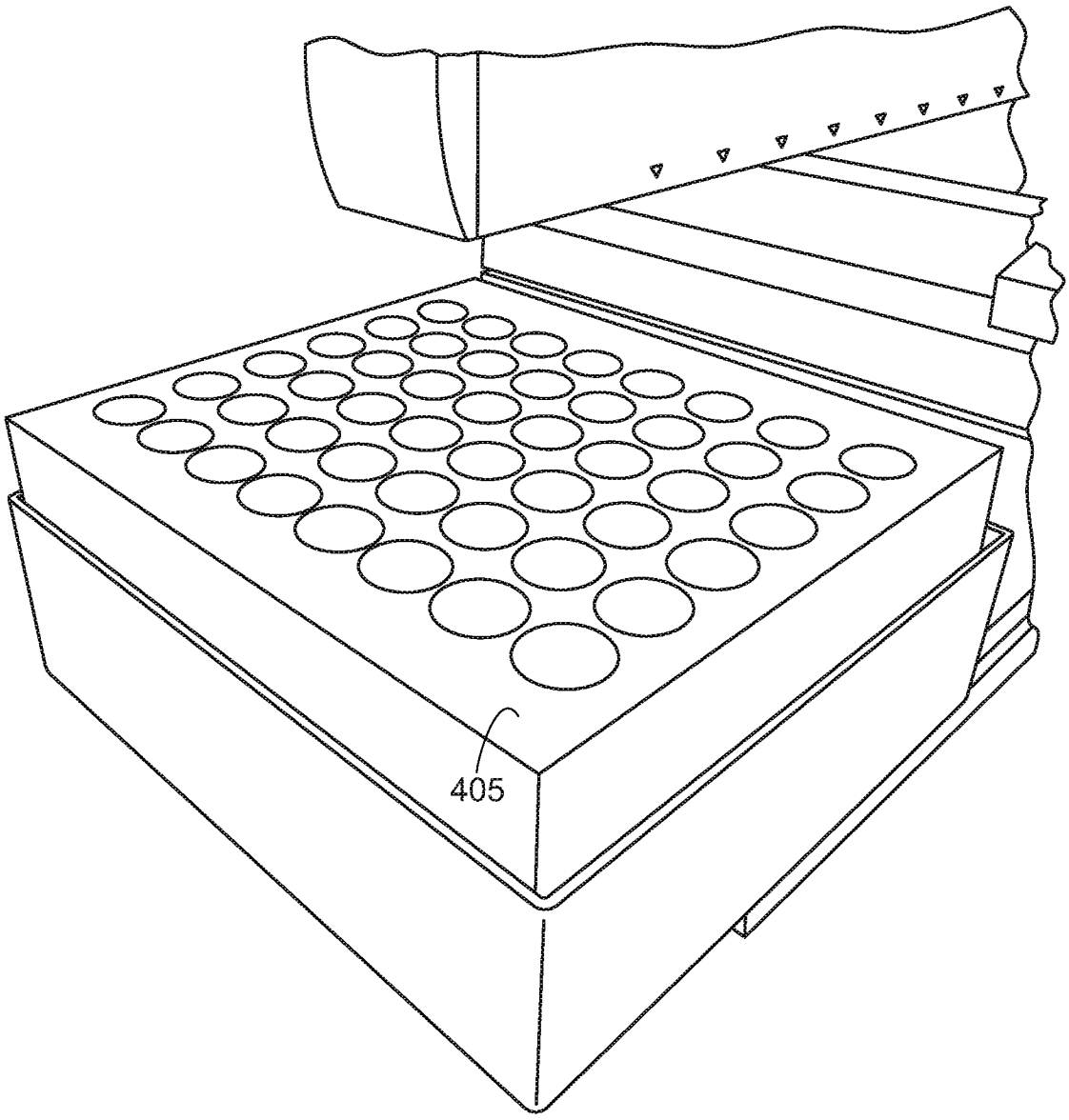

FIG. 4

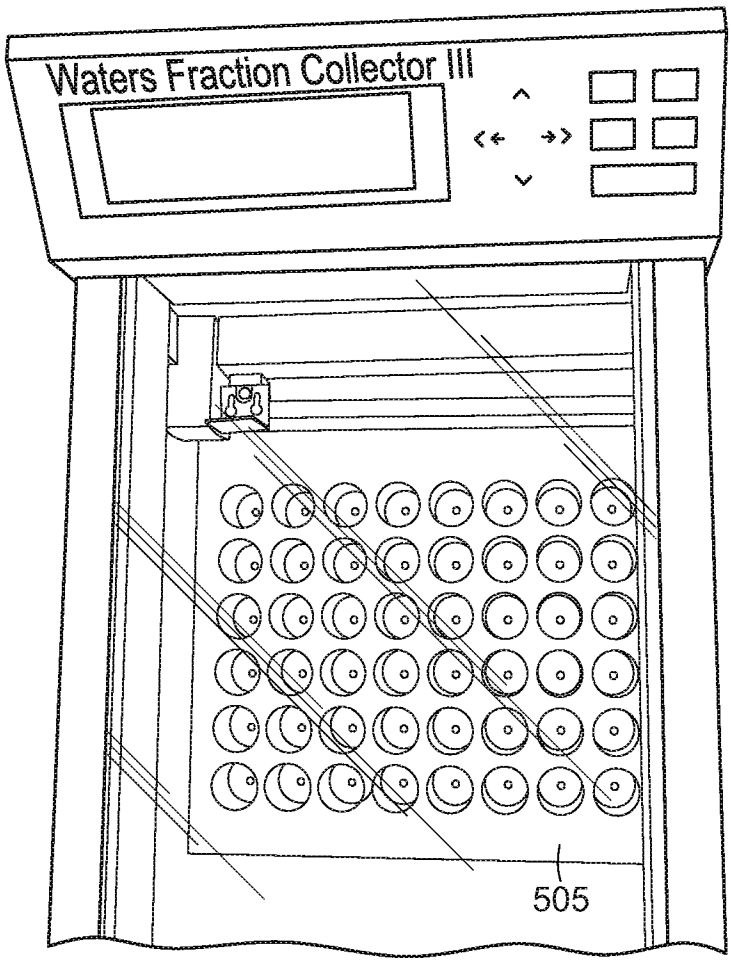

FIG. 5

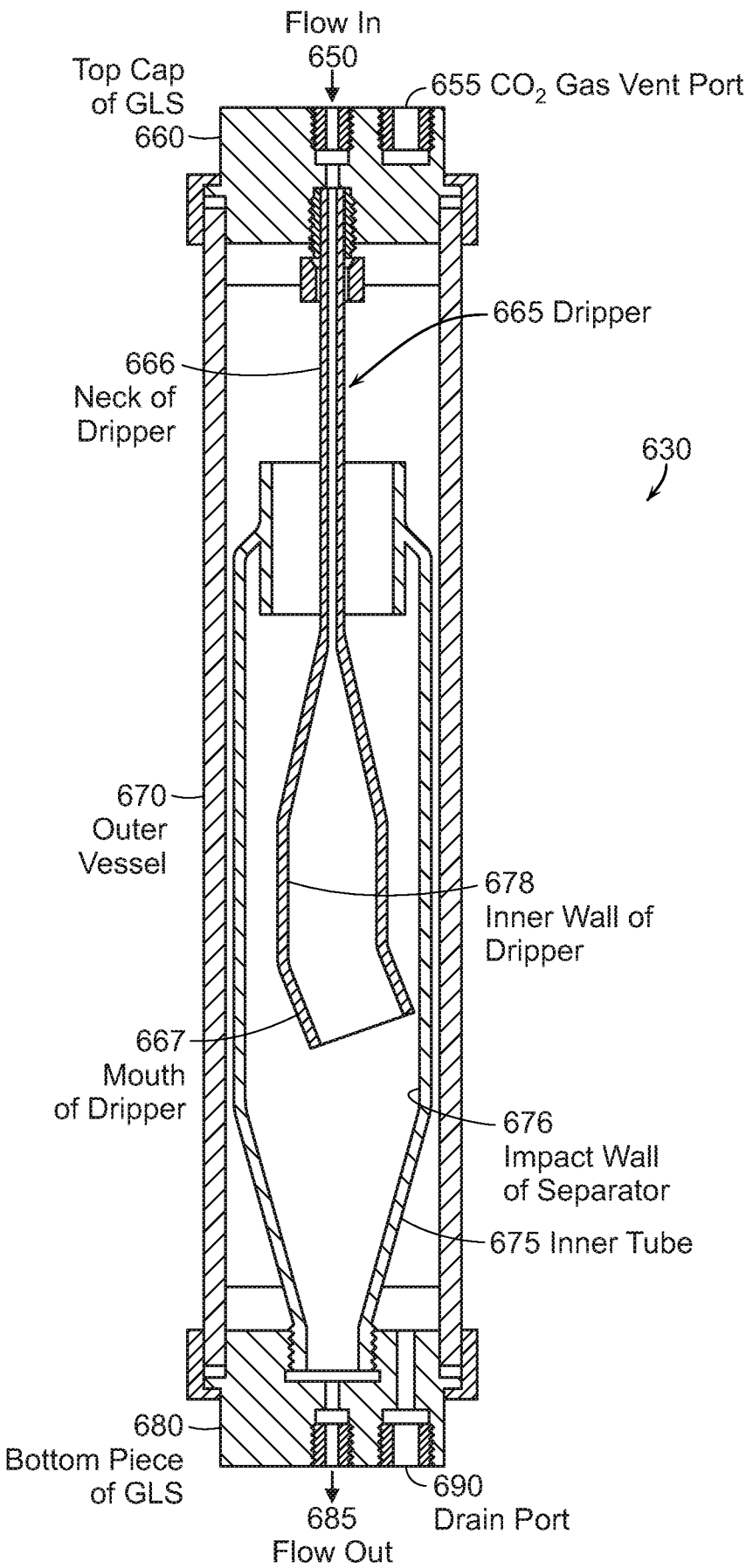
Flow In
650
Top Cap
of GLS
660
655 CO_2 Gas Vent Port
665 Dripper
666
Neck of
Dripper
630
670
Outer
Vessel
678
Inner Wall of
Dripper
667
Mouth
of Dripper
676
Impact Wall
of Separator
675 Inner Tube
680
Bottom Piece
of GLS
690
Drain Port
685
Flow Out

FIG. 6

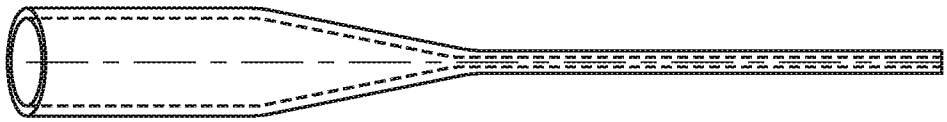

FIG. 7A

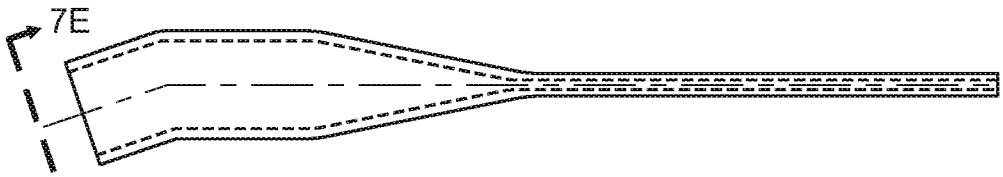

FIG. 7B

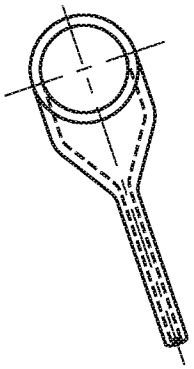

FIG. 7E

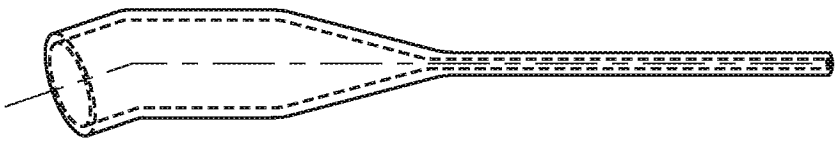

FIG. 7C

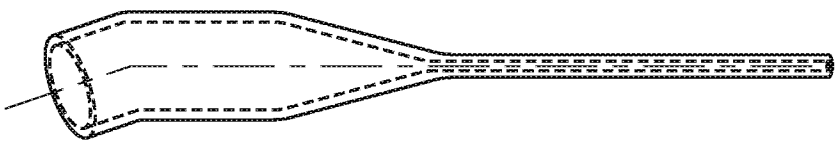

FIG. 7D

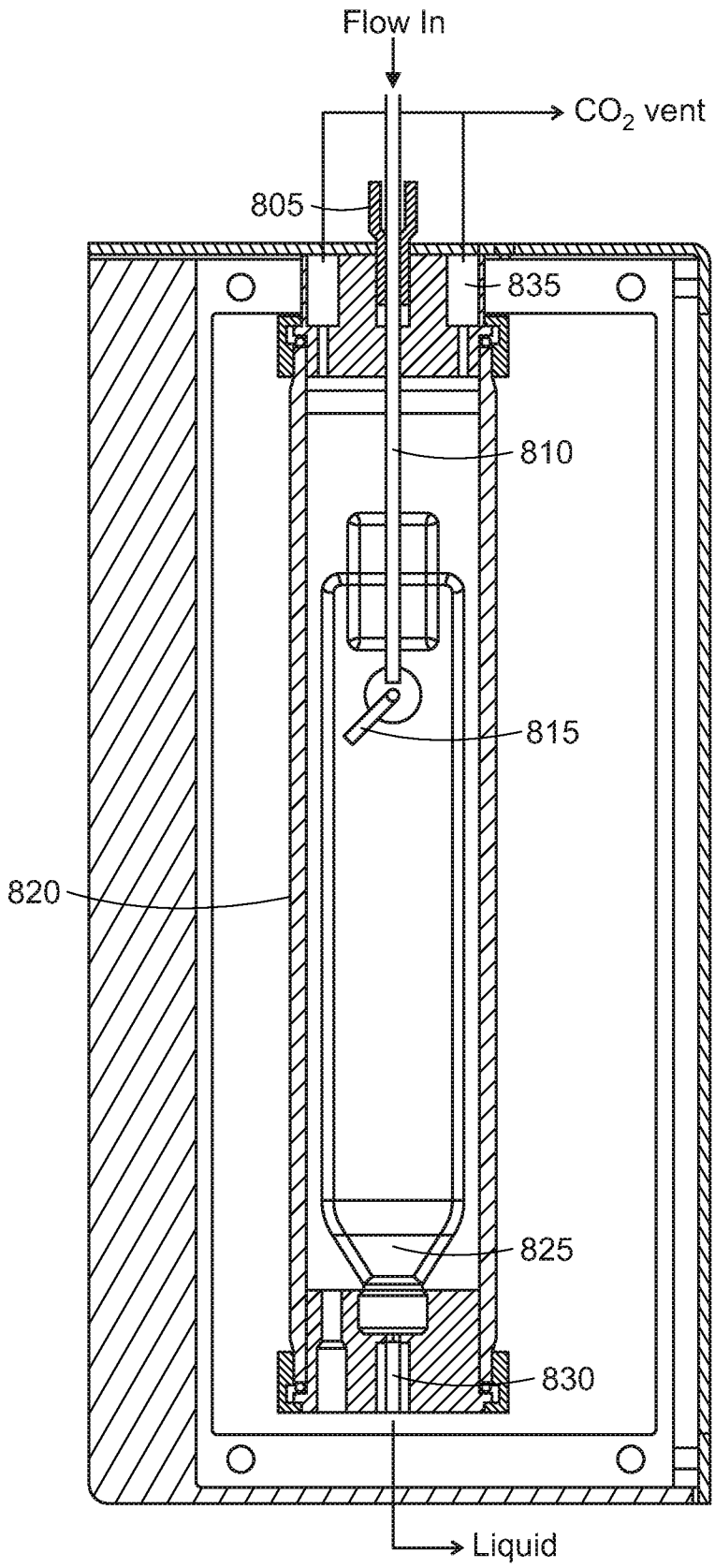

FIG. 8

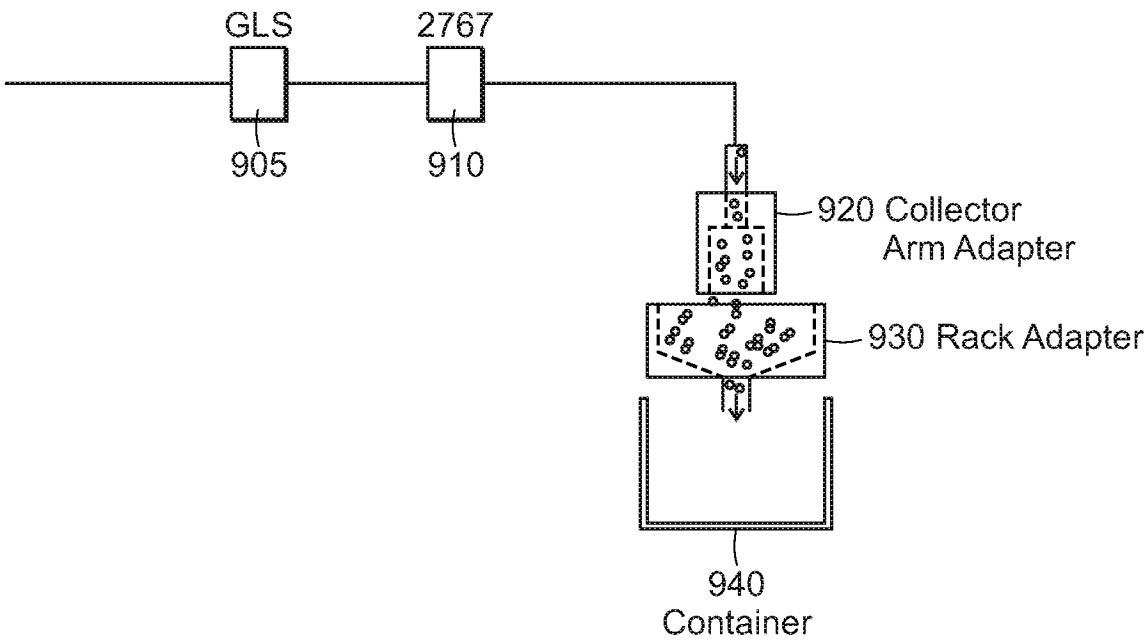
GLS
2767
905
910
920 Collector
Arm Adapter
930 Rack Adapter
940
Container

FIG. 9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/42755

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - B01D 15/08 (2012.01)
USPC - 210/198.2
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(8)- B01D 15/08 (2012.01);
USPC- 210/198.2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC- 210/656, 659, 634, 635;
Patents and NPL (classification, keyword; search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWest (US Pat, PgPub, EPO, JPO), GoogleScholar (PL, NPL), FreePatentsOnline (US Pat, PgPub, EPO, JPO, WIPO, NPL);
search terms: supercritical, compress, modifier, fluid, liquid, pump, parallel, separator, collector, open, bed, XY, well, address

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2008/0010956 A1 (FOGELMAN et al.) 17 January 2008 (17.01.2008), Fig. 9; para [0005], [0022]-[0025], [0045]-[0048]	1-11
Y	US 2001/0013494 A1 (MAIEFSKI et al.) 16 August 2001 (16.08.2001), Fig. 3A, 3B, 18; para [0012], [0013], [0021]-[0025], [0059], [0073]-[0078], [0086], [0105]-[0108], [0114]	1-11
Y	US 2010/0163490 A1 (LASALLE) 01 July 2010 (01.07.2010), para [0015]-[0101]	1-11
Y	US 2002/0139752 A1 (BERGER et al.) 03 October 2002 (03.10.2002), para [0022]-[0116]	1-11
Y	US 5,139,680 A (TARNOPOLSKY) 18 August 1992 (18.08.1992), col 3-7	1-11
A	US 2004/0018099 A1 (Berger et al.) 29 January 2004 (24.01.2004) entire document	1-11

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"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	Date of mailing of the international search report
15 August 2012 (15.08.2012)	31 AUG 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)