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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 August 2013 (08.08.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/115933 A1

(51) International Patent Classification:
A61B 5/08 (2006.01)

(21) International Application Number:
PCT/US2013/000026

(22) International Filing Date:
1 February 2013 (01.02.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/593,862 1 February 2012 (01.02.2012) US

(71) Applicant: **INVOY TECHNOLOGIES, LLC** [US/US]; 1820 E. Ray Road, Chandler, AZ 85225 (US).

(72) Inventors: **AHMAD, Lubna, M.**; 1820 E. Ray Road, Chandler, AZ 85225 (US). **SATTERFIELD, Brent**; 585 W 500 S, Bountiful, UT 84010 (US). **MARTINEAU, Rhett, L.**; 3095 E. Tiffany Way, Gilbert, AZ 85298 (US). **SMITH, Zachary, B.**; 329 W. Encanto Blvd., Phoenix, AZ 85003 (US).

(74) Agent: **SULLIVAN, Stephen, T.**; Stephen T. Sullivan, P.C., 7001 E. Paradise Drive, Scottsdale, AZ 85254-5175 (US).

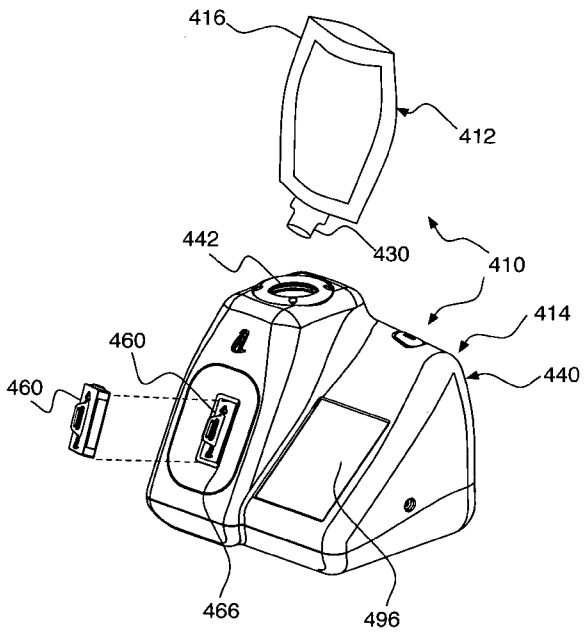
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, 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, PA, 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,

[Continued on next page]

(54) Title: SYSTEM FOR MEASURING BREATH ANALYTES

FIG. 8



(57) Abstract: In accordance with one aspect of the invention, a system is provided for sensing an analyte in breath of a user. The system comprises a base; a breath input operatively coupled to the base that receives the breath; a cartridge coupled to the base and in fluid communication with the breath input to receive the breath, wherein the cartridge comprises an interactant subsystem that is selected to undergo a reaction with the analyte when the analyte is present in the breath and to undergo an optical change corresponding to the reaction; and an optical subsystem coupled to the base and configured to sense the optical change, wherein the optical subsystem generates an output comprising information about the analyte in response to the optical detection. Methods are also provided.

WO 2013/115933 A1

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).

Published:

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

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

SYSTEM FOR MEASURING BREATH ANALYTES

FIELD OF THE INVENTION

[0001] The present invention relates generally to systems, devices and methods for measuring analytes in breath, preferably endogenous analytes in human breath.

BACKGROUND OF THE INVENTION

[0002] There are many instances in which it is desirable to sense the presence and/or quantity or concentration of an analyte in a gas. "Analyte" as the term is used herein is used broadly to mean the chemical component or constituent that is sought to be sensed using devices and methods according to various aspects of the invention. An analyte may be or comprise an element, compound or other molecule, an ion or molecular fragment, or other substance that may be contained within a fluid. In some instances, embodiments and methods, there may be more than one analyte present, and an objective is to sense multiple analytes. "Fluid" as the term is used herein is used broadly to comprise a substance that is capable of flowing and that changes its shape when acted upon by a force. It includes liquids and gases, not only in their pure forms but also when in heterogeneous states, such as with slurries, suspensions, colloidal dispersions, aerosols and the like. Newtonian fluids are best suited to application in the present invention, but some degree of non-Newtonian behavior could be acceptable, depending on the specific application, and this is not intended to be limiting. "Gas" as the term is used herein also is used broadly and according to its common meaning to include not only pure gas phases but also vapors, non-liquid fluid phases, gaseous colloidal suspensions, solid phase particulate matter or liquid phase droplets entrained or suspended in gases or vapors, and the like. "Sense" and "sensing" as the terms are used herein are used broadly to mean detecting the presence of one or more analytes, or to measure the amount or concentration of the one or more analytes.

[0003] In many instances, there is a need or it is desirable to make the analysis for an analyte in the field, or otherwise to make such assessment without a requirement for expensive and cumbersome support equipment such as would be available in a hospital, laboratory or test facility. It is often desirable to do so in some cases with a largely self-contained device, preferably portable, and often preferably easy to use. It also is necessary or desirable in some instances to have the capability to sense the analyte in the fluid stream in real time or near real time. In addition, and as a general matter, it is highly desirable to accomplish such sensing accurately and reliably.

[0004] The background matrix of breath presents numerous challenges to sensing systems, which necessitate complex processing steps and which further preclude system integration into a form factor suitable for portable usage by layman end-users. For example, breath contains high levels of humidity and moisture, which may interfere with the sensor or cause condensation within the portable device, amongst other concerns. Also, the flow rate or pressure of breath as it is collected from a user typically varies quite considerably. Flow rate variations are known to impact, often significantly, the response of chemical sensors. Breath, especially when directly collected from a user, is typically at or near core body temperature, which may be considerably different than the ambient temperature. Additionally, body temperature may vary from user to user or from day to day, even for a single user. Devising a breath analyzer thus is a non-trivial task, made all the more difficult to extent one tries to design and portable and field-amenable device.

[0005] Notably, the measurement of endogenous analytes in breath presents different challenges and requires different techniques and devices than the measurement of exogenous analytes. Endogenous analytes are those that are produced by the body, excluding the lumen of the gastrointestinal tract, whereas exogenous analytes are those that are present in breath as a result of the outside influence or as a result of user consumption. However, many analytes are produced endogenously and can also be exogenously introduced. For example, ammonia is produced endogenously through the metabolism of amino acids, but can also be introduced exogenously from the environment such as ammonia-containing household cleaning supplies. The term "endogenous" is used according to its common meaning within the field. Endogenous analytes are produced by natural or unnatural means within the human body, its tissues or organs, typically excluding the lumen of the gastrointestinal tract.

[0006] There are a number of significant challenges to measuring endogenous analytes in breath. Endogenous analytes typically have significantly lower concentrations in the breath, often on the order of parts per million (ppm), parts per billion (ppb), or less. Additionally, measurement of endogenous analytes requires discrimination of the analyte in a complex matrix of background gases. Instead of typical atmospheric gas composition (e.g., primarily nitrogen), exhaled breath has high humidity content and larger carbon dioxide concentration. This leads to unique challenges in chemical sensitivity, selectivity and stability. For example, chemistries conducive for breath ammonia measurement are preferably sensitive to 50 ppb in the presence of 3 to 6% water vapor with 3 to 5% carbon dioxide.

[0007] Because of the historical difficulty in even detecting endogenous breath analytes, other challenges have not been extensively investigated. Examples of such challenges

include: (a) correlating the analytes to health or disease states, (b) measuring these analytes given characteristics of human exhalation, e.g., flow rate and expiratory pressure, (c) measuring these analytes sensitively and selectively, and (d) doing all these in a portable, cost effective package that can be implemented in medical or home settings.

[0008] Colorimetric devices are one method for measuring a reaction involving a breath analyte. Colorimetric approaches to endogenous breath analysis have historically been plagued with lengthy response times, and expensive components. Often such analysis has to be performed in a laboratory. Thus there remains a need for a breath analyzer that can measure endogenous breath components present in relatively low concentrations, such as acetone, accurately and quickly, without a long wait period for results, in addition to being inexpensive and useable by the layperson. It is also preferable if the breath analyzer is capable of measuring multiple analytes.

SUMMARY OF THE INVENTION

[0009] In accordance with one aspect of the invention, a system is provided for sensing an analyte in breath of a user. The system comprises a base; a breath input operatively coupled to the base that receives the breath; a cartridge coupled to the base and in fluid communication with the breath input to receive the breath, wherein the cartridge comprises an interactant subsystem that is selected to undergo a reaction with the analyte when the analyte is present in the breath and to undergo an optical change corresponding to the reaction; and an optical subsystem coupled to the base and configured to sense the optical change, wherein the optical subsystem generates an output comprising information about the analyte in response to the optical detection.

[0010] The breath input optionally may comprise a mouthpiece and an attachment for attaching a non-human breath container in which the breath is contained. A preferred example of a non-human breath container would comprise a bag, such as a Tedlar bag. The cartridge preferably is detachably coupled to the base. The cartridge also optionally but preferably comprises a handle, and also preferably a light shielding device. More specifically, in some instances there is a concern that components of the cartridge, for example, such as chemical components, may be adversely affected by ambient light. Accordingly, in presently preferred embodiments and methods according to certain aspects of the invention, the base of the system comprises an exterior surface that forms an interior and shields the interior from ambient light, wherein the exterior surface comprises an aperture; and the cartridge comprises a shroud that substantially conforms to the aperture to shield ambient light from entering the aperture when the cartridge is coupled to the base.

[0011] In certain embodiments, the base is configured to accept breath from a plurality of breath inputs. The base may further be configured to accept variable volumes of breath and/or remove unneeded volume of breath.

[0012] In some instances, it is necessary or desirable to undertake a multiple-stage reaction system. Accordingly, in some presently preferred embodiments and methods, the interactant subsystem comprises a first interactant that is selected to undergo a first reaction with the analyte when the analyte is present in the breath and to generate a first intermediate; and a second interactant that is selected to undergo a second reaction with the first intermediate and to cause the optical change corresponding to the second reaction. In an illustrative but presently preferred example, the first interactant comprises a primary amine coupled to a first substrate a substantially in the absence of a tertiary amine; and the second interactant comprises the tertiary amine.

[0013] The optical subsystem can be configured to sense the optical change in a number of ways and according to a number of different criteria. It may be configured, for example, to sense the optical change at a predetermined time after the breath is inputted into the breath input. In some preferred embodiments, the system may further comprise a flow sensor that senses a characteristic of the breath as the breath moves in the system; and the optical subsystem is configured to sense the optical change in response to the flow sensor.

[0014] The system also may and preferably does comprise a processor that performs various roles in the system. One of those roles may comprise using process information, such as the identification of one or more specific analytes that the system is configured to sense, information relating to the analyte, such as expected concentration ranges, states, reactivities, temperature and/or pressure dependencies, partial pressure and other vapor state information, and the like, flow characteristics such as fluid temperature, pressure, humidity, mass or volume flow rate, etc., each measured statically or dynamically over time. The process information also may comprise information relating to the cartridge, for example, such as the type of cartridge, the analyte or analytes it is configured to sense, its capacity, its permeability or flow characteristics, its expected response times, at the like. The process information also may comprise information relating to the breath input, for example, such as the breath temperature, pressure, humidity, expected constituents, and the like. In such preferred systems and methods, the optical subsystem preferably is configured to sense the optical change in response to the processor, and in response to one more of such on the process-based information.

[0015] In some preferred system embodiments and methods, a flow facilitator also is provided, preferably coupled to the base. The flow facilitator facilitates the flow of the breath into the cartridge and into contact with the interactant subsystem.

[0016] In accordance with another aspect of the invention, a method is provided for sensing an analyte in breath of a user. The method comprises providing a cartridge comprising a cavity that comprises an interactant subsystem that is selected to undergo a reaction with the analyte when the analyte is present in the breath and to undergo an optical change corresponding to the reaction. The method also comprises providing a flow path for the breath that comprises a breath input and the cavity of a cartridge, and disposing an optical sensor in fixed relation relative to the cavity. In addition, the method comprises moving the breath through the flow path, causing the optical sensor to detect the optical change as the breath is moved through the flow path, and outputting an output that comprises information about the analyte in response to the optical detection.

[0017] In presently preferred implementations of this method, the providing of the flow path comprises providing a mouthpiece in the flow path; and the moving of the breath through the flow path comprises causing the user to exhale into the flow path through the mouthpiece. In addition or alternatively, the providing of the flow path also may comprise providing a non-human breath container in the flow path; and the moving of the breath through the flow path may comprise causing the breath to flow from the non-human breath container into the flow path.

[0018] In presently preferred implementations of the method, the cartridge is detachably coupled to the base. The method also optionally comprises shielding the interactant from ambient light as the breath is moved through the cavity.

[0019] In presently preferred implementations of the method wherein the interactant comprises a first interactant that is selected to undergo a first reaction with the analyte when the analyte is present in the breath and to generate a first intermediate; and a second interactant that is selected to undergo a second reaction with the first intermediate and to cause the optical change corresponding to the second reaction. In a presently preferred but merely illustrative implementation, the first interactant comprises a primary amine coupled to a first substrate a substantially in the absence of a tertiary amine; and the second interactant comprises the tertiary amine.

[0020] In presently preferred method implementations, the causing of the optical sensor to detect the optical change comprises sensing the optical change at a predetermined time after the breath is initially moved through the flow path. Alternatively or in addition, the method

may comprise sensing a characteristic of the breath as the breath moves in the flow path; and the causing of the optical sensor to detect the optical change may comprise sensing the optical change in response to the sensing of the characteristic. The causing of the optical sensor to detect the optical change also may comprise sensing the optical change in response to process information, such as the process information summarized herein above.

[0021] In preferred implementations of the method, the moving of the breath through the flow path comprises facilitating the flow of the breath into the cavity and into contact with the interactant subsystem.

[0022] In accordance with another aspect of the invention, a system is provided for sensing an analyte in breath of a user. This system can be used, for example, where it is necessary or desirable to use multiple steps in processing the analyte or analytes, for example, to facilitate sensing. The system comprises a base; a breath input operatively coupled to the base that receives the breath; and a cartridge coupled to the base and in fluid communication with the breath input to receive the breath. The cartridge comprises a first interactant that is selected to undergo a first reaction with the analyte when the analyte is present in the breath to generate a first intermediate. The system further comprises a dispensing device coupled to the base that dispenses a second interactant that is selected to undergo a second reaction with the first intermediate wherein an optical change corresponding to the reaction is generated. The system further comprises an optical subsystem coupled to the base and configured to sense the optical change, wherein the optical subsystem generates an output comprising information about the analyte in response to the optical detection.

[0023] The breath input may comprise a mouthpiece, an attachment for attaching a non-human breath container in which the breath is contained, for example such as a bag, or both.

[0024] The cartridge is detachably coupled to the base. It preferably but optionally comprises a handle.

[0025] Particularly where internal system components such as the interactant are light-sensitive, the base may comprise an exterior surface that forms an interior and shields the interior from ambient light, wherein the exterior surface comprises an aperture; and the cartridge may comprises a shroud that substantially conforms to the aperture to shield ambient light from entering the aperture when the cartridge is coupled to the base.

[0026] The interactant subsystem preferably comprises a first interactant that is selected to undergo a first reaction with the analyte when the analyte is present in the breath and to generate a first intermediate; and a second interactant that is selected to undergo a second reaction with the first intermediate and to cause the optical change corresponding to the

second reaction. As an illustrative but presently preferred example, the first interactant may comprise a primary amine coupled to a first substrate substantially in the absence of a tertiary amine; and the second interactant may comprise the tertiary amine.

[0027] The interactant subsystem may, in certain embodiments, comprise sodium nitroprusside, dinitrophenylhydrazine, sodium dichromate, pararosaniline, bromophenol blue, dischloroisocyanourate, sodium salicylate, sodium dichromate, crystal violet, benzyl mercaptan, or combinations thereof.

[0028] In preferred embodiments, the interactant subsystem is configured to measure endogenous levels of analytes in breath, where such levels may be 5 ppm or less.

[0029] As with embodiments and options described herein above, the dispensing device may be configured to dispense the second interactant at a predetermined time after the breath is inputted into the breath input. Alternatively or in addition, the system may comprise a flow sensor that senses a characteristic of the breath as the breath moves in the system; and the dispensing device may be configured to dispense the second interactant in response to the flow sensor.

[0030] Also as explained with respect to other embodiments and methods described herein above, the system may further comprise a processor that comprises process information, e.g., such as that described herein above; and the dispensing device may be configured to dispense the second interactant in response to the processor based on the process information.

[0031] The optical subsystem according to this aspect of the invention also may comprise the components and features as described herein above, and/or a flow facilitator as described more fully herein above.

[0032] In accordance with another aspect of the invention, a system is provided for sensing an analyte in breath of a user, wherein the system comprises a base; a breath input operatively coupled to the base that receives the breath; a cartridge detachably coupled to the base and in fluid communication with the breath input to receive the breath; and a sensing subsystem coupled to the base, wherein the base comprises an exterior surface that forms an interior and shields the interior from ambient light, and wherein the exterior surface comprises an aperture, and this aspect of the invention comprises the further improvement of a shroud coupled to the cartridge that substantially conforms to the aperture to shield ambient light from entering the aperture when the cartridge is coupled to the base.

[0033] In accordance with still another aspect of the invention, a system is provided for sensing a plurality of analytes in breath of a user. The system may comprise a base; a breath input operatively coupled to the base that receives the breath; a plurality of cartridges coupled

to the base and in fluid communication with the breath input to receive the breath, wherein each of the cartridges comprises a corresponding interactant subsystem that is unique with regard to others of the cartridges and is selected to undergo a corresponding reaction with a corresponding one of the analytes when the corresponding analyte is present in the breath to form a corresponding product state; and a sensing subsystem coupled to the base and configured to sense the product states and to generate an output comprising information about the plurality of analytes.

[0034] In accordance with still another aspect of the invention, a method is provided for sensing a plurality of analytes in breath of a user. The method comprises providing a plurality of cartridges coupled to a base and in fluid communication with the breath input to receive the breath, wherein each of the cartridges comprises a corresponding interactant subsystem that is unique with regard to others of the cartridges and is selected to undergo a corresponding reaction with a corresponding one of the analytes when the corresponding analyte is present in the breath to form a corresponding product state; and causing a sensing subsystem coupled to the base and configured to sense the product states to sense the product states and to generate an output comprising information about the plurality of analytes.

[0035] In accordance with another aspect of the invention, a system is provided for sensing an analyte in breath of a patient. The system comprises a cartridge comprising a first container, a fluid container, and a reaction volume in fluid communication with the first container and the fluid container, the first container containing a first interactant and the fluid container containing a fluid, wherein the fluid container has an initial fluid level and a space above the initial fluid level. The system also comprises a base comprising a flow path for flow of the breath within the base, a breath input receiver in fluid communication with the flow path that receives the breath and directs the breath into the flow path, a cartridge housing that detachably receives the cartridge into the base so that the reaction volume is in fluid communication with the flow path, a dispensing device that creates a hole in the fluid container below the initial fluid level and that moderates pressure in the space above the initial fluid level so that the fluid flows out of the liquid container and into the reaction volume, thereby facilitating an optical change in the reaction volume in relation to at least one of a presence and a concentration of the analyte, and an optical subsystem that senses the optical change and generates an output comprising information about the analyte in response to the optical change. The dispenser preferably comprises an elongated member, for example, such as a needle, pin, rod and the like. It may comprise a solid member, or it may comprise a fluid channel.

[0036] In various aspects of the invention and preferred embodiments of them, the dispensing device and related function involves dispensing the liquid in the liquid container. To accomplish this, a hole is created in the liquid container below the initial level of the liquid, preferably well below this level and more preferably at the bottom of the liquid container or otherwise so that the maximum amount of liquid is obtained from the container. The dispensing function also involves moderating the pressure in the space above the initial fluid level as the fluid moves out of the liquid container so that the fluid moves out of the liquid container and into the reaction volume. This preferably is accomplished by piercing or otherwise creating an opening in the space above the liquid so that gas can enter the space to equalize the pressure, to avoid creating a negative pressure or vacuum in the space, and to thereby permit the liquid to flow or otherwise move out the hole in the liquid container below the initial liquid level. Thus, preferably the elongated member is outside the liquid container to a deployed position in which the elongated member has created the hole in the fluid container below the initial fluid level and has moderated the pressure in the space above the initial fluid level so that the fluid flows out of the liquid container and into the reaction volume. The elongated member may comprise, for example, a needle, pin, rod and the like.

[0037] In accordance with another aspect of the invention, a method is provided for sensing an analyte in breath of a patient. The method comprises providing a cartridge comprising a first container, a fluid container, and a reaction volume in fluid communication with the first container and the fluid container. The first container contains a first interactant and the fluid container contains a fluid. The fluid container has an initial fluid level and a space above the initial fluid level. The method also comprises providing a base comprising a flow path for flow of the breath within the base, a breath input receiver in fluid communication with the flow path, cartridge housing, a dispensing device, and an optical subsystem. The method further comprises inserting the cartridge into the cartridge housing of the base so that the reaction volume is in fluid communication with the flow path, and causing the breath to flow in the flow path and into the reaction volume. After the breath has flowed through the reaction volume, the method comprises using the dispensing device to create a hole in the fluid container below the initial fluid level and moderating pressure in the space above the initial fluid level so that the fluid flows out of the liquid container and into the reaction volume, thereby facilitating an optical change in the reaction volume in relation to at least one of a presence and a concentration of the analyte. In addition, the method comprises sensing the optical change and generating an output comprising information about the analyte in response to the optical change.

[0038] In accordance with still another aspect of the invention, a system is provided for sensing an analyte in breath of a patient. The system comprises a cartridge comprising a reaction volume and a shroud that is opaque to ambient light. It further comprises a base comprising a flow path for flow of the breath within the base, a breath input receiver in fluid communication with the flow path that receives the breath and directs the breath into the flow path and through the reaction volume, wherein flow of the breath through the reaction volume facilitates an optical change to the reaction volume in relation to at least one of a presence and a concentration of the analyte, a cartridge housing that detachably receives the cartridge into the base so that the reaction volume is in fluid communication with the flow path, wherein the shroud of the cartridge mates with the cartridge housing of the base to block ambient light from impinging on the reaction volume, and an optical subsystem that senses the optical change and generates an output comprising information about the analyte in response to the optical change.

BRIEF DESCRIPTION OF DRAWINGS

[0039] The accompanying drawings, which are incorporated in and constitute a part of the specification, illustrate a presently preferred embodiments and methods of the invention and, together with the general description given above and the detailed description of the preferred embodiments and methods given below, serve to explain the principles of the invention. Of the drawings:

[0040] FIG. 1 shows a composite illustration of a device and disposable cartridge used in detecting colorimetric changes from reactions with breath analytes.

[0041] FIG. 2 shows an example of a breath collection bag with integrated flow measurement capabilities.

[0042] FIG. 3 demonstrates an example of an indirect breath collection performed by a breath input.

[0043] FIG. 4 depicts a general layout for an optical sensing subsystem configuration.

[0044] FIG. 5 depicts a general layout for an optical sensing subsystem configuration from a top-view.

[0045] FIG. 6 depicts one pneumatic handler suitable for high quality breath gas measurements.

[0046] FIG. 7 shows one approach to component reduction using a specialized ball valve.

[0047] FIG. 8 shows a breath analysis device according to another presently preferred embodiment of the invention.

[0048] FIG. 9 is a hardware block diagram of the device shown in FIG. 8.

[0049] FIG. 10 is a perspective drawing of a breath sample bag for collecting and storing a breath sample, and for inputting the breath sample to the breath analysis device of FIGS. 8-9.

[0050] FIG. 11 shows an exemplary reaction initiator based on a needle.

[0051] FIG. 12 shows a cartridge insertion into a base unit that makes use of a linear actuator.

[0052] FIG. 13 shows the details of an embodiment of a sliding mechanism in relation to a sensor cartridge.

[0053] FIG. 14 shows an example of a breath gas analyzer column based on Tenax TA.

[0054] FIG. 15 displays an example of a substrate sheet that can be pressed into retention disks.

[0055] FIG. 16 shows an exemplary general schematic of cartridge design.

[0056] FIG. 17 shows one alternative to the retainer (130) of FIG. 16 for containing reactive particles.

[0057] FIG. 18 shows three embodiments of a piercable foil ampoule.

[0058] FIG. 19 shows certain embodiments of a piercable ampoule.

[0059] FIG. 20 shows embodiments of a piercable can for containing liquid.

[0060] FIG. 21 shows different dry reagents packed into a single column.

[0061] FIG. 22 shows another set of stacked dry reagents packed into a single column.

[0062] FIG. 23 illustrates reagents being held in place using compressible, porous media.

[0063] FIG. 24 shows an example of how a liquid reagent can be immobilized onto a cartridge and how it can be released at the time of reaction.

[0064] FIG. 25 demonstrates another embodiment of how a liquid reagent can be immobilized onto a cartridge and how it can be released at the time of reaction.

[0065] FIG. 26 illustrates an example of a multi-liquid cartridge.

[0066] FIG. 27 illustrates another example of a multi-liquid cartridge.

[0067] FIG. 28 shows some cartridge designs that enable multiuse applications.

[0068] FIG. 29 shows an embodiment of a cartridge design.

[0069] FIG. 30 shows a depiction of the flow path after the liquid seals have been broken and a liquid seal is formed.

[0070] FIG. 31 shows an embodiment of a cartridge with a developer solution.

[0071] FIG. 32 is a schematic diagram of a presently preferred embodiment of a cartridge according to various aspects of the invention for use in the breath analysis device of FIGS. 8-9.

[0072] FIG. 33 is an embodiment of an ampoule piercing mechanism.

[0073] FIG. 34 is another embodiment of an ampoule piercing mechanism.

[0074] FIG. 35 is an embodiment of an ampoule rupturing mechanism.

[0075] FIG. 36 is another example of an ampoule piercing mechanism.

[0076] FIG. 37 is another example of an ampoule piercing mechanism.

[0077] FIG. 38 is another example of an ampoule rupturing mechanism.

[0078] FIG. 39 is an embodiment of an ampoule immobilization strategy.

[0079] FIG. 40 is another embodiment of an ampoule immobilization strategy.

[0080] FIG. 41 is another embodiment of an ampoule immobilization strategy.

[0081] FIG. 42 is another example of an ampoule rupturing mechanism.

[0082] FIG. 43 shows an embodiment of a breath sampling loop based on multiple breath exhalations into a base unit.

[0083] FIG. 44 shows an embodiment of a breath measurement system with the developer solution inside a replaceable container in the base unit instead of in disposable cartridges.

DETAILED DESCRIPTION OF THE PRESENTLY PREFERRED EMBODIMENTS AND METHODS OF THE INVENTION

[0084] Reference will now be made in detail to the presently preferred embodiments and methods of the invention as described herein below and as illustrated in the accompanying drawings, in which like reference characters designate like or corresponding parts throughout the drawings. It should be noted, however, that the invention in its broader aspects is not limited to the specific details, representative devices and methods, and illustrative examples shown and described in this section in connection with the preferred embodiments and methods. The invention according to its various aspects is particularly pointed out and distinctly claimed in the attached claims read in view of this specification, and appropriate equivalents.

Introduction

[0085] The present invention relates to devices and methods for the sensing of analytes in breath, and preferably for the sensing of analytes that are endogenously produced. The devices and methods can and preferably do include cartridges that contain or comprise breath-reactive chemistries, i.e., chemical components that react with specific or desired chemical species or components in the breath. Preferably, these breath-reactive chemistries are specific, even in the background of breath.

[0086] One area of particular interest involves breath analysis. Included among illustrative breath constituents, i.e., analytes, that have been correlated with disease states are those set forth in Table 1, below. As noted, there are perhaps 300 volatile organic compounds that

have been identified in the breath, all of which are candidate analytes for analysis using such embodiments and methods. Additionally, in some instances combinations of constituents (analytes) in breath may serve as a superior disease marker relative to the presence of any single analyte.

TABLE 1

Candidate Analyte	**Illustrative Pathophysiology / Physical State**
Acetone	Lipid metabolism (e.g., epilepsy management, nutritional monitoring, weight loss therapy, early warning of diabetic ketoacidosis), environmental monitoring, acetone toxicity, congestive heart failure, malnutrition, exercise, management of eating disorders
Ethanol	Alcohol toxicity, bacterial growth
Acetaldehyde	
Ammonia	Liver or renal failure, protein metabolism, dialysis monitoring, early detection of chronic kidney disease, acute kidney disease detection and management
Oxygen and Carbon Dioxide	Resting metabolic rate, respiratory quotient, oxygen uptake
Isoprene	Lung injury, cholesterol synthesis, smoking damage
Pentane	Lipid peroxidation (breast cancer, transplant rejection), oxidative tissue damage, asthma, smoking damage, COPD
Ethane	Smoking damage, lipid peroxidation, asthma, COPD
Alkanes	Lung disease, cancer metabolic markers
Benzene	Cancer metabolic monitors
Carbon-13	*H. pylori* infection
Methanol	Ingestion, bacterial flora
Leukotrienes	Present in breath condensate, cancer markers
Hydrogen peroxide	Present in breath condensate
Isoprostane	Present in breath condensate, cancer markers
Peroxynitrite	Present in breath condensate
Cytokines	Present in breath condensate
Glycans	Glucose measurement, metabolic anomalies (e.g., collected from cellular debris)
Carbon monoxide	Inflammation in airway (asthma, bronchiesctasis), lung disease
Chloroform	
Dichlorobenzene	Compromised pulmonary function
Trimethyl amine	Uremia

Candidate Analyte	Illustrative Pathophysiology / Physical State
Dimethyl amine	Uremia
Diethyl amine	Intestinal bacteria
Methanethiol	Intestinal bacteria
Methylethylketone	Lipid metabolism
O-toluidine	Cancer marker
Pentane sulfides	Lipid peroxidation
Hydrogen sulfide	Dental disease, ovulation
Sulfated hydrocarbon	Cirrhosis
Cannabis	Drug concentration
G-HBA	Drug testing
Nitric oxide	Inflammation, lung disease
Propane	Protein oxidation, lung disease
Butane	Protein oxidation, lung disease
Other Ketones (other than acetone)	Lipid metabolism
Ethyl mercaptane	Cirrhosis
Dimethyl sulfide	Cirrhosis
Dimethyl disulfide	Cirrhosis
Carbon disulfide	Schizophrenia
3-heptanone	Propionic acidaemia
7-methyl tridecane	Lung cancer
Nonane	Breast cancer
5-methyl tridecane	Breast cancer
3-methyl undecane	Breast cancer
6-methyl pentadecane	Breast cancer
3-methyl propanone	Breast cancer
3-methyl nonadecane	Breast cancer
4-methyl dodecane	Breast cancer
2-methyl octane	Breast cancer
Trichloroethane	
2-butanone	
Ethyl benzene	
Xylene (M, P, O)	

Candidate Analyte	Illustrative Pathophysiology / Physical State
Styrene	
Tetrachloroethene	
Toluene	
Ethylene	
Hydrogen	

[0087] Examples of other analytes would include bromobenzene, bromochloromethane, bromodichloromethane, bromoform, bromomethane, 2-butanone, n-butylbenzene, sec-butylbenzene, tert-butylbenzene, carbon disulfide, carbon tetrachloride, chlorobenzene, chloroethane, chloroform, chloromethane, 2-chlorotoluene, 4-chlorotoluene, dibromochloromethane, 1,2-dibromo-3-chloropropane, 1,2-dibromoethane, dibromomethane, 1,2-dichlorobenzene, 1,3-dichlorobenzene, 1,4-dichlorobenzene, dichlorodifluoromethane, 1,1-dichloroethane, 1,2-dichloroethane, 1,1-dichloroethene, cis-1,2-dichloroethene, trans-1,2-dichloroethene, 1,2-dichloropropane, 1,3-dichloropropane, 2,2-dichloropropane, 1,1-dichloropropene, cis-1,3-dichloropropene, trans-1,3-dichloropropene, ethylbenzene, hexachlorobutadiene, 2-hexanone, isopropylbenzene, p-isopropyltoluene, methylene chloride, 4-methyl-2-pentanone, methyl-tert-butyl ether, naphthalene, n-propylbenzene, styrene, 1,1,1,2-tetrachloroethane, 1,1,2,2-tetrachloroethane, tetrachloroethene, toluene, 1,2,3-trichlorobenzene, 1,2,4-trichlorobenzene, 1,1,1-trichloroethane, 1,1,2-trichloroethane, trichloroethene, trichlorofluoromethane, 1,2,3-trichloropropane, 1,2,4-trimethylbenzene, 1,3,5-trimethylbenzene, vinyl acetate, vinyl chloride, xylenes, dibromofluoromethane, toluene-d8, 4-bromofluorobenzene.

[0088] For acetone measurement, ranges of physiological interest vary. In preferred embodiments for diet monitoring, a preferred measurement range is 0.5 to 5 ppm with a resolution of 0.1 ppm. For monitoring ketogenic diets, a preferred measurement range is 1 ppm to 10 ppm with a resolution of 0.1 ppm. For monitoring diabetic ketoacidocis, a preferred measurement range is 5 to 50 ppm with a resolution of 1 ppm. For screening potential type II diabetes, a preferred measurement range is 1 to 10 ppm with a resolution of 0.1 ppm. For screening prediabetic individuals at risk for diabetic retinopathy, the preferred measurement range is 1 to 10 ppm with a resolution of 0.1 ppm.

[0089] For ammonia sensing or measurement, ranges of physiological interest vary. In preferred embodiments for monitoring protein metabolism, a preferred measurement range is 0.05 to 2 ppm with a resolution of 0.01 ppm. For monitoring potential kidney failure in

prediabetics, a preferred measurement range is 0.5 to 5 ppm with a resolution of 0.1 ppm. For monitoring dialysis patients, before, during or after dialysis, a preferred measurement range is 0.2 to 2 ppm with a resolution of 0.1 ppm. For monitoring for hepatic failure or related diseases such as hepatic encephalopathy, a preferred measurement range is 0.5 to 5 ppm with a resolution of 0.1 ppm. For screening for Reye syndrome, a preferred measurement range is 0.5 to 5 ppm with a resolution of 0.1 ppm. In screening infants and children for urea cycle disorders, a preferred measurement range is 0.5 to 5 ppm with a resolution of 0.1 ppm. For measuring environmental or work exposure, a preferred measurement range is 0.5 to 5 ppm with a resolution of 0.1 ppm.

[0090] In accordance with one aspect of the invention, as outlined herein above, a system is provided for sensing an analyte in breath of a user. The system comprises a base; a breath input operatively coupled to the base that receives the breath; a cartridge coupled to the base and in fluid communication with the breath input to receive the breath, wherein the cartridge comprises an interactant subsystem that is selected to undergo a reaction with the analyte when the analyte is present in the breath and to undergo an optical change corresponding to the reaction; and an optical subsystem coupled to the base and configured to sense the optical change, wherein the optical subsystem generates an output comprising information about the analyte in response to the optical detection.

[0091] In accordance with another aspect of the invention as noted herein above, a method is provided for sensing an analyte in breath of a user. The method comprises providing a cartridge comprising a cavity that comprises an interactant subsystem that is selected to undergo a reaction with the analyte when the analyte is present in the breath and to undergo an optical change corresponding to the reaction. The method also comprises providing a flow path for the breath that comprises a breath input and the cavity of a cartridge, and disposing an optical sensor in fixed relation relative to the cavity. In addition, the method comprises moving the breath through the flow path, causing the optical sensor to detect the optical change as the breath is moved through the flow path, and outputting an output that comprises information about the analyte in response to the optical detection.

[0092] To illustrate these aspects of the invention, a presently preferred embodiment will now be described with reference to FIG. 1 and others of the drawings, and a presently preferred method implementation will be illustrated using that embodiment. It should be understood, however, that the invention according to these aspects is not necessarily limited to such specific and illustrative device and method.

[0093] Devices and methods according to aspects of the invention can include or incorporate any or all of a base, a breath input, an insertion mechanism for a cartridge, a sensing subsystem, a pneumatic handler, a reaction initiator, a kinetic enhancer, a breath conditioner, a digitizer, or a cartridge. Each of these components can also contain subcomponents. Any or all of the components of the present invention can be contained within or otherwise coupled to the base. In one embodiment of the invention, the pneumatic handler is contained within the base. In another embodiment, the breath input is contained within the base. Additionally, the device can contain tracking and/or monitoring software.

[0094] The base optionally forms a housing or a connection point for the other components that make up the breath analyzer device.

[0095] FIG. 1 is a presently preferred embodiment of a system according to certain aspects of the invention for measuring at least one analyte in breath. The system comprises a base in the form of a base unit (2), dispensing device here in the form of an insertion mechanism (8) for a cartridge, an optical sensing subsystem (10), a flow facilitator, here specifically in the form of a pneumatic handler (12) and a digitizer (14). The base unit (2) receives breath from a user via a breath input (4). The insertion mechanism for a cartridge includes means for a cartridge to be inserted, where the cartridge contains a reactive chemistry capable of reacting with at least one analyte when present in the breath in concentrations of less than about 5 ppm to generate an optical change. The optical sensing subsystem measures an optical change. The pneumatic handler is preferably included within the base unit, although this is not always the case. The pneumatic handler allows for the breath to interact with the reactive chemistry in the cartridge. The digitizer quantifies the optical change measured by the optical sensing subsystem and outputs a display containing information regarding the at least one analyte in the breath.

[0096] The base unit can be any apparatus that receives breath from a user. In certain embodiments, the base unit contains the pneumatic handler. In preferred embodiments, the base unit is portable and capable of individual patient use. The base unit may also be capable of withstanding (measuring and compensating for) temperature and humidity changes so as to improve the accuracy of the measurement process.

[0097] A breath input can be anything capable of receiving breath from a user, and optionally perform the function of breath metering. The breath input may optionally include the step of breath conditioning, but this may also be handled by the base unit itself. The breath input can also include breath sampling, which preferably utilizes a reservoir for containing the breath sample.

[0098] In general, breath collection involves the collection of a breath sample. Such breath collection may be direct or indirect. An example of direct breath collection involves a user exhaling directly into the device or into the base unit. Such an example is shown in FIG. 29. Indirect breath collection involves, for example, a user breathing into a collection vessel (e.g., a collection bag) where the vessel is connected to the device for evacuation. FIG. 3 demonstrates an example of an indirect breath collection performed by a breath input. A three-way non-rebreathing valve (30) with an additional outlet tap (32) enables portions of numerous breaths to be sequentially deposited into a collection bag (34). A mouthpiece, with or without an integrated anti-bacterial/viral filter (35), protects a user from cross-contamination.

[0099] For improved relevance of the measurement results made by the breath analyzer, breath collection can be performed with attention to details such as: (a) total volume of breath collected; (b) source of collected breath (e.g., upper airways vs. alveolar air); (c) number of breaths collected; (d) physiological status of the subject prior to and during breath collection (e.g., rested state with normal breathing vs. active state with increased breath rate vs. hyperventilation, as examples); and (e) breathing effort of the sample collection mechanism (e.g., does the subject need to breath through a high-resistance collection apparatus at extended duration, or does the mechanism allow for normal breath exhalations).

[00100] As mentioned, the breath input can optionally meter the breath being collected. Metering of the breath means measuring the volume of breath being input. This can be accomplished in a number of ways by one of skill in the art, including actually measuring the amount of breath sampled (e.g., using a pneumotachometer, and recording the total volume of breath over a given amount of time), or by sample volume restriction, such as by having a user breathe into a fixed volume container.

[00101] In one aspect of the invention involving indirect breath collection, the breath input can have integrated metering capacities, such as a breath collection bag with integrated flow measurement capabilities.

[00102] FIG. 2 shows an example of a breath collection bag with integrated flow measurement capabilities. A breath sampling bag (20) comprised of wall materials impermeable to the analytes of interest and in some cases also their ambient interferents contains a breathing inlet (24) fitted with a mouthpiece (22). An upper portion of the assembly houses electronics and/or mechanical devices useful in analyzing or conditioning breath samples, including in some cases a visual indicator (26). The electronics can consist of a variety of assets, including temperature probes, pressure transducers, timing circuits,

humidity sensors, and others depending on the application. Mechanical devices can include one-way breathing valves, flow restrictors, scrubber or desiccant chambers, computer-controlled or automatic valves, manual valves, and others. In one embodiment, the one-way valve (24) is designed to mate with a receiver port on a base unit which is equipped with fingers or protrusions designed to open the one-way valve. This system enables a breath sample to be collected from a user and to be contained within the sampling bag without user interaction. Attaching the bag to the base unit allows the fingers or protrusions to open the one-way valve (for example, a flapper valve) so that the contents of the bag can be removed by, for example, a pneumatic handler of the base unit. No manual interaction with the valve is required by the user. Also shown in FIG. 2 is a user interface button (28), exemplifying a possible interaction of the user with the electronics, such as to start a timer. A second end of the bag (25) can be fitted with similar facilities. For example, fitting the lower portion (25) with a second one-way valve, such that the user breathes into a first one-way valve (24) and out through the second (25) results in the last exhaled portion of air being captured in the bag. This can be used to sample, for example, the deep alveolar airspace whereas without the second one-way valve the air collected is the first portion blown into the device. The bag may likewise be fitted at other points, for example on the sides or front/back faces.

[00103] Although it is desirable to obtain a representative breath sample, it is not necessarily advantageous or necessary for the entire sample volume to be analyzed. Rather, in some embodiments, a representative sample may be analyzed. One reason why it may not be necessary to analyze the full volume of breath is gelling of a desiccant material. As mentioned, the breath input may optionally include breath sampling, which preferably uses a sample reservoir. For example, the sample reservoir may be a one-milliliter syringe that extracts a representative sample from, for instance, a breath bag. In this configuration, the user breathes into a breath bag, which contains some number of exhaled breath samples. The breath bag may, and preferably does, contain metering capabilities to determine sample volume and/or sample volume per unit time as the user is inflating the bag. Once the bag is inflated, a sampling mechanism is triggered which extracts some smaller volume of exhaled breath and stores this in the sample reservoir. The sampling mechanism may be an active pump, but it may also be a passive tool such as a syringe that requires the user to exert force to collect the sample. The bag may then be deflated. The user then is left with a smaller breath sample in a sample reservoir. This sample reservoir may be used to "inject" a breath sample into the base unit.

[00104] Particular examples of breath conditioning include: (a) desiccation (e.g., removal of water); (b) scrubbing (e.g., removal of carbon dioxide or volatile organic compounds); and (c) heating or cooling of the gas stream (condensation prevention/instigation). As noted, the breath condition function, if performed, can be carried out by the breath input or a separate system.

[00105] In one embodiment of the present invention, the breath collection is performed separately from the breath analysis. Separating the steps creates certain advantages that can be well suited for certain applications. For example, if the breathing resistance through the chemically reactive element is high (e.g., packed bed reactor), the user will experience more comfort breathing into a collection vessel with little to no breathing resistance. The device itself can then deliver the sample or a portion thereof to the reactive chemistry for sensing purposes.

[00106] One method of performing the breath collection separately from the breath analysis is by using active gas sampling. Specifically, in the breath analysis device, the breath sample must be directed to the reactive or analyte-sensitive region of the sensor system. Passive or active mechanisms can be used for this purpose. Passive systems involve use of components such as flow restrictors, flow partitioning devices, and other mechanical means that do not require the input of energy (other than the pressure applied during exhalation). In contrast to these passive systems where the user forcibly exhales breath into the reactive region, active gas sampling equipment can be used to decouple user breathing from delivery of gas to the reactive region. Sensor constraints such as controlled gas delivery flow rate, stable drive pressure, high pressure drop of flow over sensor region, etc. can be divorced from user breathing requirements. In particular, extended breaths through high pressure drop systems or a requirement that a user blow with a stable pressure or flow rate are eliminated. In addition, gas delivery parameters outside of a user's ability can be achieved. For example, the maximum pressure that a healthy adult can produce via forcible exhalation is only approximately 0.3 psi, whereas active gas handling equipment does not bear that limitation. This enables a wide range of sensor configurations. As another example, a low flow rate of 50 ml per minute can be sustained for several minutes using active gas delivery means without imposing the burden of sustained breath output over that same period. (Comfortable human breath rates are on the order of 6 L per minute with negligible breathing resistance).

[00107] Detectors are well developed for numerous applications and can be applied to breath analysis. Suitable detection modalities for a given application are dependent upon the nature of the chemical reaction that is being harnessed to detect a given analyte.

[00108] The optical sensing subsystem can be any detector or other sensor that is capable of measuring an optical change. This may be a direct measurement of optical change. It may also be an indirect measurement of optical change (e.g., transduction through other energy states). The optical change may involve any of the following, alone or in combination, without limitation: reflectance, absorbance, fluorescence, chemiluminescence, bioluminescence, polarization changes, phase changes, divergences, scattering properties, evanescent wave and surface plasmon resonance approaches, or any other optical change known to those skilled in the art.

[00109] The optical sensing subsystem may be contained within the base unit or it may be a separate module that is plugged into the base unit. The optical sensing subsystem may be single use or it may be used multiple times. The optical sensing subsystem may also comprise an array of detectors that work in tandem to measure the optical change.

[00110] In a preferred embodiment utilizing any of reflectance, absorbance and fluorescence, excitation light is supplied to the system and changes in that light are tracked in relation to changes in the chemical state of the sensor system. It is preferred to minimize the amount of unmodulated light that enters the sensing subsystem and to measure only the light that is being changed by the chemical system. For example, a chemical system that produces a maximum absorbance change at 400 nm is preferably implemented with excitation light at 400 nm as opposed to unfiltered broadband light sources such as incandescent lamps. However, if a base unit is intended to measure numerous chemistries with various spectral characteristics, broadband excitation sources may be preferable.

[00111] Excitation sources include, but are not limited to, incandescent lamps, such as tungsten filaments and halogen lamps; arc-lamps, such as xenon, sodium, mercury; light-emitting diodes, and lasers. Excitation light may benefit from conditioning efforts, such as filtering, polarization, or any of the other methods known by those skilled in the art. For example, allowing only light of the wavelength that matches the wavelength of the chemical system's peak response is useful in increasing the signal to noise ratio of the optical system.

[00112] Each of these modalities can be employed with spot interrogations or with scanning mechanisms. A scanning system can be useful in breath measurement devices, especially where analyte concentration varies along an axis and where that variation is indicative of analyte concentration in the breath.

[00113] FIG. 4 and FIG. 5 depict optical configuration embodiments useful for endogenous breath sensing. FIG. 4 depicts a general layout for an optical sensing subsystem configuration comprising a camera (36) in relation to a light source (38) and cartridge (40).

FIG. 5 depicts similar components from a top-view, illustrating the relative angle of the excitation source (42) to the incident plane of the cartridge (44) and to the focal plane of the camera (46). Such an embodiment reduces glare from the excitation source and is suitable for capturing high-quality images of the sensor chemistry. The images can be processed to derive or to interpolate from correlations of analyte breath concentrations and developed color. A camera is especially well-suited to base systems where multiple chemistries are to be detected due to the additional power afforded by both a wide spectral range, a degree of spectral sensitivity (images are captured onto red, green, and blue pixels), and a high degree of spatial resolution. In particular, spatial resolution allows very simple instrumentation setups to be used for a wide range of applications, for example quality assurance. Other embodiments such as semiconductor photodetectors can provide low processor overhead and compact size.

[00114] In various presently preferred embodiments and method implementations of the invention, the device contains a flow facilitator to facilitate the flow of the breath or breath samples through the flow path of the device. The flow facilitator may comprise any apparatus that facilitates gas dynamics to cause or allow the breath to interact with the reactive chemistry in the cartridge. For example, the flow facilitator may comprise a series of specialized tubing that does not allow for condensation of endogenous breath analytes. The flow facilitator may also comprise a pneumotachometer for differential pressure measurement. In presently preferred embodiments, the flow facilitator is coupled to, and preferably contained within, the base unit. The flow facilitator can be used to sample gases from various sources, including breath sample bags, mixing chambers, and ambient air.

[00115] FIG. 6 depicts a flow facilitator in the form of a pneumatic handler (12) suitable for high quality breath gas measurements. A breath sample is connected to a pump configured to withdraw (48). The breath sample is then pushed through a pulse dampener (50) and then into a flow laminarization element (52). Pulseless, laminarized flow is then easily measured with a pressure transducer over a fluidic restrictor (54). The pressure drop over the known restriction can be used to quantify the amount of gas flowing through the restrictor, especially where viscosity of the gas can be accurately estimated.

[00116] Viscosity estimation has been well characterized, and the procedure makes use of gas constituency estimations/knowledge as well as temperature and pressure measurements of the gas itself. Such a configuration of components with appropriate algorithms can be used to accurately measure the amount of gas that flows through the channel, in terms of moles of gas per unit time. With the downstream valve (58) in the closed position in FIG. 6, the

sample pump pushes the breath sample through the column (62). Depending on the components selected, the flow rate and achievable drive pressure can be selected appropriate to the application. The user force of exhalation is decoupled from the sensor exposure to the gas sample, greatly increasing the range of applications that can be successfully implemented. Also, the duration of gas delivery to the sensor element can be easily controlled and can exceed comfort level or ability of a user breath input system. Flow through the cartridge can be reversed by closing the upstream valve (56) and activating a second pump (60) configured to withdraw.

[00117] Compact pneumatic components to populate this scheme are available. Other pump and valve configurations may be preferable, particularly systems based on reversible, stopped-flow, and metering pumps. In the case of a pump that allows gas flow to be reversed without switching plumbing inlets, components (58) and (60) can be eliminated from the schematic and pump (48) can be used to both push and pull gas through the cartridge in one embodiment. Also, pumps that stop back-flow when not being actuated can obviate the need for valves (56) and (58). Furthermore, pulse dampeners (50) and laminarization elements (52) may be combined into a single component, as well as combination pulse dampeners (50), laminarization elements (52), and pressure transducers over flow restrictors (54). Pumps with built-in metering capabilities, such as piston pumps with set stroke volumes, can also be used to obviate some of the components described here. Another approach to component reduction makes use of a specialized ball valve, as shown in FIG. 7. The specialized valve has two flow positions, (64) and (66). In flow position (64), the pump (70) can withdraw from a breath bag (68) and push the air through a sensor column (72). In flow position (66), the same pump (70) with the same plumbing connections can withdraw gas from the column and exhaust it to the atmosphere (assuming that the breath bag (68) has been completely evacuated). This is one example of a system where the pneumatic handler is capable of accepting variable volumes of breath and removing unneeded volume.

[00118] To further illustrate various aspects of the invention, an apparatus 410 for sensing ammonia in a breath sample according to another presently preferred embodiment of the invention will now be described. FIG. 8 shows a perspective view of the apparatus, and FIG. 9 provides a hardware block diagram of it. In this preferred embodiment, apparatus 410 is a portable device suitable for field use, or in the home of a patient or subject, and thus is not confined to use in a laboratory or hospital setting.

[00119] Apparatus 410 comprises a breath sample collection subsystem 412 and a breath sample analysis subsystem 14. Breath sample collection subsystem 412 and breath sample

analysis subsystem 414 in this preferred but merely illustrative embodiment are physically separate, attachable and detachable components, but this is not necessarily required or limiting. Alternative configurations, e.g., in which the breath sample collection subsystem 412 and analysis subsystem 414 are contained in a single unit, are within the scope of the invention.

[00120] Although breath sample collection subsystem 412 may comprise a direct flow-through conduit to the analysis subsystem 414, in this embodiment it provides a means to retain or store the breath sample until it is ready for use in the breath analysis, and when called upon to do so, to deliver the breath sample to the analysis subsystem. The breath sample collection subsystem 412 may comprise a variety of forms, provided it can perform the functions required of it as described herein.

[00121] In this embodiment, breath sample subsystem 412 comprises a breath sample bag assembly 416 for retention of a breath sample, and for delivery of the breath sample to the breath sample analysis subsystem as further described herein below. Breath sample bag assembly 416 according to this embodiment, shown separately and enlarged in FIG. 10, comprises a detachable breath sample input unit 416a and a bag unit 416b, the latter comprising a breath sample bag 418.

[00122] The breath sample input unit 416a provides a means for inputting the breath sample into the bag unit 416b in a manner so that contamination or otherwise unwanted external gases or substances (external to the breath sample itself) are not allowed to infiltrate into the bag 418. Although a variety of breath sample inputs are possible, in presently preferred breath sample subsystem 412 the breath sample input unit 416a comprises a mouthpiece 420. Examples of alternative breath sample inputs would include tubular or conduit-based inputs, inputs that segregate the breath sample into components or segments, and the like.

[00123] Breath sample bag 418 comprises a flexible, air-tight bag that has insubstantial or no permeability for breath samples of the type for which this system is used. The permeability of analyte or analytes of interest out of or through the bag under storage or retention conditions should be zero or as close to zero as possible over anticipated or desired retention times, and certainly below the lower range of detectability for the overall device so that such leakage does not affect the sensing results. Examples of bags generally suitable for present uses include Tedlar and mylar foil bags. Breath sample bag 416 according to this embodiment comprises a mylar foil bag, which is generally preferred based on its relatively low permeability for ammonia.

[00124] The breath sample subsystem, and more specifically the breath sample input unit 416a in this embodiment, also includes a breath conditioning device that conditions the original breath sample so that it has a desired level or range or water, or relatively humidity. In the presently preferred embodiment, the breath conditioning device comprises a pre-filter 422 in fluid communication with bag 418 between the bag itself and the mouthpiece 420 so that a breath sample inputted into the mouthpiece passes through pre-filter 422 and into the interior of the bag 418.

[00125] Pre-filter 422 comprises a granular desiccant 424. The grain size (including the grain size distribution) of desiccant 422 preferably is selected so that it is effective but the risk of inadvertent inhalation or ingestion of the desiccant by the patient or other user is minimized. This balancing must take into account the fact that larger particle sizes generally decrease the total surface area available for interaction with and removal of the water. This latter potential impact in some instances can be mitigated, for example, by increasing the porosity or tortuosity of the grains themselves. In view of these criteria, the granular desiccant 424 preferably has a mesh size of at least 1, and more preferably has a mesh size of between about 1 and about 100. Given the relative importance of accurate and reliable removal of the water to the desired levels, the desired mesh size preferably is at the lower end of the broader range, e.g., between about 5 and about 80, and more preferably between about 10 and about 30-40.

[00126] The desiccant material preferably is selected so that it does not extract the analyte or analytes of interest ammonia from the breath sample, or does so only minimally. By this is meant that the desiccant 424 either does not extract any of the available analytes to be sensed, or that to the extent some is extracted, the amount is well below the sensing or measurement threshold so that the measurement of the analyte or analytes in the breath sample analysis device is not adversely affected within its sensitivity and margin of error. Given the granular nature of the desiccant and the potential for ingestion risk, screens 426 are disposed at each flow end of pre-filter 422.

[00127] The breath sample input unit 416a, and more specifically the mouthpiece 420, comes into direct contact with the patient, and therefore cannot be re-used unless thoroughly disinfected. In addition, the pre-filter 422 traps or contains certain components of the breath sample, including water and potentially water-borne microorganisms or other contaminants, and similarly cannot be re-used without thorough disinfection. Accordingly, in presently preferred embodiments, the detachable breath sample input unit 417a comprising the mouthpiece 420 and pre-filter 422 is detachable and disposable.

[00128] The bag unit 416b in this embodiment is configured to receive and retain the breath sample during a "collection" mode, during which breath sample input unit 416a is attached, and to provide that breath sample to the breath sample analysis subsystem 414 while unit 416b is detached from unit 416a. A ferrule 430 is fixedly coupled to the end of bag 418 adjacent to pre-filter 422. Bag unit 416b, and more specifically ferrule 430, is detachably coupled to the breath sample input unit 416a, and more specifically to pre-filter 422, using a coupler 432. These components are conjoined in air-tight fashion so that, when a patient blows breath into mouthpiece 420, the breath sample travels through pre-filter 422 and ferrule 430 and into the interior of bag 418 without leakage. A one-way valve 434, in this embodiment a simple flapper valve, is disposed at the interface between ferrule 430 and the top interior of bag 418 so that breath blown into mouthpiece 420 and passing into bag 418 via pre-filter 422 and ferrule 430 is trapped in the bag interior and is not allowed to escape.

[00129] To reiterate and clarify, breath sample collection subsystem 412 comprises two primary and detachable components, i.e., breath sample input unit 416a and breath sample bag unit 416b. Input unit 416a comprises mouthpiece 420 and pre-filter 422 fixedly coupled to one another. Bag unit 416b comprises bag 418 with fixedly-coupled ferrule 430. These two components 416a and 416b are detachably coupled to one another by coupler 432. When detached, bag unit 416b can be used with the breath sample analysis subsystem 414 as described herein below. The input unit 416a, having been directly contacted by the patient, is disposable and can be discarded.

[00130] Turning to the breath analysis subsystem 414, and with reference to FIG. 9, it comprises a base unit 440 (also shown in FIG. 8) that houses its various components as described more fully below. An input port 442 is provided at the top of base unit 440 for receiving the distal end of ferrule 430 and thereby forming an air-tight seal and flow path between the interior of bag 418 and an interior flow path 444 of base unit 440. A post or stanchion 442a is disposed in port 442 to interact with and open one-way valve 434 in bag unit 416b so that the breath sample in bag 418 is allowed to flow in to flow path 444. The flow path 444 begins at input port 442 and extends through base unit 440, as described more fully herein below, to and outwardly from an exhaust port 446. For directional reference, flow or movement along the flow path 444 in the direction from the bag 418 and toward exhaust port 446 is referred to herein as "downstream," and flow in the opposite direction, from exhaust port 446 toward input port 442 is referred to herein as "upstream."

[00131] It is useful and in most cases important to quantitatively measure certain flow characteristics of the conditioned breath sample within flow path 444. Examples of such

flow characteristics include flow velocity, flow rate (mass or volumetric), and the like. Accordingly, in this embodiment a flow meter 448 is positioned in flow path 444 downstream from input port 442. Flow meter 448 measures flow velocity and flow volume of the breath sample at that location.

[00132] Breath sample analysis subsystem 414 further includes a flow modulator in the form of a flow restrictor 450 downstream from flow meter 438, and a pump 442 downstream from flow restrictor 448. Pump 452 is appropriately sized and powered so that it is suitable for drawing the conditioned breath sample from bag 418 and causing the breath sample to flow through the flow path 444 and out exhaust port 446, taking into account the full system configuration as described herein. Flow restrictor 450 functions to absorb and smooth perturbations created by pump 452.

[00133] Breath sample analysis unit 414 further comprises a sensor or sensing unit that analyzes the conditioned breath sample and detects the presence and, preferably, the concentration, of ammonia in the sample.

[00134] Apparatus 410 senses the analyte or analytes of interest using colorimetric principles. More specifically, the breath sample analysis subsystem according to this aspect of the invention comprises an interactant region that receives the conditioned breath sample and causes it to interact with an interactant. The interactant interacts with the analyte or analytes in the conditioned sample and causes a change in an optical characteristic of the interactant region in relation to the amount of the analyte or analytes in the breath sample. As the analyte reacts with the interactant, in other words, contents of the reaction volume undergo an optical change relative to the initial optical conditions. The system is designed so that the desired information about the analyte, e.g., its presence and concentration, is embodied in the optical change.

[00135] Optical characteristics that can be used in connection with this aspect of the invention comprise any optical measurement that is subject to change in relation to a change in the presence of the analyte, or in relation to the concentration of the analyte. Examples include the color, colors or spectral composition of the reaction vessel, the intensity of the radiation at a particular frequency, frequency band, range of frequencies, reflectance, absorbance, fluorescence, and others.

[00136] As embodied in apparatus 410, the sensing unit of breath sample analysis subsystem 414 comprises a detachable cartridge 460 that includes a reaction volume, in this case comprising column 462 containing an interactant 464. As shown, for example, in FIG. 8, the front exterior surface of base unit 440 has a cartridge receiving portion or cartridge

housing in the form of rectangular aperture 466. Cartridge 460 is sized and configured to mate with this aperture 466 in substantially light-tight or light-sealing form. The column 460 comprises a tubular or cylindrical space that comprises reaction volume or vessel 462 ,with an inlet aperture 468 and an outlet aperture 470 at respective ends.

[00137] The interactant 464 is configured to interact with the analyte or analytes of interest in the breath sample to yield a "product" (e.g., a reaction product or resultant composition) and to cause a change in an optical characteristic between the interactant and the product in relation to the amount of the analyte that interacts with the interactant. The interactant may comprise a solid-state component, such as a plurality of beads or other substrates with selectively active surfaces or surface active agents, for example, in a packed bed configuration. Interactant 464 also may comprise other forms, for example, such as liquid-phase, slurries, etc. Note that the term "react" as used herein is used in its broad sense, and can include not only chemical reactions involving covalent or ionic bonding, but also other forms of interaction, e.g., such as complexing, chelation, physical interactions such as Van der Wals bonding, and the like.

[00138] In presently preferred embodiments and method implementations of the present invention, it is desirable to use a small disposable cartridge such as cartridge 460 for personal, regular (e.g., daily) use in a clinical or home. Large consumables (namely the interactant) are inconvenient and relatively more expensive. To reduce the size of the consumable and that of the overall device required to analyze the analyte or analytes of interest, a smaller particle size for the interactant generally is preferred.

[00139] Further in accordance with this aspect of the invention, the apparatus comprises a sensor that senses the change in the optical characteristic and outputs a signal representative of the change in the optical characteristic. As embodied in apparatus 410, and with reference to FIG. 9, the sensor comprises an optical detection subsystem that comprises a camera 490, preferably a digital camera, with associated an illuminating device 492, that can obtain optical characteristics, and changes in optical characteristics, of reaction volume 462. Illuminator 492 is disposed to provide light or an appropriate electromagnetic radiation at or through the reaction vessel 464 in a manner so that the radiation interacts with the contents of the reaction vessel and is then directed to camera 490. The light or electromagnetic radiation may comprise essentially a single frequency (a single, narrow band), a set of such single frequencies, on or more frequency ranges, or the like. In presently preferred apparatus 410, illuminator 492 provides white or broad-band light at a fixed level of intensity. (See arrows in FIG. 9 at illuminator 492.)

[00140] Digital camera 490 generates a signal that embodies the optical information on the optical characteristic or characteristics of interest. Signal generation can be accomplished using a wide variety of known transduction techniques. Commercially-available digital cameras, for example, typically provide automatic download of digital images as they are obtained, or transmit timed or framed video signals.

[00141] Apparatus 410 further comprises a processor 494 disposed within the interior of base unit 440 and operatively coupled to digital camera 490 to receive the signal from it. Processor 494 in this embodiment comprises a commercially-available general-purpose microprocessor or microcontroller appropriately configured and programmed to carry out the functions as described herein, in addition to standard housekeeping, testing and other functions known to those in the art. A power supply (not shown) is disposed in base unit 440 and is operatively coupled to processor 492 and the sensor components to provide necessary power to those devices.

[00142] Apparatus 410 may output the information gleaned from the breath analysis using any one or combination of output forms or formats. In this specific embodiment, apparatus 410 comprises a touch screen display 496 disposed at the exterior of base unit 440 and operatively coupled to processor 494. Processor 494 is configured and programmed to present options, commands, instructions and the like on touch screen display 496, and to read and respond to touch commands received on it as they are received from the user. Processor 494 also outputs the sensed information to the user, e.g., in the form of a concentration of the analyte in the breath sample. This is not, however, limiting. The output also, or otherwise, may comprise a wired or, more preferably, a wireless data link or communications subsystem 498 with another device, such as a centralized database from which a care giver, such as a physician, family member, watch service or the like can monitor the output.

[00143] There are many reactions that can be used to sense the various analytes that may be of interest. In some of those reactions, a relatively simple one-step reaction can be used, e.g., wherein the breath sample is contacted with the interactant, whereupon the change in the optical characteristic is manifested. In others, however, it is necessary to carry out multiple process steps. An illustrative but important example would be reactions in which the breath sample must be contacted with a first interactant, and then subsequently be contacted with another interactant, such as a second reactant, solvent, enzyme, or the like. The devices of the present invention, for example, can also optionally comprise a reaction initiator or dispensing device. A reaction initiator or dispensing device may be any apparatus that allows the developer solution or the like to contact the reactive chemistry. (The reaction initiator or

dispensing device may comprise a needle that pierces a canister of developer solution such that the solution passively contacts the reactive chemistry, as described more fully herein below.) In some breath analysis applications, it may be necessary or desirable to have three, four or more separate materials (interactants, solvents, developers, etc.) that are introduced at various times, e.g., simultaneously, sequentially, and so on, but which materials require separate storage prior to use. Such situations can be particularly demand when the material is in liquid phase (including but not limited to liquids, liquid suspensions, and the like).

[00144] To address such needs and circumstances, the invention according to various aspects comprises the use of a separate liquid container, or a plurality of such liquid containers (subcontainers), and a dispensing device that dispenses those liquids when and as needed for the particular application at hand.

[00145] To illustrate this aspect of the invention, FIG. 11 shows an exemplary dispensing device or reaction initiator 73 based on a needle 80. In this example, a linear actuator 75 with an attached needle is housed in the top portion (74) of a cartridge positioning clamp (76). To release liquid contained within a piercable vessel (78), the linear actuator 75 drives the needle (80) through first the top seal and then the bottom seal. Once the seals are broken, the liquid is released to either be pumped by external pneumatic handlers as described elsewhere or to wick through the reactive bed.

[00146] Another optionally included component of the devices of the present invention is a kinetic enhancer. In a preferred embodiment, the kinetic enhancer is contained within the base unit. The kinetic enhancer increases the reactivity between the analyte and the reactive chemistry. One example is shaking the reaction vessel to allow for increased mixing. Temperature control can also be used to increase reactivity or otherwise improve sensor system performance. Temperature control can be accomplished in numerous fashions, including IR heating and conduction heating using resistive heaters. In IR heating, IR emitting lamps are targeted to regions of interest, and illumination causes non-contact heating. Resistive elements in contact with thermal conductors built into the cartridge, for example foil seals surrounding a developer solution, can be used to increase the temperature of reaction and thus the reaction speed.

[00147] Temperature control, including cooling, can also be useful for controlling adsorption and desorption from adsorptive resins, for example Tenax TA or silica gel. Conductive cooling via Peltier elements can be helpful in increasing the adsorption capacity of resins.

[00148] The insertion mechanism for the cartridge can take a variety of forms. Means for cartridge insertion comprise, for example: (a) spring-loaded insertion, (b) linear actuated insertion, (c) annular gasket, o-ring insertion, (d) taper compression fit, and (e) snap-in fit. The insertion mechanism for the cartridge may comprise control mechanisms for such parameters as humidity, temperature, pH, and optical phenomenon such as light. For example, the insertion mechanism for the cartridge may include light blocking apparatuses. Preferably, the insertion mechanism enables the cartridge to be inserted at an angle in the base unit with respect to the floor. This angle improves user comfort during the cartridge insertion step but should not be too reclined to diminish gravitational forces which are helpful in dispersal of liquid developer solution. The angle is preferably in the range of 15-45 degrees with respect to a vertical line normal to the floor.

[00149] In a spring-loaded insertion approach, a sliding head under spring force can be used to compress the cartridge against a gasket on the base unit. The pressure of the cartridge base against the gasket forms a tight fluidic face seal, sufficient for the moderate pressures (for example up to 5 psi) that may be required to drive samples through the reactive elements housed in a sensor cartridge. To insert a cartridge, the user slides the cartridge into the sliding carrier and pushes against the spring until the cartridge can be seated against the gasket, similar to the insertion of cylindrical batteries into common consumer devices. A lever can be used to provide an alternative means to pushing against the spring.

[00150] Another approach to cartridge insertion into a base unit makes use of a linear actuator. As shown in FIG. 12, in such an example the cartridge (82) is compressed between a top (84) and bottom (86) surface. In this example, the sliding mechanism of the spring-loaded insertion embodiment described above is used in conjunction with a linear actuator instead of with a spring. In preferred embodiments, the top surface will be moveable and the bottom surface will be fixed, and the leak-free junction and inlet plumbing will attach to the bottom fixed surface.

[00151] FIG. 13 shows the details of an embodiment of a sliding mechanism in relation to a sensor cartridge. In Figure 13, a linear actuator (88) pushes a sliding platform (90) up and down to engage and disengage with the cartridge (92). The sliding platform can contain other elements, for example a separate linear actuator (94) useful in piercing operations. In this configuration, the plumbing that interacts with the cartridge is in the bottom portion (96) of the clamping mechanism, which remains fixed in order to reduce functional requirements of the plumbing. In this case, prior to cartridge insertion, the actuator is positioned into a retracted state that lifts the clamping head away from the topside of the cartridge. Sufficient

distance is created to allow unobstructed insertion of the cartridge into the cartridge receptacle. Once the cartridge is positioned, a user presses a button to indicate to the control electronics that the cartridge is loosely positioned, after which the linear actuator extends until a desired force is perceived to be acting against further extension (as estimated using the force/current curve of the particular actuator) or until a specified position is attained.

[00152] Another embodiment of the cartridge insertion mechanism is an annular gasket or o-ring. In such an embodiment, an o-ring fitted over a cylindrical base stem of the cartridge can be used to provide necessary sealing. In this case, an o-ring groove retains the o-ring as the base stem is inserted into a round receptacle. The receptacle walls are sized appropriately to seal against the o-ring. Alternatively, the o-ring can be captive in the receptacle wall of the base unit. Insertion force can be provided using a spring, linear actuator, or user force.

[00153] A tapered compression fit can also be used as an insertion mechanism for a cartridge. In this embodiment, a tapered base stem of the cartridge can be used to form a leak-free fluidic connection without an o-ring or gasket. In this case, the tapered base is compression fit into a slightly dissimilar tapered receptacle. User force is used to insert and remove the cartridge. Alternatively, a linear actuator and pin engagement scheme can be used to push the cartridge into the receptacle and to pull it out subsequent to measurement conclusion.

[00154] Another example of a cartridge insertion based on user force input is a snap-in design. In this design, snap receptacles are fashioned into the base of the cartridge. When the cartridge is compressed tightly against a soft gasket in the device base, the snap receptacles engage with mating snaps in the base device. To release the cartridge, the spring-loaded snaps in the base unit are retracted.

[00155] Raw breath may be unsuitable for direct interaction with sensing chemistries. Problems due to humidity, oxygen, or carbon dioxide are particularly problematic when a desired chemical system is adversely impacted by the presence of these chemicals. Breath conditioning apparatuses and methods can be optionally used by the devices of the present invention. Breath conditioning can potentially include any or all of: moisture removal, carbon dioxide scrubbing, oxygen removal, removal of interfering breath-born volatile organic compounds, heating of gas samples, cooling of gas samples, reacting gas samples with derivatizing agents, compression or decompression of gas samples, and other methods of preparing the breath for analysis.

[00156] In one embodiment utilizing breath conditioning, desiccants can be used for removal of moisture. In general, a given desiccant has varied affinity for a number of

chemicals. For example, anhydrous calcium chloride is known in general to preferentially bind water in the presence of acetone, and thus calcium chloride in the proper amount can be used to strip breath of water content while leaving acetone concentrations intact. Examples of other desiccants are well-known, including $CaSO_4$ (calcium sulfate), molecular sieve 4A, and activated carbon. Each of these examples can be used to remove water but care must be taken to ensure that the analyte of interest is not also being removed from the gas sample.

[00157] For aqueous chemistries where varied pH may be a contributor to assay success, it may be desirable to remove CO_2 from the breath samples. Soda lime is routinely used as a scrubber of CO_2 from exhaled breath in re-breathing circuits but may also be very valuable as a component to a breath gas analysis system. Numerous other adsorbent materials are known, for example Tenax TA, activated carbon, and Ascarite.

[00158] Many adsorbents may be useful as pre-concentration elements. Silica gel can be used to capture acetone such that large volumes are captured into microliter volumes. For example, the acetone from a 450 mL breath sample can be collected and packed onto silica particles occupying a volume of approximately 35 microliters, a more than 10,000-fold concentration. Pre-concentration may be used to gather sufficient analyte to cause a detectable reaction and may also be useful in speeding the rate of reaction and thus lowering a sensor's response time. In some cases, the adsorbed reagents can be reacted in situ. In other cases, elution of the analyte off the adsorbent may be beneficial. One preferred reagent in this regard is Tenax TA. Acetone adsorbs strongly to the Tenax particles in comparison to water such that humid breath samples can be passed over beds of Tenax particles to trap acetone and retain very little water. The breakthrough volume for water at 20°C is as small as 65 ml per gram of Tenax TA, meaning that the water can be removed from the Tenax column with small volumes of gas. The breakthrough volume is even smaller at elevated temperatures. In contrast, the breakthrough volume for acetone is about 6 liters per gram.

[00159] An example of a breath gas analyzer based on Tenax TA is shown in FIG. 14. In this figure, a two-piece cartridge is comprised of a top piece (98) and a bottom piece (100) that are snap-fit together. A container of developer solution (102) is positioned in the top piece (98) with foil barriers, as described previously. A porous, open-cell foam plug or other porous material (104) is positioned to compress a column of Tenax TA particles (106) against a woven mesh barrier (108). Alternatively, components (104) and (108) can be replaced by a single component that is porous and rigid enough to be compression fit into the pocket, such as porous polyethylene. A humid breath sample is passed over the reactive chemistry from the bottom side, exhausting through the non air-tight interface between the top (98) and

bottom (100) pieces of the cartridge. Next, the foil barriers are broken and a developer solution is pulled over the Tenax particles with the trapped acetone. Reagents in the developer solution interact with the acetone and other bound reagents to produce a color product. In this configuration, dedicated desiccation materials may no longer be necessary even if the system chemistry is sensitive to the presence of water.

[00160] Tenax TA and other adsorptive resins may also be useful in trap and release systems. In these approaches, the analyte of interest is captured and concentrated onto the resin while interferent materials, in particular water, freely pass without being retained. The captured analyte is later released via thermal desorption or elution to be reacted elsewhere. Such schemes are useful in controlling the chemical reactions in light of interfering substances that cannot be selectively removed through other means, or in conducting the colorimetric detection in a location more amenable to optical readout.

[00161] In FIG. 3, a three-way non-rebreathing valve (30) with an additional outlet tap (32) enables portions of numerous breaths to be sequentially deposited into a collection bag (34). A mouthpiece, with or without integral anti-bacterial/viral filter (35), protects a user from cross-contamination. The user first inhales, opening a first one-way valve in the non-rebreathing valve allowing ambient air to fill the lungs. Upon exhalation, the second one-way valve opens (the first closes), allowing the expired air to pass into the collection bag (34) and out the additional outlet tap (32). The proportion of gas filling the bag with each breath can be adjusted by adjusting the ratio of entrance resistances of the bag and the outlet tap. Also displayed in FIG. 3, is a flow circuit example, where V_a and V_b represent the ambient pressure (a) and bag pressure (b); R_i, R_o, and R_b represent the inlet resistance (i), outlet resistance (o), and bag entrance resistance (b); D_i, D_b and D_o represent the inlet (i), bag outlet (b), and ambient outlet one-way valves. The dead-volume of the valve housing should be minimized to reduce the amount of ambient air that is blown into the sample bag. An alternative embodiment of this approach is based on sensing of the breath flow direction (such as with embedded pressure transducers) and active control of the one-way valves to virtually eliminate dilution of the breath sample by leaked ambient air due to dead-volume crossover.

[00162] In an analogy to a circuit, voltages represent gas pressures and currents represent gas flows. The user controls voltage at the diode junction while exhaling (positive with respect to V_a) and inhaling (negative with respect to V_b). When a small portion of exhaled air is collected, and the resistance ratios are known, then the total volume of gas exhaled by the user over a set time is proportional to the gas in the bag. Knowing the total amount of

exhaled gas over a set time is valuable for estimating the moles of analyte expired by an individual over a certain time. This information can be useful in interpreting the physiological significance of breath analyte concentrations. Note that the resistance divider performs reliably without measuring the pressure in the sample (Vs) as long as the bag does not begin to inflate substantially such that the walls of the bag are pushed out against the pressure of the bag. A timing unit, similar to that described for FIG. 2, can be used to record the time spent in breath collection and to optionally control the one-way valves. An alternative use of the device in FIG. 3 is to allow breath averaging. Instead of filling a bag with a single exhalation, a user can breathe multiple exhalations and have a portion of each mixed with the others in the bag. Such averaged sampling can be used to increase repeatability between samples.

[00163] Cartridges comprise another aspect of the invention. Cartridges comprise reactive chemistry capable of reacting with at least one breath analyte, and preferably at least one endogenous breath analyte. There are a variety of cartridge configurations that can work with systems according to the invention for measuring at least one analyte, preferably an endogenous analyte, in breath.

[00164] In one embodiment, cartridges comprise an encasement that has a flow path for breath that is further coupled to an automated reaction initiator that allows the developer solution to contact the reactive chemistry. Cartridges preferably contain a porous media located adjacent to the reactive chemistry. The cartridge may contain a single reactive chemistry or a plurality of reactive chemistries.

[00165] In another embodiment, cartridges contain a pneumatic loader that transports developer solution through the cartridge.

[00166] In yet another embodiment and aspect of the invention, cartridges block ambient light when inserted into the base unit and preferably comprise a handle. As noted herein above, where internal system components such as the interactants, intermediate products, etc. are light-sensitive, the base may comprise an exterior surface that forms an interior and shields the interior from ambient light, wherein the exterior surface comprises an aperture; and the cartridge may comprises a shroud that substantially conforms to the aperture to shield ambient light from entering the aperture when the cartridge is coupled to the base.

[00167] Cartridges can be designed into various shapes and sizes to facilitate different applications. In one embodiment, the cartridge is comprised of: (a) reactive chemistry, (b) a first chamber containing a first developer, and (c) a second chamber containing a second developer. The first and second developer can be the same or different. In another

embodiment, the cartridge is comprised of: (a) reactive chemistry, (b) a chamber containing a developer, and either (c) mechanism for coupling the cartridge to a pneumatic loader or remover, or (d) mechanism for coupling to a reaction initiator. In a preferred embodiment, the cartridge requires no external liquid flow to the cartridge.

[00168] An exemplary general schematic of cartridge design is shown in FIG. 16. This cartridge is preferably used for optical detection, and preferably includes reactive chemistry that can be used to detect endogenously produced analytes in human breath. Here, the reactive chemistry (128) is contained within a cartridge housing (120) consisting of a single piece. Preferably, but not necessarily, the housing is comprised of material that is optically clear. There is a membrane (122) that separates the reactive chemistry from a breath conditioner (124). In this embodiment, the breath conditioner (124) is a desiccant, but this may also be a scrubber or pre-concentrator. The breath conditioner is kept tightly packed by a porous membrane (126). In some embodiments, a peelable or piercable barrier material can be affixed to the underside of the cartridge to enhance storage of the reactive chemistries and breath conditioners. On the other side of the reactive chemistry is a retainer (130). The retainer serves to keep the reactive chemistry tightly packed. This retainer can be molded compression fittings, on-cartridge gaskets, o-rings, etc. Atop this retainer is a porous media (132). The porous media is designed to allow liquid developer solution (133) to flow towards the reactive chemistry. In an alternative embodiment, components (130) and (132) are replaced by a single component that can be both compressive fit into the packing pocket and porous. Hydrophilic, porous polyethylene disks are useful for this purpose. Developer solution is contained within a breakable ampoule (133) that sits within a receptacle in the upper portion of the cartridge housing (131), which is formed with vertical channels to facilitate venting of air when developer solution flows down into the channel filled with reactive chemistries (128). The ampoule-containing receptacle (131) is sealed with a piercable membrane (134). Once the cartridge is inserted in the base unit, the piercable membrane and the piercable container are pierced by the reaction initiator of the base unit so that liquid flows to the reactive chemistry. To ensure that residual liquid does not leak out post-use of the cartridge, there is a rubber septum (136) that seals the cartridge. The cartridge preferably is designed such that the developer solution is "absorbed" by the reactive chemistry and/or conditioner (e.g., desiccant) such that it does not leak through the bottom of the cartridge. One optional addition is coupling to a pneumatic loader or remover (not shown). This pneumatic loader/remover acts as a pump and pulls/pushes the developer solution through the cartridge. Thus, while the cartridge can be oriented such that the liquid

interacts with the reactive chemistry due to gravitational pull or wicking, it can also be designed to allow for automated, active interaction via a pneumatic loader/remover.

[00169] FIG. 17 shows one alternative to the retainer (130) of FIG. 16 for containing reactive particles (128). A plastic cartridge (138) forms the main housing for a packed bed of reactive materials (142). A permeable retainer (140) is affixed on the underside of the column as discussed elsewhere. A porous material, for example plastic, metal, ceramic; or fibers such as glass or metal wool is compression fit into the channel. The porous plug is pressed tightly against the packed materials (142) to prevent shifting during usage or transportation.

[00170] The porous seal (132) exemplified in FIG. 16 is preferably comprised of a material with the following properties: fine pore (able to retain small particles, for example 75 micron particles), high open area (low pressure drop, low resistance to flow), inert to analyte of interest, amenable to pick and place automation, able to adhere sufficiently to the substrate. Materials in sheet form are often amenable to mass production. Sheets of various substrates are easily pressed into laminates. A sheet that is porous to begin with is easily processed into retention disks. FIG. 15 displays an example of a substrate sheet that can be pressed into retention disks. A sheet of thin polyimide (0.001" – 0.003") with adhesive backing is punched with an array of holes (110) (for example Devinall SP200 Polyimide film with FastelFilm 15066 adhesive backing). A sheet of fine woven nylon mesh (307x307 mesh, 9318T48 from McMaster-Carr) is pressed into a laminate with the punched polyimide. The laminate is then punched with a larger diameter tool to create laminated disks with a porous center (118). The outer region contains a topside annulus of polyimide. Such disks are easily picked up by vacuum means to be positioned easily, even into deep recesses. Disks are adhered to receiving surfaces using heat pressing tools. The particular adhesive melts at 66 C, well below the melting points of numerous plastics suitable as cartridge wall materials. Disks can be fashioned by this method using commercial rotary cutters and other common production tools. These disks are especially well-suited to retaining reactive media in deep wells, for example (324) in FIG. 29, discussed infra.

[00171] Foils and numerous other plastics are also available with adhesive backing. Polyimide top layers can be preferable to foil layers in some attachment methods since foil layers can have a greater tendency to separate from their adhesive backing during certain heat pressing processes, especially where the contact surface area is large. Polyimide may be preferable to other plastics due to its potentially high heat transfer and resistance to heat damage, especially when thermal grade polyimides are used.

[00172] Liquids can be contained in the pockets of cartridges, using the cartridge material as side walls with foil or other membrane barriers adhered to the cartridge surfaces. For aggressive solvents, for example dimethylsulfoxide or methanol, such solutions may be temporary due to solvent attack of the adhesives. One embodiment of the present invention uses a separate part to contain the liquid reagent. This allows complete materials control of liquid contact (the walls of the cartridge do not need to be a materials concern as far as solvent interaction is concerned). Various "cans" of liquid can be configured, and these cans can be dropped into an open pocket in the top piece of a cartridge. Preferably a liquid can or ampoule is completely inert to the retained liquid. FIG. 18 shows three embodiments of a piercable foil ampoule, described in the following paragraphs.

[00173] Breakable solvent ampoules can be manufactured by a variety of methods. For example, in one case, a flanged conical foil base (152) is welded or otherwise adhered to a weldable or heat-sealable intermediate material (150) to form the bottom half of a clamshell. A top foil layer (146) is likewise attached to a weldable or heat-sealable intermediate material (148) to form the top half of the clamshell. The bottom half is then filled with volatile liquids and the top half ultrasonically welded or heat sealed to the bottom half. The volatile liquid is contained within four barriers: the foil material forming the major contact surface, the weldable/sealable intermediate material (for example low thermal conductivity thermoplastic), the weld joint between the foil and the plastic (adhesive), the weld joint between the weldable intermediate materials (low thermal conductivity thermoplastic). This configuration is useful because (a) it allows an adhesive time to cure independent of solvent presence (the adhesives can be fully cured before filling of the solvent), thus enabling a wide range of adhesives to be employed; (b) conductive heating caused by ultrasonic welding is shielded by low thermal conductivity thermoplastic, eliminating or controlling the amount of fill solvent lost to evaporation during ultrasonic welding.

[00174] A thermal barrier material is another example of a breakable solvent ampoule. A second case ultrasonically welds the two foil half clamshells to one another, using a bottom half insert material as a thermal barrier. That is, a top foil (154) is attached to the bottom foil (156) by direct ultrasonic welding of the metal foil. The solvent is pre-loaded for welding, thermally protected by a thermal barrier, such as a hollowed out wax cone (164). The thermal barrier must protect the solvent from conductive heating caused during ultrasonic welding, but it must also be easily pierced. Other materials, such as thin plastics, rubber, or spray-on silicone adhesives may also be suitable.

[00175] An adaptation of the thermal barrier method is to perform ultrasonic welding in the presence of appropriate heat sinking. The ultrasonic weld jig contains an annular clamp made of highly conductive metal. The clamp engages the top and bottom metal foils inward from the outer locations of ultrasonic welding such that any heat conducting away from the weld joint sinks into the conductive clamp. Alternative methods of heat sinking, such as blowing the bottom foil with cold air may also be suitable, depending on the solvent in use.

[00176] A third method for solvent encapsulation relies on a crimp seal between a top foil (158) and a bottom foil (162). A wax gasket or gasket comprised of solvent-resistant material (160) is included between the layers to increase the retention time of the volatile liquid into the ampoule. The gasket material must be chosen with the appropriate resilience and barrier properties to the solvent of interest.

[00177] Ampoules can also be blow-molded from numerous materials including glasses and plastics. These single-material ampoules are constructed of thin walls to enable ampoule piercing, but sufficiently thick walls to obtain the necessary barrier properties.

[00178] Metals are excellent as barrier materials and can be sealed in gas-tight fashion through crimping (such as a beverage can). Miniature ampoules made of aluminum and other metals can be manufactured and dropped into the head portions of disposable cartridges.

[00179] FIG. 19 shows certain embodiments of a piercable ampoule. In this embodiment, a cold-formed foil (176), or other formed, piercable barrier material, is attached into the head portion of a base plastic carrier (172) using points of adhesive. These points may make contact with a series of bosses (188) and are intended to adhere the floor of the ampoule to the base plastic carrier in a non-airtight fashion. The floor of the ampoule (176) is filled with solution, and a temporary barrier (180) may be affixed to seal the liquid. The temporary barrier can be affixed through pressure sensitive adhesives, thermally set adhesives, or any other convenient method. The adhesive for the temporary barrier does not need to resist and retain the solution beyond the time required to complete the sealing process. A circular bead of adhesive (182) is next applied. This adhesive forms a permanent barrier for the entrapped solution, but a temporary barrier (180) allows the permanent barrier material (182) to cure independent of solution activity. The liquid is capped with a disc of barrier material (184). A separate material (186), such as a rubber septum, is optionally placed to prevent temporary passage of liquid after the barriers have been broken.

[00180] This method can be used to retain particles in a packed state. That is, by positioning of a compressible, porous material (190) directly beneath the bottom floor (176), particles can be immobilized.

[00181] FIG. 20 shows embodiments of a piercable can. In this example, a thin-bottomed can (192) is cast of a thermoplastic material. After filling with the desired liquid, a thin barrier material (a laminated foil with a thermoplastic layer, for example) can be attached via an appropriate method, such as ultrasonic welding or heat-sealing. As necessary, more extensive barrier materials (196, 198) can be affixed after the can is filled with liquid. Optionally, depending on the material requirements of the liquid to be contained, barrier materials (196, 198) can be attached directly to the can through pressure sensitive adhesives, thermally set adhesives, or other methods (note that the can does not need to be constructed of thermoplastic materials). A variation on this design uses a thick-walled plastic cylinder as the body of the ampoule and is sealed on both ends with piercable barrier materials.

[00182] Single analyte cartridges can be configured in numerous ways to facilitate various chemical reactions. Sequential columns of dry reagents can be packed into stacked columns (where shifting of particles is not a concern) or into partitioned pockets within the device. Some examples are shown in FIG. 21 and FIG. 22.

[00183] In FIG. 21, three distinct dry reagents (200, 202, 204) are packed into a single column. Porous membranes (206) and (208) are in place to retain the reagents. Reagents can be of dissimilar size when membranes are in place. Additional reagents can be packed using increasing diameter sections, such that flat ledges are created whereupon retention means can be affixed.

[00184] In FIG. 22, reagent stacking is shown. When distinct reagents of similar size (212 and 214) need to be immobilized, they can be packed into a single column as shown. Larger particulates (218) will need means of separation and retention (216). One method of separation makes use of thin disks of porous material, such as nylon mesh as described in FIG. 15, but porous plastics or other porous media can be used in additional embodiments. The outer ends can be sealed using retention membranes (210) and (220). It is often desirable to pack columns with reagents in such a manner that the reagents are not free to move. In this case, materials can be held using compressible, porous media. FIG. 23 illustrates such a configuration. In this illustration, a cartridge is comprised of two pieces, a top (222) and a base (228). A first dry reagent (232) is packed into the lowermost pocket of the base, retained by two porous membranes (230 and 234). A second dry reagent (226) is packed into the central column of the cartridge. At the topmost end of the central column, a wider bore has been molded to accommodate slight overfilling of the dry reagent (to relax filling tolerances) and to facilitate compression of the reagents with a porous, compressible material.

This material, when compressed by the top (222), still allows fluidic communication through the top and bottom pieces while compressing the dry reagents 226) to keep them immobile.

[00185] Liquid reagents can be packed into sensor cartridges to facilitate numerous chemical reactions useful in breath analysis. FIG. 24 shows an example of how a liquid reagent can be immobilized onto a cartridge and how it can be released at the time of reaction. In a top piece of a cartridge (240), a containment means (238) is provided for the liquid reagent. This can be a distinct component (238) that is dropped into a pocket in the top piece (240) or it can be integral to the top piece. In any case, this reagent ampoule (238) can contain liquid reagent between two piercable membranes (252) that are impermeable or otherwise amenable to the reagent of interest. A needle (236), solid or hollow, is pressed through the membranes at the required time, causing the liquid reagent to flow through a conical cutout (250) in the cartridge and through a downcoming channel (246) toward the reactive bed (244). In this configuration, the seal between the top piece (240) and base piece (242) is not airtight (to allow gas flow from the bottom of the reactive bed (244) through to the top and out the sides). Thus, the liquid reagent is preferably of low viscosity and appropriate surface tension such that the liquid drops all the way to the top of the reactive bed and is drawn into the reactive bed when a suction pump (248) is activated.

[00186] FIG. 25 provides another embodiment. In this alternate configuration, a hole (260) is cut into the top piece so as to provide a gas exit port when the top piece (254) and the bottom piece (256) are fastened with an airtight seal. In this case, gas is flown over the reactive bed and out the exit port (260). Next, a pin (262) is pressed through a top and then bottom barrier to free the contained liquid and to create a hole to allow gas to fill the vacated space. The liquid fills a downcoming channel (264), blocking the exit port and creating a liquid seal so that a suction pump (268) can pull the liquid through the channel and through the reactive bed.

[00187] An extension of the liquid containment/release mechanism as described above allows multiple liquid reagents to be integrated into a single cartridge. FIG. 26 and FIG. 27 illustrate examples of a multi-liquid cartridge. In FIG. 26, two reagent wells A and B contain two reagents (or one reagent, if desired) between breakable seals as discussed. The downcoming channels are merged into a single line. When the first seal is broken, liquid from A fills the downcoming channel as before, where it is then suctioned away by a connected pump. Next, the seals containing liquid B are broken, and the same procedure is followed. FIG. 27 shows a top piece that contains four such containers of liquid. This

method allows very sophisticated fluidic handling to be done with reagents that are located on a single disposable piece.

[00188] Although chemical reagents may be consumed with each reaction, cartridges of the present invention need not be limited to single-use. Multiple use devices can be comprised of strips or carousel wheels of devices in a single substrate. This same form factor can be used to allow multiple analytes to be measured in a single breath sample, either with sequential or parallel processing.

[00189] FIG. 28 shows some cartridge designs to enable these applications. Displayed on the left side of the diagram is a strip or blister pack of reactive channels. Each of the four channels (292, 294, 296, 298) depicted can be filled with identical or different reagents, depending on whether the application is to measure, as examples, acetone on four occasions, acetone and ammonia each on two occasions, or to measure 4 separate analytes from a single sample. Each channel can be sealed with a separate foil barrier (300) or with a single foil strip placed over the entire top portion. Windows to reduce material volume and wall thickness for optical clarity can be fashioned next to each packed column. The base device must contain four fixed channels or moving parts (to move either actuators or the table containing the multi-channel cartridge). Also shown in FIG. 28, multiple channels are incorporated into a carousel-type device (306) which rotates to align each channel with a fixed-position seal breaking/fluid driving head.

[00190] FIG. 29 shows an embodiment of a cartridge design that facilitates or accomplishes the following tasks: (a) sample desiccation, (b) sample concentration, (c) sample reaction, (d) built-in fluid direction control (via one non-reversible one-way valve, schematically similar to three one-way valves), (e) two-phase reagent containment (solid reactive chemistry, liquid developer). (f) inexpensive reagent interfaces (retention means), (g) easy insertion into base device, and (h) low reagent volume.

[00191] The exemplary cartridge in FIG. 29, in connection with appropriate reagents, is appropriate to measure acetone in human breath. The cartridge is comprised of two pieces that are mechanically fastened together, for example with snap fits. A top piece (312) attaches to a base piece (314). The top piece and base piece, by design, do not form an air-tight seal. Liquid reagent is contained in a pocket (316) in the top piece. One embodiment consists of a developer solution contained between two foil seals, one on the top plane of the pocket and a second on the bottom plane. Beneath the bottom foil seal, a conical pocket (318) is fashioned to facilitate liquid reagent dropping without intermittent air bubble entrapment. Reactive chemistry is packed into a column (322) running through the center of

the base piece. To ease tolerances on reactive chemistry packing, the top-most portion of the reactive column is widened. A porous, compressible medium is deposited in the top-most, widened column portion such that when the top piece (312) is sealed against the base piece (314), the reactive material loaded into the column (322) is packed tightly. In general, open cell foams, both foam-in-place and pre-formed and cut, are well-suited as porous, compressible retention barriers as long as the chemistry is compatible with the system. Columns that are not packed tightly are subject to material shifting, a situation which hampers reproducibility and increases measurement errors. Desiccant materials are packed into a lower, wider column (326). A porous seal (324) is attached to the ceiling of (326) to provide a gas-permissive retention mechanism for the reactive material. In one embodiment, woven nylon mesh provides this means while incurring negligible resistance to gas flow. A similar barrier (328) forms the floor of column (326). The base of the cartridge is formed to facilitate compression against a trapped gasket in the base device to enable leak-free communication with the gas delivery plumbing. Pockets have been fashioned into the cartridge walls to enhance colorimetric detection. The pocket depth is selected to minimize wall thickness while simultaneously preserving the mechanical integrity of the cartridge, especially in relation to the wider bores required for the pockets that contain accessory reagents. The wall angle, with respect to the four relatively square sides of the cartridge, can be adjusted to promote effective illumination and to attenuate harsh reflections of excitation light in particular.

[00192] One preferred example of how a cartridge interacts with a base unit is in the following manner. First, the user opens a door through the wall of the base device and places the cartridge into a cartridge receptacle. No significant force is required of the user to make the insertion, and insertion orientation is restricted by mechanical stops. Either of two (of the four) sides of the cartridge must be oriented toward the optical setup. A cartridge receptacle that receives the cartridge at an angle (whereby the top portion of the cartridge is inclined away from the user with respect to the bottom portion) increases user accessibility and comfort during cartridge insertion. Once the cartridge is loosely placed within the device, mechanical means are provided whereby the topside of the cartridge is compressed against a captive gasket in the base device. See FIG. 12 and FIG. 13. This compression forms a face seal between the gasket and the bottom of the cartridge, providing a leak-free fluidic connection capable of withstanding the driving pressure required to move breath samples and developer solution through the cartridge and its various compartments. Once the cartridge is in position, a breath sample is collected through various means, for example a breath

collection bag or sidestream sampling. Once a sample of gas is ready for measurement, a pneumatic handler is actuated which withdraws breath gas from the gas collection vessel and pumps it first through the desiccant bed, next through the reactive column, and out through the cartridge. See FIG. 30. The cartridge is designed to be open to gas flow at both ends. The bottom side (desiccant side) is open through a woven mesh barrier, the top-side is open through the non air-tight sealing of the top piece (338) to the base (340). Thus, when gases are pushed through the bottom of the column, they can vent through the top although the developer containment barriers have not been broken. After the proper volume of breath sample has been pushed through the column at the selected rate of flow, the developer solvent containment means is ruptured. See FIG. 24. A sharp pin (236) is driven through the lid of the cartridge such that it breaks the top barrier (252) of the containment means first, then the bottom. Slower pin drive speeds and appropriate contained volumes of developer are preferred to prevent developer spillage during rupture. Also preferred is the ability of the containment means to withstand deformation during rupture when such deformations result in spilled developer solution. Once the developer is released, it fills the conical pocket (250). The conical pocket assists in creating a liquid seal (251), such that when fluid is pulled through the column there is a continuous pull of developer into the column. The amount of developer pulled through the column can be controlled (open-loop) by adjusting the duration of the pulling pump's on cycle, or closed-loop means can be employed. An imaging system (see FIG. 4 and FIG. 5) is used to record colorimetric responses which result from analyte reaction with the reactive bed and developer solution. Developer solution can be largely contained in the desiccant bed. Optional top and bottom septa can be built into the cartridge when potential user exposure to especially deleterious solvents should be prevented.

[00193] FIG. 16 shows a preferred method for single-analyte cartridge construction. A single piece of molded clear plastic (120) such as acrylic forms the cartridge housing. A particle retention barrier (122), as previously described, is attached to the bottom of the flow channel but is comprised preferentially of thermal adhesive-backed (Fastel 15066, 3 mil thick) polyimide (Devinall, 2 mil thickness) with woven nylon center (198 x 198 mesh, 0.0031" opening, 49% open). Desiccant material (30-60 mesh anhydrous calcium chloride) fills a desiccant chamber (124). A particle retention barrier (126) similar to (122) is placed on the bottom to contain a desiccant. The reactive materials (100-140 mesh aminated and nitroprusside-attached particles in a 2:1 ratio) are placed in the flow column (128), and the top portion of the channel opens to facilitate low-tolerance filling. A porous material (130) such as glass wool, stainless steel mesh, or porous hydrophilic polyethylene plastic

(preferentially) is placed over the reactive particles. In some embodiements, the reactive particles (128) and porous barrier (130) may need additional means to be compressed tightly against the particles. An o-ring, external toothed push-on ring, or deformable retainer ring may be suitable for this purpose, but porous plastic can make its own compression fit without the need of these means. A piercable liquid ampoule (133), comprised preferentially of a thermoplastic, heat-sealed can with pierceable barriers on top and bottom, is placed into a holding housing in a manner that does not occlude airflow. The top of the cartridge is sealed with a piercable foil (134) and a liquid barrier septum layer (136), such that liquid cannot leak through the lid after the cartridge has been used.

[00194] FIG. 31 shows a preferred method for using the cartridge discussed in FIG. 16. With the piercing needle (342) in the fully retracted position (A), the top barriers (344) have not been breached and airflow through the cartridge is not possible. With the needle in a first extended position (B), the top barriers are breached such that gas can flow from the bottom of the cartridge through the various porous barriers, reactive bed, around the liquid ampoule, and through the hole in the piercing needle (348). In a second extended position (C), liquid is released from the ampoule (346) and is pulled by suction force of a pump or by wicking downward through the reactive bed. A needle in the base unit (343) can be used to pierce a bottom barrier material to allow gas flow into the cartridge. This method allows the cartridge to be sealed for storage and shipping and to be automatically pierced upon usage without extra user steps. Also, the septum on top and extra barrier on bottom can be used to contain the liquid inside the cartridge after use. Note that the barrier to contain desiccant or other conditioning materials is not shown in this figure.

[00195] A cartridge 510 according to another presently preferred embodiment of the invention is shown in FIG. 32. This cartridge preferably would be used in a breath analysis device, for example, as shown in and described in connection with Figs. 8-9 herein above. Cartridge 510 comprises a body or housing 512, which in this embodiment comprises a solid plastic cylindrical component. Housing 512 has an inlet 514, wherein the breath sample is inputted into cartridge 510. The breath sample travels upwardly through the substantially cylindrical flow channel centered about the longitudinal axis of the cartridge 510. Note that the direction from the inlet of cartridge 510 toward its output (upwardly in FIG.32) is referred to herein as the "downstream direction," (given that the gas (breath sample) flows in this downstream direction), and the opposite direction, i.e., downwardly in the drawing figure toward inlet 514, is referred to herein as the "upstream" direction.

[00196] Cartridge 510 at its input comprises a porous polyethylene disk 516. Immediately downstream from disk 516 is a conditioner 518 that comprises a desiccant. A fibrous polyethylene disk 520 is disposed immediately downstream from and contacting the desiccant conditioner 518. A porous polyethylene disk 522 is disposed immediately downstream from disk 520. Disk 520 forms a lower boundary of a container or region 524 for one or more interactants 526 disposed within container 524. In this embodiment, the interactant or interactants 526 comprise solid-phase material, for example, such as those described herein. A porous polyethylene disk 528 is disposed at the downstream end of container or region 524 and forms its upper or downstream boundary. Container 524 in this embodiment comprises a slightly enlarged neck portion 524a that includes overfill of the solid-phase material. A foil laminate 530 comprising a layer of foil sandwiched between two layers of thermoplastic material is disposed immediately downstream from disk 528. Cartridge housing 512 includes a well 532 that is open at its lower end (as shown in FIG. 32) to reaction volume 524 via disk 528. Foil laminate 530 is disposed in the bottom of this well.

[00197] A liquid container 534 is disposed in well 532. Liquid container 534 has a diameter that is slightly smaller than the diameter of well 532, so that an annular channel or vent 536 is provided in fluid communication with reaction volume 524 via disk 528. Liquid container 534 contains a liquid 538 that comprises an interactant, a developer, a catalyst, a solvent, or the like. In its initial state, i.e., prior to use, the liquid 538 has an initial liquid level 540 in container 534. The bottom portion of liquid container 534 comprises foil laminate 530. Liquid container 534 also has a top, which in this embodiment comprise a foil laminate 542, preferably similar to or identical to foil laminate layer 530. Immediately above foil laminate layer 542, however, is a layer of material 544, in this embodiment a fibrous polyethylene, that provides a resilient seal for container 534, and which also absorbs liquid 538. The sides of container 534 may comprise a rigid and relatively brittle material, such as glass, polycarbonate, and acrylic resin or the like. At each end of cartridge 510, a foil laminate layer 548, preferably as described above, encloses and seals the contents of the cartridge. They preferably are heat-sealed to the ends of the housing 512. The top, bottom and sides of container 534 of course should be inert with respect to the liquid 538 to avoid structural deterioration, fouling or poisoning of the liquid, and the like.

[00198] The layer which, in this embodiment comprises foil laminate 530, functions to seal the bottom of ampoule or can so that leakage of liquid is prevented. It also serves as a boundary for the flow of the breath sample emanating from reaction zone 524 as it flows downstream. The gas (breath sample) in channel 536 incidentally vents through the top

layers 542 and 544 after the hole or holes have been created in them by the dispensing device, e.g., device 73. The dispensing device may and in this instance preferably is used at the initial stage of the analysis, as the breath sample travels through and out column 524, but prior to dispensing of the liquid 538, to provide this exhaust route for the gas. The foil laminate top and bottom of liquid container 534 also are sufficiently resilient, are sufficiently tough (non-brittle), so that the dispensing device, such as dispensing device 73, can create one or more holes in each such foil laminate of sufficient size to achieve their desired functions without breakage.

[00199] As in other embodiments described herein above, cartridge 510 is configured to operate in conjunction with a dispensing device, such as the elongated devices (e.g., a needle, pin, rod, and the like). For illustrative purposes, dispensing device 73 is shown in FIG. 32.

[00200] In many preferred embodiments or applications, it is desirable that the liquid container, or at least the hole or holes in it through which the liquid is dispensed, be in close proximity to, and more preferably immediately adjacent to, the reaction volume. In such embodiments and applications, it is preferred, and in some instances even necessary, that a medium be provided at the exit hole or holes in liquid container to facilitate movement or flow of the liquid out of and away from the liquid container and toward the reaction volume, through wicking or capillary action. More preferably, the bottom of the liquid container and the top of the reaction volume should abut one another, but be separated only by this wicking material. It is also preferred that there be no air gaps or other spacing between those two surfaces, except the wicking material. This is provided in cartridge 510 by porous polyethylene disk 528, which is contiguous with foil layer 530 at the bottom of liquid container 534 and which is contiguous with and open to interactant container and reaction volume 524.

[00201] When a breath sample analysis begins, input seal 548 at input 514 is pierced by a seal piercing assembly 550. Assembly 550 comprises a block 552 that is coupled to a moveable actuator 554. Assembly 550 also comprises a needle 556 that includes a fluid channel 558 fluidically coupled to the breath sample, e.g., from the flow path 444 of base unit 440 in FIG. 9. In its normal state prior to analysis, block 552 is spaced from the cartridge 510. When the breath sample analysis begins, actuator 554 moves block 552 to the input 514 of cartridge 510, and needle 556 is inserted through layer 548 so that the breath sample flows through flow path 444 and into the cartridge input 514.

[00202] As can be seen, for example, in FIG. 32, cartridge 510 has a flow path that extends from its inlet 514, through conditioner 518 and container-reaction volume 524, and out

around ampule 534 . Cartridge 510, when inserted into the cartridge housing 454 of the base 430 of FIGS 8 and 9, is configured as described herein regarding the insertion mechanisms so that this flow path within cartridge 510 aligns with and becomes part of flow path 434, as described herein above with respect to FIG. 9.

[00203] FIG. 33 shows an alternate means of piercing the liquid container described previously as a piercable can (FIG. 17). In this drawing, a needle 601 inclined at an angle to the can illustrates that a needle need not pierce the can from the top through the bottom in order to both pierce the can below the liquid line and to also control the pressure in the container to facilitate liquid flow. The needle 601 is first held in a reserve position as shown in panel A. To pierce the ampoule 602, the needle is driven through the ampoule at two locations, one above the liquid line and one below as shown in panel B. With one hole below the liquid line and another above the liquid line, the liquid is free to flow out of the ampoule into the reactive zone 603 as shown in panel C.

[00204] FIG. 34 illustrates how two needles in a single action can be used to create a hole in a piercable ampoule below the liquid line and one above the liquid line to moderate intra-ampoule pressure and facilitate liquid flow. In this case, an ampoule 608 constructed as a piercable can (FIG. 17) is laid on its side inside the cartridge housing 609. A needle carrier 610 is positioned to actuate through the side of the cartridge to interact with the ampoule. The ampoule 608 may or may not consist of a partially filled flooring; as shown here, the floor of the ampoule is inclined ('filled') so that very little fluid is left in the ampoule after rupture. Using this hardware for breath measurement would consist broadly in the following steps: first, as shown in panel A, a needle carrier 610 is poised to break a piercable barrier material 611. With the barrier broken, as in panel B, the gas sample is able to flow upwards from the pump 612 or breath sample source, through the reactive zone 613, around the ampoule 608 and through the pierced barrier material 614, venting to the atmosphere or wherever exhaust gas may be intended. Panel C illustrates that a further progression of the needle assembly 610 leftward results in piercing the ampoule 608 at two points: one below the liquid line, and one above. The hole above the liquid line mediates the pressure (vacuum) formation in the ampoule, while the hole below allows the liquid to drain into the reactive zone 613.

[00205] FIG. 35 shows one example of how a hole can be generated in an ampoule below the liquid line without a needle, and how the pressure within the ampoule can be moderated to facilitate liquid flow without creating a hole in the ampoule above the liquid line. In this example, an ultrasonic horn, IR heater, or contact heater head 620 is used to generate heat

within an ampoule 621 which has been fashioned to create a pressure relief valve 622 below the liquid line. This can be done, for example, using blow-fill-seal technologies using plastic container materials, where the seal joint is designed to fracture when the pressure within the ampoule is sufficiently high. To free the liquid from the ampoule, as shown in panel B, the ultrasonic horn, IR heater, or contact heater head 620 couples heating energy to the ampoule fill contents or to a foil laminate barrier material 621 on the top-side of the ampoule. The elevated temperature increases the pressure within the sealed ampoule, causing the ampoule to rupture at the pressure relief valve 622 and then to facilitate the emptying of the ampoule into the reactive zone 623.

[00206] FIG. 36 shows how liquid can be released from an ampoule that has been filled at higher than ambient pressures. In this example, a piercing member 626 is positioned in a receiving pocket of a cartridge 627. The piercing member can be integral to the cartridge material or can be a drop-in component. A piercable ampoule 627 is placed over the piercing member, but without sufficient weight to cause piercing by the piercing member. To release the liquid from the ampoule 628, a pressing member 629 is brought down upon the ampoule as in panel B. Pressing down on the ampoule with sufficient force causes the piercing member 626 to rupture the floor of the piercable ampoule 628 creating a hole below the liquid line. In this case, the ampoule is comprised of two interior spaces 630 and 631. The lower space 631 is filled with liquid reagent. The upper space 630 is filled with a pressurized medium. Separating the two spaces is a distensible membrane or material interfacial region 632 which keeps the two interior spaces 630 and 631 (and their contained media) distinct and unmixed. When the press 629 causes the piercing member 626 to pierce the bottom of the ampoule 628, the increased pressure in the top interior space 630 causes the membrane or material interfacial region 632 to extend and to thus remove any vacuum in the lower interior space 631 that would otherwise impede flow; liquid is dispensed into the reactive zone 633.

[00207] FIG. 37 illustrates an example of how the pressure within an ampoule can be moderated after an ampoule is broken to facilitate liquid flow out of the ampoule, without creating a hole in the top portion of the ampoule. In this example, an ampoule 636 with a piercable bottom can be pushed into a piercing member 637 as described earlier to cause the formation of a hole below the liquid fill line. To moderate against the vacuum that would form in the ampoule after rupture which would impede liquid evacuation of the ampoule, an ultrasonic horn, IR heater, or conductive contact heater head 638 couples heat to an expandable balloon material 639 filled with a substance that readily contracts when heated. Thus, after the ampoule is pierced as in panel B, the heater head 638 is activated as in panel C

in order to expand the filled balloon material 639, resulting in the removal of the vacuum inside the ampoule which would otherwise impede liquid dispensing.

[00208] FIG. 38 shows how a hole can form in an ampoule below the liquid line and the vacuum can be moderated using injected air. In this example, a needle with an internal flow path 640 is brought down into an ampoule 641 with a pressure relief valve 642 as shown in panels A and B. The top piercable portion of the ampoule 643, most preferably a piercable can (contrary to the depiction) is comprised of a rubber or septum material, such that piercing by the needle creates an air-tight mating of the needle walls and the top piercable portion of the ampoule. Injection of air as shown in panel C, for example by a pump, creates a pressurized internal region of the ampoule causing both the rupture of the pressure relief valve 642 and the mitigation of vacuum that would otherwise develop in the ampoule in response to the vacating fluid.

[00209] FIG. 39 illustrates a means to keep a pierced ampoule fixed in position in order to facilitate liquid flow during ampoule piercing. A cartridge 650 is manufactured with a star-shaped pocket 651. A piercable ampoule 652 is press-fit into the pocket. The star configuration, or other non-circular geometry, is designed to provide contact points whereby the ampoule can be press fit into the pocket while preserving air vents 653 which promote liquid dispensing. Press fit as such, a retracting piercing needle will not carry the ampoule upwards with it which can in many instances impede fluid flow downward into reaction zones as described elsewhere.

[00210] FIG. 40 illustrates an example of a means for keeping a piercable ampoule fixed in position so that it is not lifted up when a needle retracts. In this example, a piercable ampoule 656 is placed into a pocket of a cartridge 657. A disk of fibrous plastic such as fibrous polyethylene 658 is placed on top of the ampoule. The fibrous plastic is spongy and acts as a spring to compress against the top of the ampoule. A barrier material 659, such as a plastic/foil laminate, is placed on top and heat sealed (or adhesive fixed) to the cartridge 657. Thus, when a needle retracts upwardly after piercing the ampoule, as described elsewhere, the ampoule is restricted in its upward motion and will stay fixed in position, tightly coupled to a wicking material 660 such as porous polyethylene to promote liquid dispensing. Panel A shows an isometric view of these components, and panel B shows these components in a side view.

[00211] FIG. 41 shows an example of a means to keep a piercable ampoule in place after piercing with a needle as described elsewhere. In this example, an ampoule 663 is fashioned like the piercable can (FIG. 20) with a top and bottom piercable membrane. In this example,

however, the body of the can is comprised of a star-shaped extrusion. This ampoule can be press-fit into a circular hole 664 in a cartridge 665 such that the ampoule is fixed in position and will not be drawn up during needle retraction. Gaps between the ampoule and the circular hole walls create air vents which facilitate liquid dispensing from the ampoule. The extrusion profile of the ampoule need not be star-shaped; any profile that provides contact points with the cartridge receiving pocket enabling a press-fit but that also preserves sufficient gaps to promote venting as the ampoule drains can be used.

[00212] FIG. 42 shows an example of an ampoule that can be pierced with pressure alone. An ampoule 669 is manufactured with two pressure relief valves 670 and 671. A pressure nozzle with sealing gasket 672 is brought down to contact the ampoule as shown in panel B. Flow into the nozzle causes the rupture first of the top pressure relief valve 670, followed by the rupture of the bottom pressure relief valve 671. The rupture of the bottom pressure relief valve 671 causes a hole below the ampoule's liquid fill line; the incoming gas (through the pressure nozzle with sealing gasket 672) mediates the vacuum that might form in the ampoule to impede flow. Alternatively, after rupturing the pressure relief valves, the pressure nozzle with sealing gasket 672 may be retracted, leaving the holes in the ampoule to facilitate liquid evacuation from the ampoule.

[00213] Breath can be input into the device using direct means. FIG. 43 illustrates how this can be done. A user blows into the end of a hose fitted with a three-way non-rebreathing valve and optional bacterial/viral filter which attaches to an inner containment vessel (361). As the user continuously exhales into the inner containment vessel, the air is pushed out through a breath flow measurement device (362), such as a pneumotachometer or turbine flowmeter. Other means of flow measurement are known to those skilled in the art and can be used here as well. A sensor sampling loop (360) uses a pump to withdraw gas from the inner containment vessel at a controlled rate using methods as described earlier. The gases are then passed into the cartridge or sensing area for analysis. This method of using a breath flow measurement device enables the gathering of analyte rate of production information, which can have greater utility than simple concentration measurements.

[00214] A method for sensing an analyte in breath of a patient according to another aspect of the invention will now be described using preferred breath analysis system 410 and cartridge 510. It will be appreciated, however, that the method is not necessarily limited to these preferred apparatus, and that other apparatus and components may be employed to practice or implement the method.

[00215] According to this method, one first provides a cartridge comprising a first container, a fluid container, and a reaction volume in fluid communication with the first container and the fluid container, wherein the first container containing a first interactant and the fluid container containing a fluid, wherein the fluid container has an initial fluid level and a space above the initial fluid level. These aspects of the method are provided in this implementation by providing cartridge 510 as described herein above.

[00216] The method also comprises providing a base comprising a flow path for flow of the breath within the base, a breath input receiver in fluid communication with the flow path, a cartridge housing, a dispensing device, and an optical subsystem. These aspects of the method are provided in this preferred implementation by providing base unit 430 of FIG. 8 as described herein above, including one of the dispensing device embodiments disclosed herein.

[00217] The method further comprises inserting the cartridge into the cartridge housing of the base so that the reaction volume is in fluid communication with the flow path. In the preferred implemented herein, this comprises inserting cartridge 510 into cartridge housing 452 of base unit 430.

[00218] The method then comprises causing the breath to flow in the flow path and into the reaction volume.

[00219] After the breath has flowed through the reaction volume, the method comprises using the dispensing device to create a hole in the fluid container below the initial fluid level and moderating pressure in the space above the initial fluid level as the fluid moves out of the liquid container so that the fluid moves out of the liquid container and into the reaction volume, thereby facilitating an optical change in the reaction volume in relation to at least one of a presence and a concentration of the analyte.

[00220] The method also comprises sensing the optical change and generating an output comprising information about the analyte in response to the optical change. This preferably is implemented by using the optical detection subsystem (including illuminator 92 and camera 90), processor 94 and outputs (display 96 and/or communications output 98) of system 410.

[00221] The "interactant" or "interactant subsystem" can interact with the analyte by any of a variety of ways, including but not limited to chemical reaction, catalysis, adsorption, absorption, binding effect, aptamer interaction, physical entrapment, a phase change, or any combination thereof. Biochemical reactions such as DNA and RNA hybridization, protein interaction, antibody-antigen reactions also can be used as mechanisms for the interaction in

this system. Examples of "interaction" regimes might comprise, for example, physical or chemical absorption or adsorption, physical or chemical reaction, Van der Waals interactions, transitions that absorb or release thermal energy, transitions that cause an optical change, and the like. As used herein, "interactant" and "reactive chemistry" are used interchangeably.

[00222] Reactive chemistries are preferably interactive even in the background typical of exhaled breath (e.g., large moisture concentrations, CO_2, etc.) Reactive chemistries should further respond to endogenous levels of analytes in breath. Some examples of reactive chemistries useable in embodiments of the present invention and the analytes they are used to detect are found in the Table 2.

TABLE 2

Breath Species	Reactive Chemistry	Method of Attaching Chemistry to Surface
Acetone	Sodium Nitroprusside	Anion exchange
Acetone	Dinitrophenylhydrazide	Reverse phase
Alcohol	Sodium Dichromate	Anion exchange
Aldehydes	Pararosaniline	Cation exchange and/or reverse phase
Ammonia	Bromophenol blue	Anion exchange and/or reverse phase
Ammonia	Dichloroisocyanourate, Sodium salicylate	Anion exchange and/or reverse phase
Carbon dioxide	Sodium dichromate and crystal violet	Anion exchange (dichromate); Cation exchange and/or reverse phase (crystal violet)
Carbon disulfide	Benzyl mercaptan	Reverse phase

[00223] In one embodiment of the present invention, the reactive species are attached to a surface. Surfaces can be of varied geometry and also of varied composition. For example, a surface can be a set of beads comprised of silica. Or, a surface can be a set of nanotubes comprised of quartz. In a preferred embodiment, the surface comprises a set of beads. Preferably the beads have diameters between about 40 and about 100 microns. Different materials that can be used to compose the surface. Types of surfaces include metals, ceramics, polymers and many others. Some specific examples of materials that can be used with silane coupling agents include, but are not limited to, silica, quartz, glass, aluminum oxide, alumino-silicates (e.g., clays), silicon, copper, tin oxide, talc, inorganic oxides and many others known to those skilled in the art. Examples of materials that can be used with amino coupling agents include all types of polymers with epoxide, aldehyde or ketone functional chemistries, among others. Examples of materials that can be coupled with free

radical forming coupling agents include acrylates, methacrylates and numerous polymers with aromatic bonds, double carbon bonds or single carbon bonds, and many others known to those skilled in the art.

[00224] In some embodiments, the reactive chemistry is coupled to the surface by using a coupling agent. "Coupling agents" are broadly defined as chemicals, molecules or substances that are capable of coupling (see definition for "react") a desired chemical functionality to a surface. Preferred coupling agents either have branched chemical functionalities or are capable of branching during coupling with the surface. "Branched chemical functionalities" or "branching" refers to having more than one chemically reactive moiety per binding site to the surface. Branching may be contained within a single coupling agent or may be achieved through the reaction of several coupling agents with each other. For example, tetraethyl orthosilicate may be mixed with aminopropyl trimethoxysilane for enhanced branching during the reaction.

[00225] There are numerous coupling agents known to those skilled in the art. In the class of silanes, there are literally thousands of functional chemistries attached to a silane. Silanes can be coupled to dozens of surfaces, with a preference for silica surfaces and metal oxides, and are capable of *de novo* surface formation. Examples of common functional silanes include aminopropyl trimethoxysilane, glydoxypropyl triethoxysilane, diethylaminopropyl trimethoxysilane and numerous others.

[00226] Coupling agents possessing a free amine are readily coupled to surfaces with epoxides, aldehydes and ketones, among other chemical moieties. Coupling agents with epoxides, aldehydes and ketones can also be used with surfaces containing a moderate to strong nucleophile, such as amines, thiols, hydroxyl groups and many others.

[00227] Some coupling agents are attached to the surface through a free radical reaction, such as acrylates and methacrylates among others.

[00228] Some coupling agents do not directly react with the breath analyte. Rather, they are intermediate agents. An "intermediate agent" is a coupling agent whose chemical functionality is to react with yet another coupling agent. For example, diethylaminopropyl trimethoxysilane is an intermediate agent in the reaction with acetone. It does not directly react with acetone, but reacts with sodium nitroprusside, which in turn reacts with acetone. Another example of an intermediate agent would be the use of glycidoxypropyl triethoxysilane, whose epoxide functional group could be reacted with a host of other molecules to achieve a desired functionality. Numerous intermediate agents are known to those skilled in the art.

Example 1

[00229] Reactive chemistry for acetone is described.

[00230] Two sets of silica beads (130 mesh to 140 mesh) are coupled with either DEAPMOS or aminopropyltriethoxysilane (APTES). 3 g of silica beads are placed in a mixture of 8.1 mL 2-propanol, 1.2 mL 0.02N HCl, and 2.7 mL APTES or alternatively, 1.5 g of beads are placed in a mixture of 4.05 mL 2-propanol, 0.6 mL 0.02N HCl, and 1.35 mL DEAPMOS. Beads are vortexed for a few seconds and then allowed to rock for 10 min at room temperature. Then the beads are centrifuged briefly to pellet the beads at the bottom of the tube. The excess solution is decanted off, leaving the beads with enough DEAPMOS or APTES mixture to just cover them. Then the beads are incubated at 90°C for 1 to 2 hrs, until they are completely dry. The DEAPMOS beads are further coupled to sodium nitroprusside (SNP). 3.75 mL of SNP solution (10% SNP, 4% $MgSO_4$ in diH_2O) are added to 1.5 g of DEAPMOS coupled beads, which is then rocked for 5 min at room temperature. The fluid is then pulled off by vacuum filtration. Then the beads are dried under vacuum at room temperature for 2 hours.

[00231] 1.5 g of SNP reacted beads are added to 3.0 g of APTES coupled beads and shaken until evenly mixed. Approximately 0.025 g of mixed beads are placed in a glass capillary (0.25" long with a 2.7 mm inner diameter). 450 mL of breath sample in a tedlar bag is pumped across a $CaCl_2$ pretreatment section (0.35" long, 0.25" id) and then the beads at 150 mL/min. A developer solution (0.5% ethanolamine in 25% dimethylsulfoxide in methanol) is added to the beads. After a period of 1 to 3 minutes, a blue color bar appears if acetone is present at levels above 0.1 ppm. The length of the color bar increases with increasing concentrations of acetone.

Example 2

[00232] Reactive chemistry for acetone is described.

[00233] A concentrated solution of DNPH is made by dissolving 20 mg of DNPH in 40 uL of concentrated sulfuric acid at 90C for 5 to 10 min. 8 uL of this solution is added to 200 uL of propanol. 0.1 g of 130 to 140 mesh silica beads are added to the solution and after briefly vortexing, are incubated at 90C for 1 hr until the beads are dry and free flowing.

[00234] Prepared beads are placed in a glass capillary (0.25" long with a 2.7 mm inner diameter). 450 mL of breath sample in a tedlar bag is pumped across a $CaCl_2$ pretreatment section (0.35" long, 0.25" id) and then the beads at 150 mL/min. A dark yellow stain, whose length is concentration dependent, indicates the presence of acetone.

Example 3

[00235] Reactive chemistry for ammonia is described.

[00236] A concentrated bromophenol blue mixture is made by adding 0.1 g of bromophenol blue to 10 mL of propanol. After rocking for 1 hr, the mixture is ready for use. Not all the bromophenol blue will go into solution. From this stock solution, a 1:10 dilution is made in propanol. 200 uL of 0.1 N HCl are added to 4 mL of the 1:10 dilution and mixed. 1.8 g of 35 to 60 mesh silica beads with a 60 angstrom pore size are added to the mixture, vortexed and incubated at room temperature for 10 minutes. Then the beads are incubated at 80C for 25 min. The liquid should have evaporated, but the beads should still stick together. At this point, the beads are placed under vacuum for 1 hour to finish drying. Aliquots (about 0.05 g/aliquot) are made and stored in a freezer or under vacuum.

[00237] Prepared beads are placed in a glass capillary (0.25" to 1" long with a 1.2 mm inner diameter). 900 mL of breath sample in a tedlar bag is pumped across an Ascarite II pretreatment section (0.7" long, 0.25" id) and then the beads at 225 mL/min. A navy blue stain, whose length and kinetics of reaction are concentration dependent, indicates the presence of ammonia. The detection limit is less than 50 ppb.

Example 4

[00238] Reactive chemistry for oxygen is described.

[00239] Under dry nitrogen, 0.1 g of titanium trichloride are dissolved in 10 mL of acetone or acetonitrile. 200 uL of this solution is added to 0.1 g of 130 to 140 mesh silica beads. The mixture is dried at 90C for 1 hr.

[00240] Under dry nitrogen, a 0.25" long glass capillary with a 2.7 mm id is filled with the prepared beads and sealed air tight. During analysis, the seal is removed or pierced and 150 mL of breath sample in a tedlar bag is passed across the beads at 150 mL/min for 30 seconds. A length dependent color change from dark purple to colorless is observed based on the concentration of oxygen present. A silica gel bed at the end of the capillary should be used to trap released HCl.

Example 5

[00241] Reactive chemistry for carbon dioxide is described.

[00242] 0.1 g of crystal violet are dissolved in 10 mL of propanol. A 1:10 dilution is made in propanol. 10 uL 1M NaOH is added to 200 uL of this solution. Then 0.1 g of 130 to 140 mesh silica beads are added and mixed. The mixture is dried at 90C for 1 hr.

[00243] A 0.25" long glass capillary with a 2.7 mm id is filled with the prepared beads and sealed air tight. During analysis, the seal is removed or pierced and 150 mL of breath sample

in a tedlar bag is passed across the beads at 150 mL/min for 30 seconds. A length dependent color change from colorless to blue is observed based on the concentration of carbon dioxide present.

Example 6

[00244] Reactive chemistry for aldehydes is described.

[00245] A set of silica beads (100 mesh to 140 mesh) may be coupled with DEAPMOS. 1.5 g of beads are placed in a mixture of 4.05 mL 2-propanol, 0.6 mL 0.02N HCl, and 1.35 mL DEAPMOS. The acid in the solution during coupling creates a positive charge on the tertiary amine in addition to catalyzing the reaction. Beads are vortexed for a few seconds and then allowed to rock for 10 min. Then the beads are centrifuged briefly to pellet the beads at the bottom of the tube. The excess solution is decanted off, leaving the beads with enough DEAPMOS mixture to just cover them. Then the beads are incubated at 90°C for 1 to 2 hrs, until they are completely dry. The DEAPMOS beads are further coupled to either fuschin or pararosanilin. 3.75 mL of solution (0.2% fuschin or pararosanlin in diH_2O) is added to 1.5 g of DEAPMOS coupled beads, which is then rocked for 5 min. The fluid is then pulled off by a vacuum filter. Then the beads are dried under vacuum at room temperature for 2 hours.

[00246] Approximately 0.1 g beads are placed in a glass capillary (1" long with a 2.7 mm inner diameter). 450 mL of breath sample in a tedlar bag is pumped across the beads at 150 mL/min. A developer solution (0.2 M sulfuric acid) is added to the beads to catalyze the reaction. After a few minutes, a magenta color bar appears if aldehyde is present. The length and intensity of the color bar increases with increasing concentrations of aldehyde.

Example 7

[00247] One embodiment of the device is useful for measuring multiple analytes via distinct analyte cartridges in conjunction with a single base unit. For example, if the user is interested in measuring acetone, then an acetone cartridge is inserted into the device. If carbon dioxide is of interest, then a carbon dioxide cartridge is inserted into the device. Any of the chemistries described in this disclosure can be measured this way when: 1) all reactive chemistries are contained in cartridges that are closely matched in size so that the optical system of the base reader can sample the reactive beds properly, 2) the base unit that can adjust sample volume, 3) the base unit can adjust sample flowrate, 3) the base unit cartridge receptacle height is adjustable to accommodate cartridges of variable heights, as necessary, and 4) the base unit is capable of delivering excitation light of suitable and possibly variable spectrum.

[00248] A system designed to measure acetone and ammonia through distinct cartridges but a single base unit is described in detail here. Analysis of other breath analytes, whose chemistries are described elsewhere, will be analogous to the description contained here. A base unit is comprised of an automated sliding clamp mechanism, as described earlier, whereby the means used to end the stroke to clamp the cartridge is done using either: a) knowledge of the required cartridge clamp height either acquired using visual cues in the cartridge itself, as discerned automatically using the camera or software, or entered manually into the base unit software, b) setting the clamping force, such that the clamping stroke ends when a particular force is required to advance it further. Measuring the current through a linear actuator is a means whereby the applied force can be ascertained and used to end the stroke advancement. The base unit is capable of adjusting sample volume by using a volumetric flow measurement system comprised of a differential pressure transducer, an ambient temperature sensor, an ambient pressure sensor, and appropriate algorithms to transform the raw sensor data into mass flow data. The volumetric flow rate can be adjusted in the base unit by using the mass flow data to provide feedback to the air pump, resulting in steady delivery at various flowrates despite potential variations in cartridge packing and resultant resistance to gas flow. The base unit contains lighting that is based on surface mount LEDs with white emission spectra. The LEDs may or may not be under computer control and their intensity variable. An acetone cartridge is comprised of a reactive bed size of 0.25" long with a diameter of 2.7 mm, with SNP beads as detailed in Example 1. A gas pretreatment section of the cartridge is upstream of the reactive bed and is comprised of anhydrous calcium chloride contained within a 0.35" long by 0.25" diameter region of the cartridge. Gases are delivered to the column at 150 standard cubic centimeters for approximately 3 minutes. Developer solution is contained in a breakable canister above the reactive bed such that breaking of the canister results in wicking of the developer solution into the reactive bed, producing a color which is easily evaluated by the optical system comprised of white LEDs, a miniature CMOS camera, and simple algorithms as discussed previously. The same base unit is also capable of evaluating color produced in an ammonia column which is based on the ammonia chemistry detailed in Example 3. The reactive bed is 0.25" to 1" long with a 1.2 mm diameter. A gas pretreatment column is comprised of Ascarite II which is 0.7" long and 0.25" diameter. 900 standard cubic centimeters of breath sample are passed over the reactive bed at 225 standard cubic centimeters per minute. No developer solution is required, and the optical system described earlier in this example is used to evaluate the developed color and to correlate that color to the concentration of ammonia in the breath.

Example 8

[00249] A multi-analyte cartridge with reactive chemistry in a single flow path is described here. In this example, a single cartridge is capable of measuring both ammonia and acetone in a single instance from a single source. In this example, the cartridge is configured to quantitatively assess acetone concentration (for example, between the breath concentration range of 0.5-5 ppm) and to only qualitatively assess ammonia concentration (for example, to assess whether or not the breath ammonia concentration is in excess of 0.5 ppm). The cartridge is comprised of reactive chemistries from Examples 1 and 3. A pretreatment region is comprised of anhydrous calcium chloride in the column size described in Example 7. Into a 2.7 mm ID column of length 0.3625" is first deposited a layer of 0.05" of ammonia reactive particles. A bead separation plug of porous plastic (1/16" thick, 50-90 micron pores, hydrophilic polyethylene) is placed over the ammonia layer, and then acetone beads are next deposited to a thickness of about 0.25". Alternatively, the bead sizes can be matched to obviate the separation membrane. A developer solution is contained in a canister above the column. Analysis of the breath sample is as follows: 450 standard cubic centimeters of breath sample are pumped over the analytical column at 150 standard cubic centimeters per minute. After the sample delivery, the optical system comprised of a CMOS camera and white LEDs assesses the color developed in the ammonia beads. Then, the developer solution is freed to react with the acetone beads. After a set development time, for example 3 minutes, the color in the acetone reactive bed is assessed using the same optical system. Note that addressable LEDs of different spectral emissions can be used to alter the sensitivity of the optical system. It may be beneficial for certain applications, for example, to assess acetone concentration using white LEDs as excitation sources and to assess ammonia concentration using blue LEDs, for example with peak excitation at 470 nm.

[00250] A conceptual modification to Example 8 uses multiple reactive chemistries in the same flow path to more accurately measure a single analyte of interest. In this example, the chemistries for carbon dioxide (and/or water) and ammonia are co-immobilized in a 1.2 mm ID column that is approximately 0.5" long. The concentration of carbon dioxide (and/or water) is used to compensate the apparent concentration of ammonia, as the ammonia reaction is a pH reaction that is susceptible to interference from concentrations of water and carbon dioxide that are found in human breath.

Example 9

[00251] This example details a means whereby multiple analytes in a single breath sample can be assessed using chemistries contained in multiple flow paths. The multiple flow paths

can be contained in a single cartridge or in multiple cartridges, although this example details the case of a single cartridge with multiple flow channels.

[00252] The hardware required for this embodiment (based on simultaneous detection of acetone and ammonia) consists of redundant or slight modifications to the hardware systems described earlier. A cartridge is molded with two channels for reactive chemistries and pre-conditioners. As the acetone channel requires a developer and the ammonia does not, the base unit contains a single ampoule breaking needle, positioned to interact with the acetone channel of the cartridge. The sampling pump system is also redundant, with a mass flow meter and sampling pump dedicated to each analytical channel. The ability to independently vary flow rate and delivered volume is preserved. Using a single pump and metering system to split the flow over the two analytical channels is less desirable since the flowrates are not independently variable and variability issues due to column packing impose a lack of control over the delivery volumes. Nevertheless, for some applications a single gas delivery system to drive both analytical channels can be useful. To detect the color development in the two channels, a single camera must either be focused to contain the entire region of interest (spanning two channels), contain movable optics (a mirror system which 'points' the camera to the appropriate channel), be itself movable (mounted on a sliding rail), or multiple cameras must be used.

Example 10

[00253] One method to increase the detection range for a given column is to vary the volume of gas that is flowed over a column. In general, lower detection limits can be achieved by increasing the volume of gas that is flowed over the column. For example, a cartridge may be tuned for 0.5-5 ppm acetone sensitivity range using a breath volume of 450 standard cubic centimeters. If the sample to be measured is anticipated to be within a lower range, for example 0.1-0.5 ppm acetone, a larger volume of gas can be flowed over the column to produce a color change similar to that produced with a lower volume of gas of higher concentration. Thus, for a given flowrate, the concentration of analyte in the gas can be determined using a calibration curve appropriate to the sample time. A limitation to this approach, however, is the consumption of pre-conditioning components. Doubling the volume of breath sampled requires a doubling of the desiccant action of anhydrous calcium chloride, for instance. Fortunately, over-packing of anhydrous calcium chloride does not have a dramatically deleterious effect on the acetone concentrations, so if this approach is to be used to extend the measurement range of devices by adjusting sample volumes, then the cartridge should be packed with desiccant appropriate to the lowest desired detection limit.

[00254] Reaction time can be used to assess the concentration of a sample. In this approach, the rate of change of color production is used to determine the analyte concentration in the sample. This works because, in general, the rate of chemical reaction, in addition to the final color achieved, is affected by the concentrations of the reactants. Thus, an optical system and appropriate algorithms will make a concentration assessment by taking multiple readings of the color and determining the color production rate. Calibration curves of color production rate vs. analyte concentration (under given conditions, for example sample volume, flowrate, and reaction temperature) can be produced and used to make more rapid assessments of analyte concentration. By adjusting the flowrate of gas through the columns, this approach enables the selection of various column sensitivities.

Example 11

[00255] All of the examples described thus far in this disclosure presume that all liquid reagent components are housed in a disposable cartridge and freed for reaction using a reaction initiator. For some applications, it may be preferable to house the liquid developer solutions inside the base unit and not in the disposable cartridge. A scheme for how this can be accomplished is shown in FIG. 44. In this scheme, a gas sample from a bag is evacuated using a first pump (1), which pushes the sample through a lower fixed jaw of a clamping mechanism (2), through the reactive column (3) with appropriate pre-conditioning components, through an upper movable jaw of a clamping mechanism (4), and out a three-way valve (5). When developer solution is required, the three-way valve (5) position is switched to allow flow of solution through a feed hose (6) from a pressurized liquid reagent bottle (7). A second pump (8) is used to apply pressure to the headspace of the bottle to cause the bottle contents to be drawn into the feed hose (6) and into the reactive bed of the cartridge (3). Alternative pump/valve configurations result in different swept volumes and different liquid contact points which may have certain advantages depending on the developer solution required for a given application. The advantages of this scheme are: a) the gas sampling path is never wetted by developer solution (that is, when inserting a second cartridge from analysis, the sampled gas does not need to blow through tubing that has been wetted by a previous development except downstream of the reactive bed), b) the second pump (8) does not contact the developer solution and thus does not require wettable materials particular to the application, and c) the liquid path is not exposed to the air (and fluid line drying) due to the three-way valve (5).

Example 12

[00256] Acetone Reagent and Cartridge preparation example. A method for measuring acetone in human breath is described here. Reagents to pack a cartridge were prepared as follows. APTES beads were made by adding 0.5 g 140 to 170 mesh silica gel to 200 ul APTES and 400 ul propanol. The beads were vortexed thoroughly for 10 seconds. 0.4 ml 1N H2SO4 was added and vortexed for 10 seconds. The beads were incubated at 80C for 10 minutes and then cured at 110C for 1 hour.

[00257] 1.67% and 6.67% solutions of SNP were made by dissolving SNP in 25% DMSO in methanol. Solutions are stored in light-proof containers. 20-30 mesh Ascarite II is available off the shelf and used as a scrubber and desiccant.

[00258] A cartridge is prepared for use as follows: a porous polyethylene disk, 1/16" thick is placed into a pocket in a plastic cartridge. A disk of fibrous polyethylene, also 1/16" thick but compressible to roughly 1/32" thickness is next inserted. 0.9 ml of Ascarite II are then added to a 5/16" diameter pocket. Another disk of porous polyethylene is pressed into the 5/16" diameter pocket to retain the Ascarite II. From the other end of the cartridge, 170 mesh APTES beads, as prepared above, are added to a reactive zone, comprising a region with extruded cross section of roughly 2 mm x 4.5 mm, channeled 4 mm deep, spilling over into the retention disk pocket by approximately 1 mm. A 1/8" thick porous polyethylene disk is firmly pressed into the pocket to tightly retain the APTES beads. An ampoule is dropped into the pocket above the 1/8" retention disk. (An ampoule is prepared by filling a 5/16" diameter polyethylene hollow cylinder with 75 microliters of 1.67% SNP in 25% DMSO in methanol, sealed at both ends with laminated polyethylene/foil). A 1/16" thick fibrous polyethylene disk is placed over the ampoule, and the cartridge is sealed on top and bottom with laminated polyethylene/foil barrier materials. The top barrier should compress against the fibrous polyethylene to hold the ampoule in position firmly and preclude the possibility of the ampoule shifting during operation to form an air gap between the bottom of the ampoule and the top of the porous polyethylene which retains the APTES beads into the reactive zone.

Example 13

[00259] Example of using a cartridge with the base and breath sample to measure acetone. An assay is performed as follows: A user breaths into a breath bag of approximately 500 ml volume. The bag is positioned in the bag receptacle, and a cartridge, prepared as illustrated above, is inserted into the base of the device. After clicking start on the base unit's computer interface, the cartridge is sealed with the base device's internal plumbing as the linear actuator engages the bottom of the cartridge. A needle in the bottom sealing piston pierces

the cartridge's bottom-side outer barrier. A needle from the top of the cartridge is brought down to pierce the cartridge's top-side outer barrier. The pump and pump flow rate hardware deliver approximately 400 ml of breath from the bag through the bottom side of the cartridge, with the gas passing first through the Ascarite II bed and then into the APTES bead bed. The gases flow past the ampoule and exhaust through the holes in the top barrier as recently punctured. After about 3 minutes, with gases delivered at about 135 standard cubic centimeters per minute (SCCM), the ampoule is broken with the top needle passing first through the top barrier of the ampoule and then through the bottom barrier. With the porous polyethylene tightly packed against the bottom of the ampoule, the SNP developer solution wicks easily through the APTES reactive bead. After approximately 3 minutes, an image is taken of the reactive zone and the amount of color formation is used to estimate the concentration of acetone that was in the breath sample.

We claim:

1. A system for sensing an analyte in breath of a patient, the system comprising:

a cartridge comprising a first container, a fluid container, and a reaction volume in fluid communication with the first container and the fluid container, the first container containing a first interactant and the fluid container containing a fluid, wherein the fluid container has an initial fluid level and a space above the initial fluid level; and

a base comprising

a flow path for flow of the breath within the base,

a breath input receiver in fluid communication with the flow path that receives the breath and directs the breath into the flow path,

a cartridge housing that detachably receives the cartridge into the base so that the reaction volume is in fluid communication with the flow path,

a dispensing device that creates a hole in the fluid container below the initial fluid level and that moderates pressure in the space above the initial fluid level as the fluid moves out of the liquid container so that the fluid moves out of the liquid container and into the reaction volume, thereby facilitating an optical change in the reaction volume in relation to at least one of a presence and a concentration of the analyte, and

an optical subsystem that senses the optical change and generates an output comprising information about the analyte in response to the optical change.

2. A system as recited in claim 1, wherein the first container and the liquid container are adjacent to one another.

3. A system as recited in claim 1, wherein the reaction volume is within the first container.

4. A system as recited in claim 1, wherein the liquid container comprises a first sealed surface disposed above the liquid and above the space, and the first sealed surface comprises a pressure actuated seal that opens when pressure on the seal reaches a predetermined level.

5. A system as recited in claim 1, wherein the liquid container comprises a second sealed surface disposed below the liquid, and the second sealed surface comprises a pressure actuated seal that opens when pressure on the pressure actuated seal reaches a predetermined level.

6. A system as recited in claim 1, wherein the liquid container has an exterior surface at the hole, and a wicking material is disposed at the exterior surface at the hole.

7. A system as recited in claim 6, wherein:

the first container comprises a top surface; and

the exterior surface of the liquid container is adjacent to the top surface of the first container, so that the wicking material contacts the exterior surface of the liquid container at the hole and the wicking material contacts the top surface of the first container.

8. A system as recited in claim 7, wherein the wicking material contacts the exterior surface of the liquid container at the hole and the wicking material contacts the top surface of the first container without an air gap.

9. A system as recited in claim 1, wherein the liquid container is opaque to ambient light.

10. A system as recited in claim 1, wherein the liquid container is opaque to ambient light.

11. A system as recited in claim 1, wherein the reaction volume is opaque to ambient light.

12. A system as recited in claim 1, wherein the dispenser comprises an elongated member and an actuator for moving from an initial position wherein the elongated member is outside the liquid container to a deployed position in which the elongated member has created the hole in the fluid container below the initial fluid level and has moderated the pressure in the space above the initial fluid level so that the fluid flows out of the liquid container and into the reaction volume.

13. A system as recited in claim 1, wherein the elongated member comprises a needle.

14. A system as recited in claim 1, wherein the elongated member comprises a rod.

15. A system as recited in claim 1, wherein the elongated member comprises a fluid channel.

16. A system as recited in claim 12, wherein the liquid container comprises a first sealed surface disposed above the liquid and above the space, and the first sealed surface comprises a material that produces a hole when the elongated member contacts the material with a predetermined level of force.

17. A system as recited in claim 12, wherein:

the liquid container comprises a first sealed surface disposed above the liquid, and a second sealed surface below the liquid; and

the elongated member extends through the first and second sealed surfaces.

18. A system as recited in claim 12, wherein the elongated member extends through the liquid container in a first location that is above the initial liquid level and in a second location that is below the initial liquid level.

19. A system as recited in claim 1, wherein the fluid container comprises a plurality of fluid subcontainers.

20. A system as recited in claim 19, wherein the plurality of fluid subcontainers are disposed adjacent to one another along a line.

21. A system as recited in claim 19, wherein the plurality of fluid subcontainers are disposed adjacent to one another in a carousel.

22. A system as recited in claim 1, wherein the base further comprises a pump to facilitate movement of the breath in the flow channel and through the reaction volume.

23. A system as recited in claim 1, wherein the base comprises a pump that facilitates flow of the liquid from liquid container.

24. A system as recited in claim 1, wherein the base comprises a pump that moderates pressure in space above liquid in liquid container.

25. A system as recited in claim 1, wherein:

the liquid container comprises a first sealed surface disposed above the liquid and above the space;

the first sealed surface comprises a pressure actuated seal that opens when pressure on the seal reaches a predetermined level; and

the base comprises a pump facilitates opening of the pressure actuated seal.

26. A system as recited in claim 1, wherein:

the liquid container comprises a second sealed surface disposed below the liquid;

the second sealed surface comprises a pressure actuated seal that opens when pressure on the pressure actuated seal reaches a predetermined level; and

the base comprises a pump facilitates opening of the pressure actuated seal.

27. A system as recited in claim 1, wherein the cartridge comprises a shroud the blocks ambient light from impinging upon the reaction volume when the cartridge is disposed in the base.

28. A system as recited in claim 1, wherein the liquid container comprises an exterior surface that blocks ambient light from impinging upon the liquid.

29. A method for sensing an analyte in breath of a patient, the method comprising:

providing a cartridge comprising a first container, a fluid container, and a reaction volume in fluid communication with the first container and the fluid container, the first container containing a first interactant and the fluid container containing a fluid, wherein the fluid container has an initial fluid level and a space above the initial fluid level;

providing a base comprising a flow path for flow of the breath within the base, a breath input receiver in fluid communication with the flow path, a cartridge housing, a dispensing device, and an optical subsystem;

inserting the cartridge into the cartridge housing of the base so that the reaction volume is in fluid communication with the flow path;

causing the breath to flow in the flow path and into the reaction volume;

after the breath has flowed through the reaction volume, using the dispensing device to create a hole in the fluid container below the initial fluid level and moderating pressure in the space above the initial fluid level as the fluid moves out of the liquid container so that the fluid moves out of the liquid container and into the reaction volume, thereby facilitating an optical change in the reaction volume in relation to at least one of a presence and a concentration of the analyte; and

sensing the optical change and generating an output comprising information about the analyte in response to the optical change.

30. A system for sensing an analyte in breath of a patient, the system comprising:

a cartridge comprising a reaction volume and a shroud that is opaque to ambient light; and

a base comprising

a flow path for flow of the breath within the base,

a breath input receiver in fluid communication with the flow path that receives the breath and directs the breath into the flow path and through the reaction volume, wherein

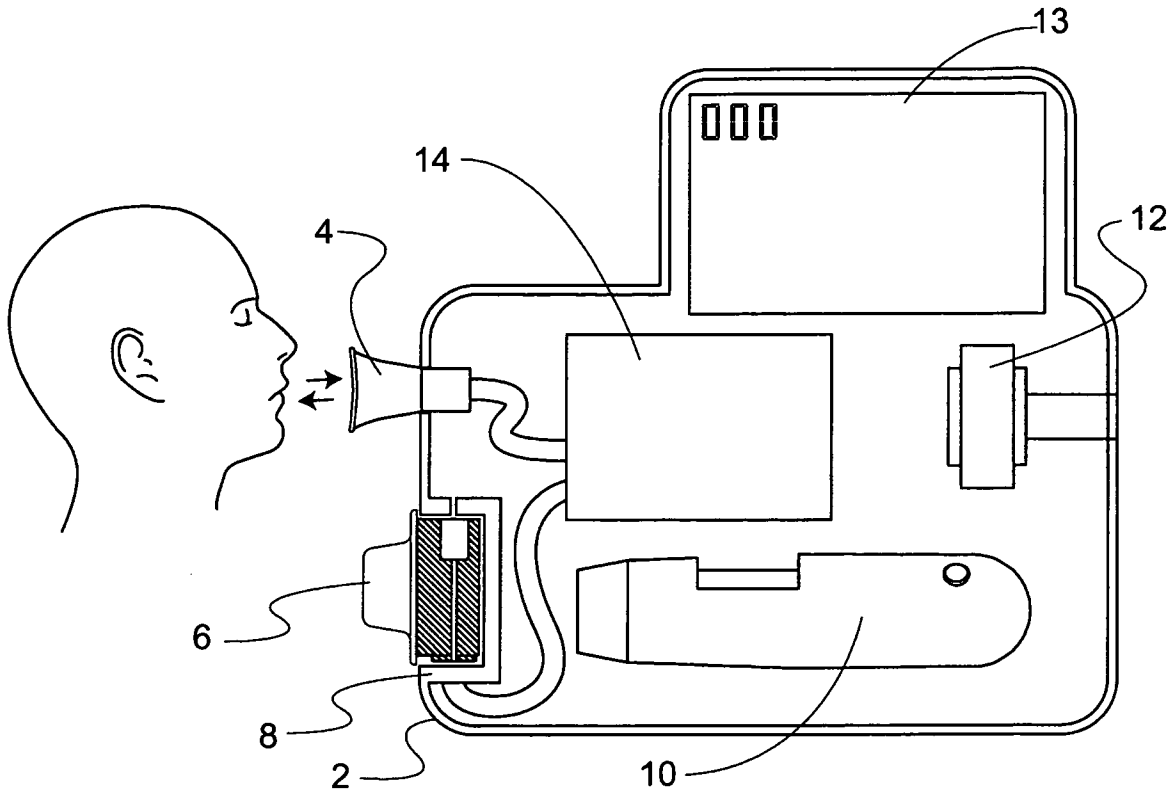
flow of the breath through the reaction volume facilitates an optical change to the reaction volume in relation to at least one of a presence and a concentration of the analyte,

a cartridge housing that detachably receives the cartridge into the base so that the reaction volume is in fluid communication with the flow path, wherein the shroud of the cartridge mates with the cartridge housing of the base to block ambient light from impinging on the reaction volume, and

an optical subsystem that senses the optical change and generates an output comprising information about the analyte in response to the optical change.

31. A cartridge for use in sensing an analyte in breath of a patient using a base, wherein the base comprises a flow path for flow of the breath within the base, a breath input receiver in fluid communication with the flow path that receives the breath and directs the breath into the flow path, a cartridge housing that detachably receives the cartridge into the base, and an optical subsystem that senses the optical change and generates an output comprising information about the analyte in response to the optical change, the cartridge comprising a reaction volume and a shroud that is opaque to ambient light, wherein the cartridge is configured to be detachably disposed in the cartridge housing so that reaction volume is in fluid communication with the flow path to receive the breath, wherein flow of the breath through the reaction volume facilitates an optical change to the reaction volume in relation to at least one of a presence and a concentration of the analyte, and wherein the shroud of the cartridge mates with the cartridge housing of the base to block ambient light from impinging on the reaction volume.

FIG. 1



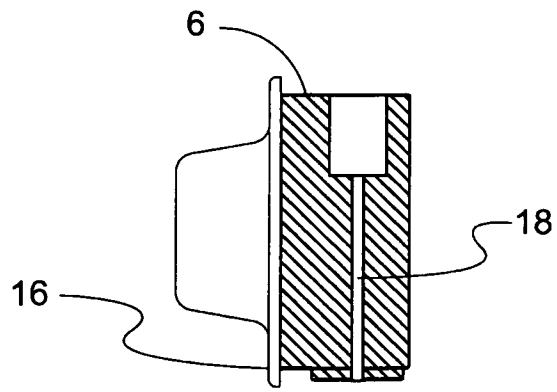


FIG. 2

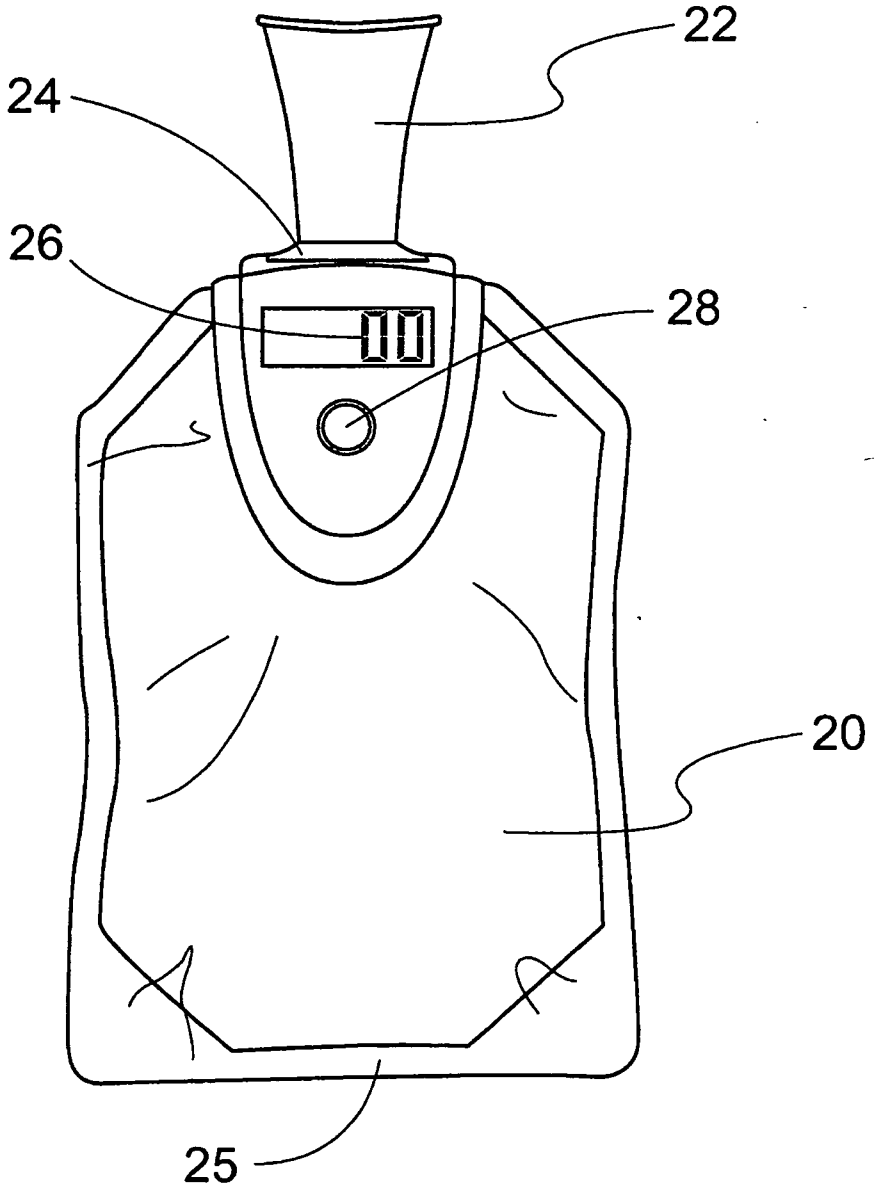
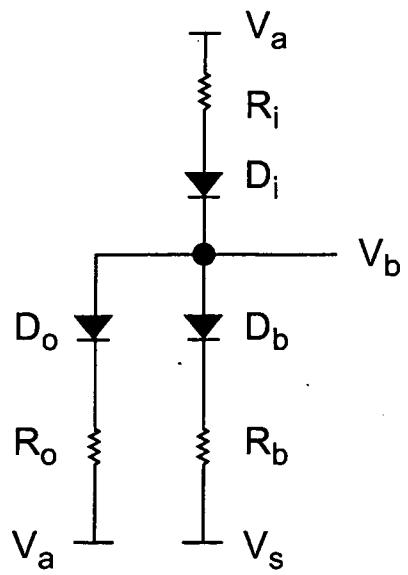


FIG. 3



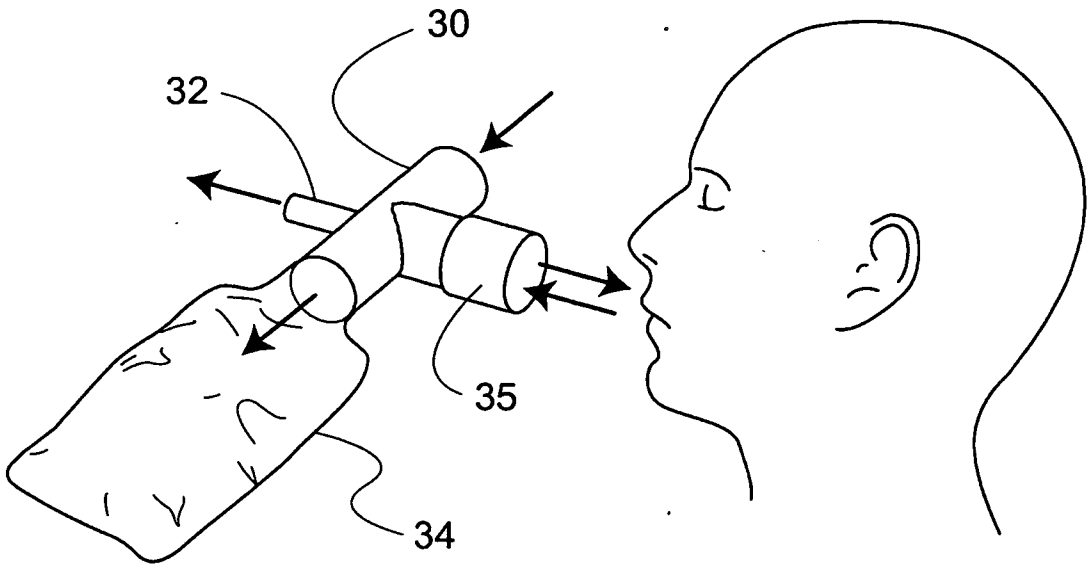


FIG. 4

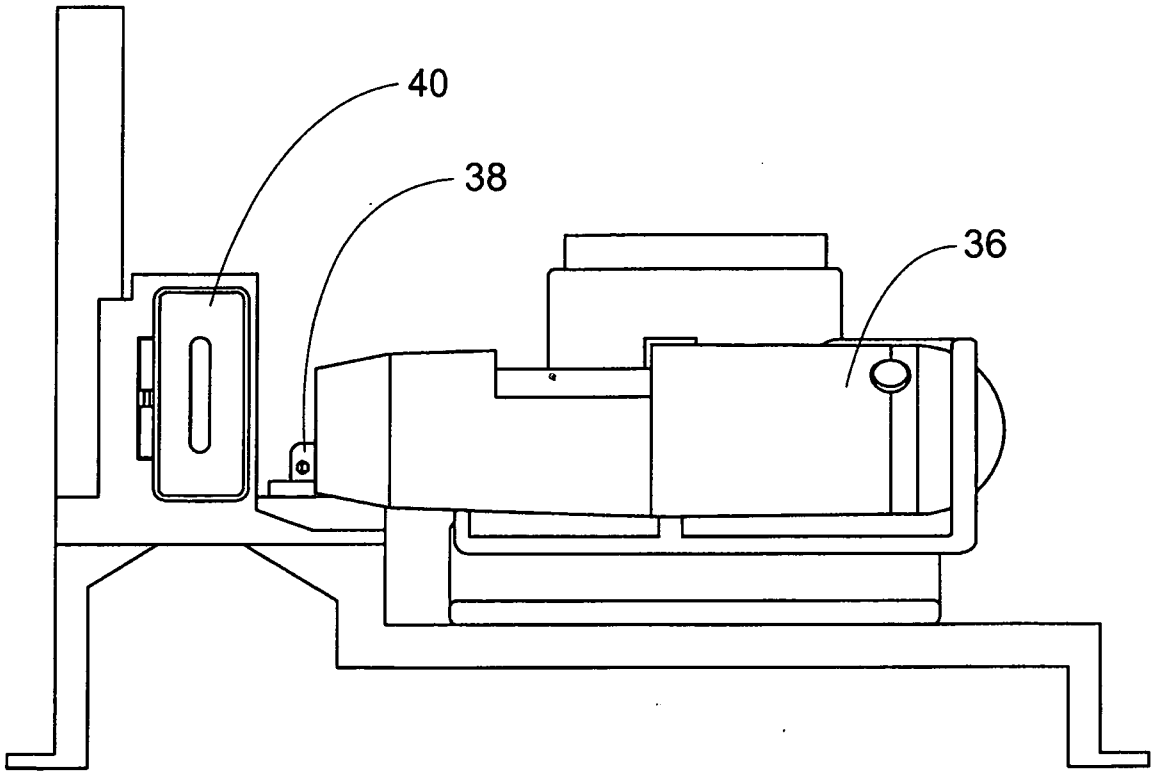


FIG. 5

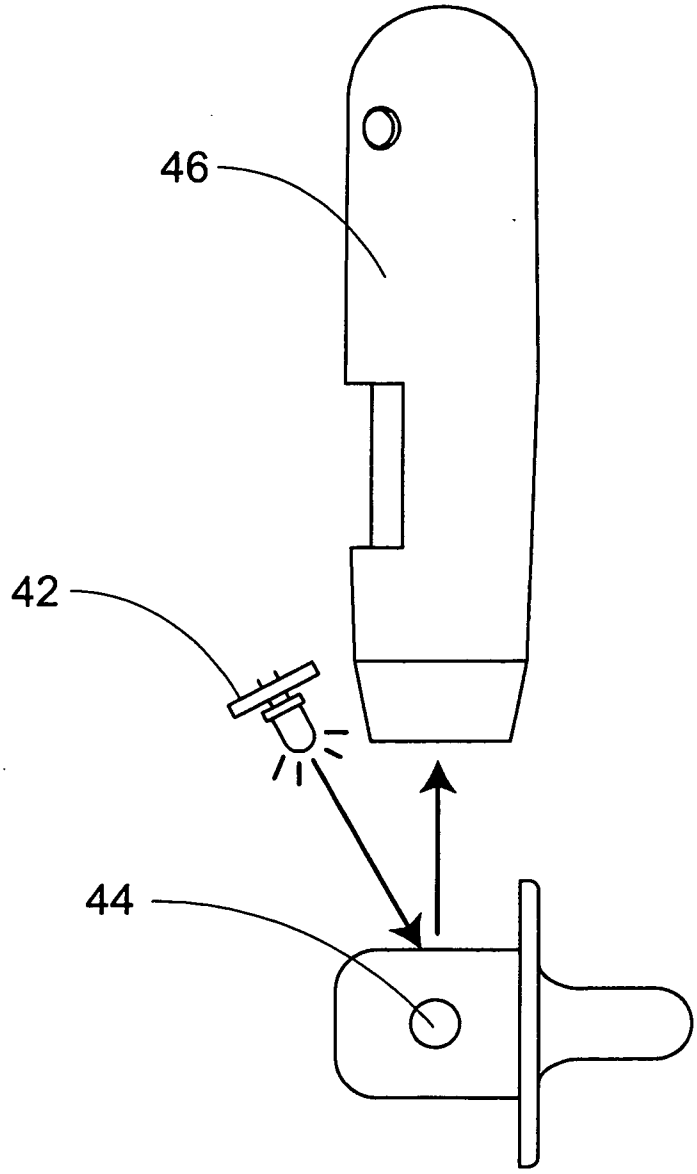


FIG. 6

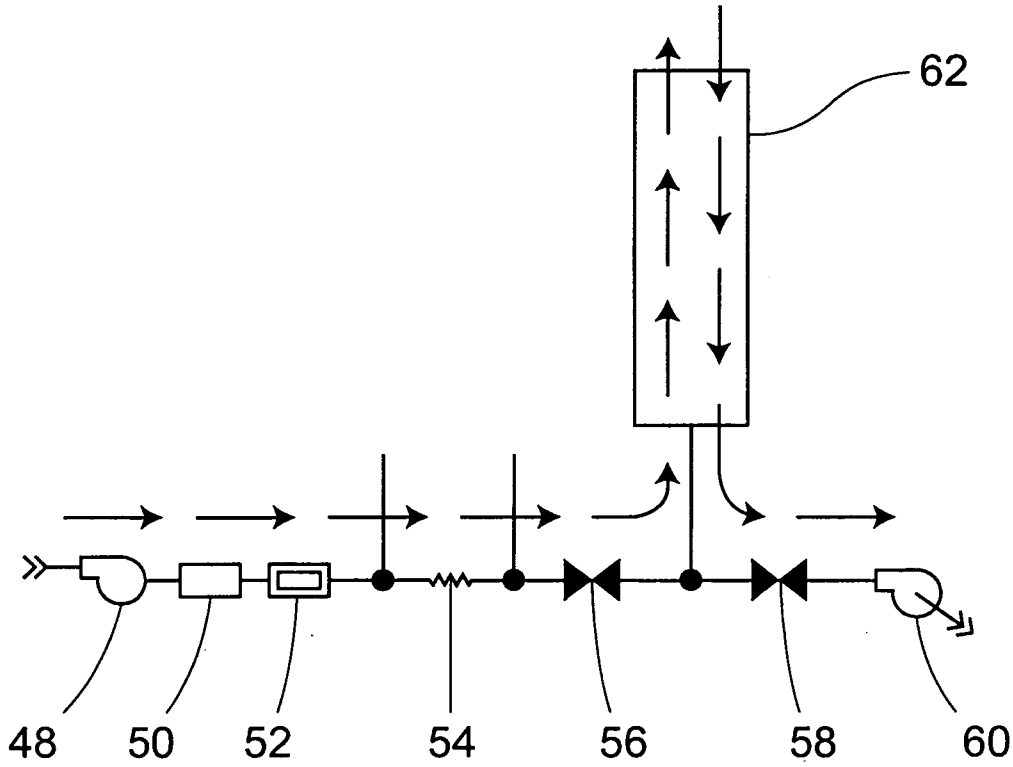
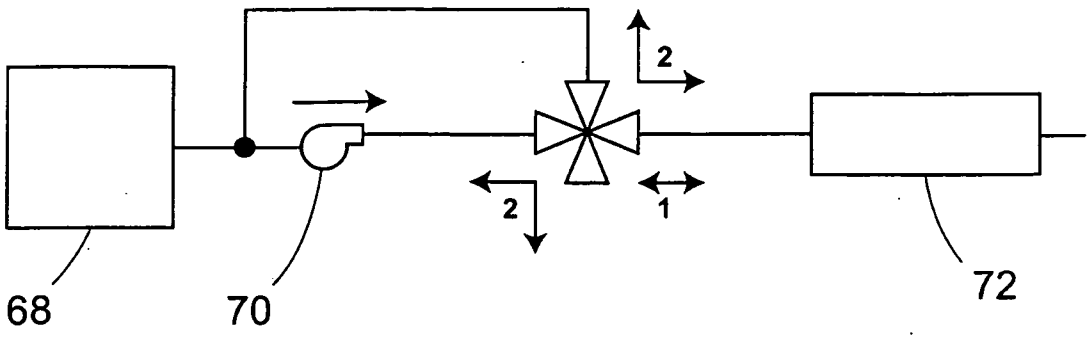


FIG. 7



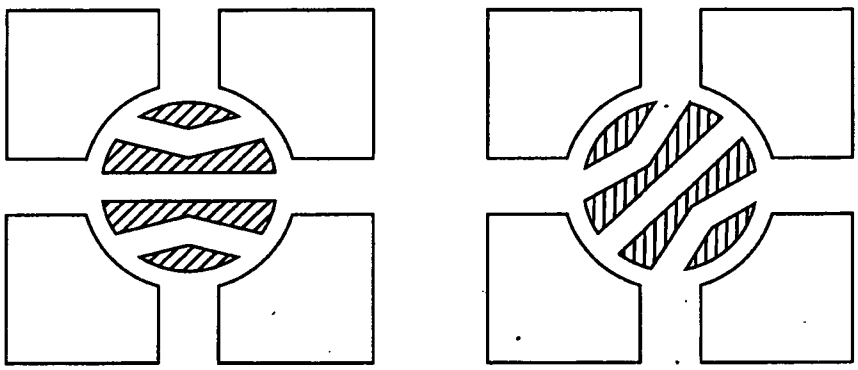


FIG. 8

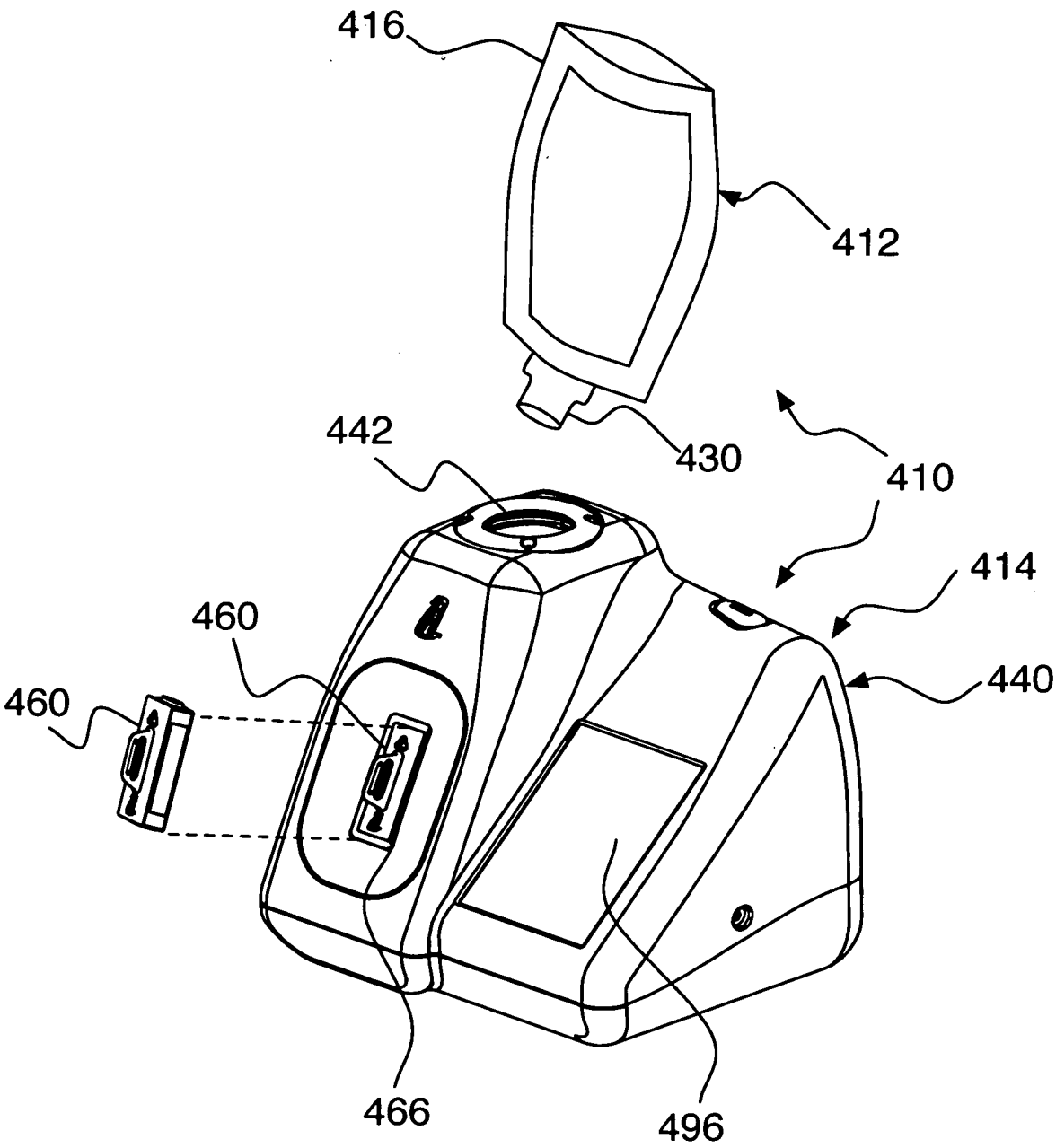


FIG. 9

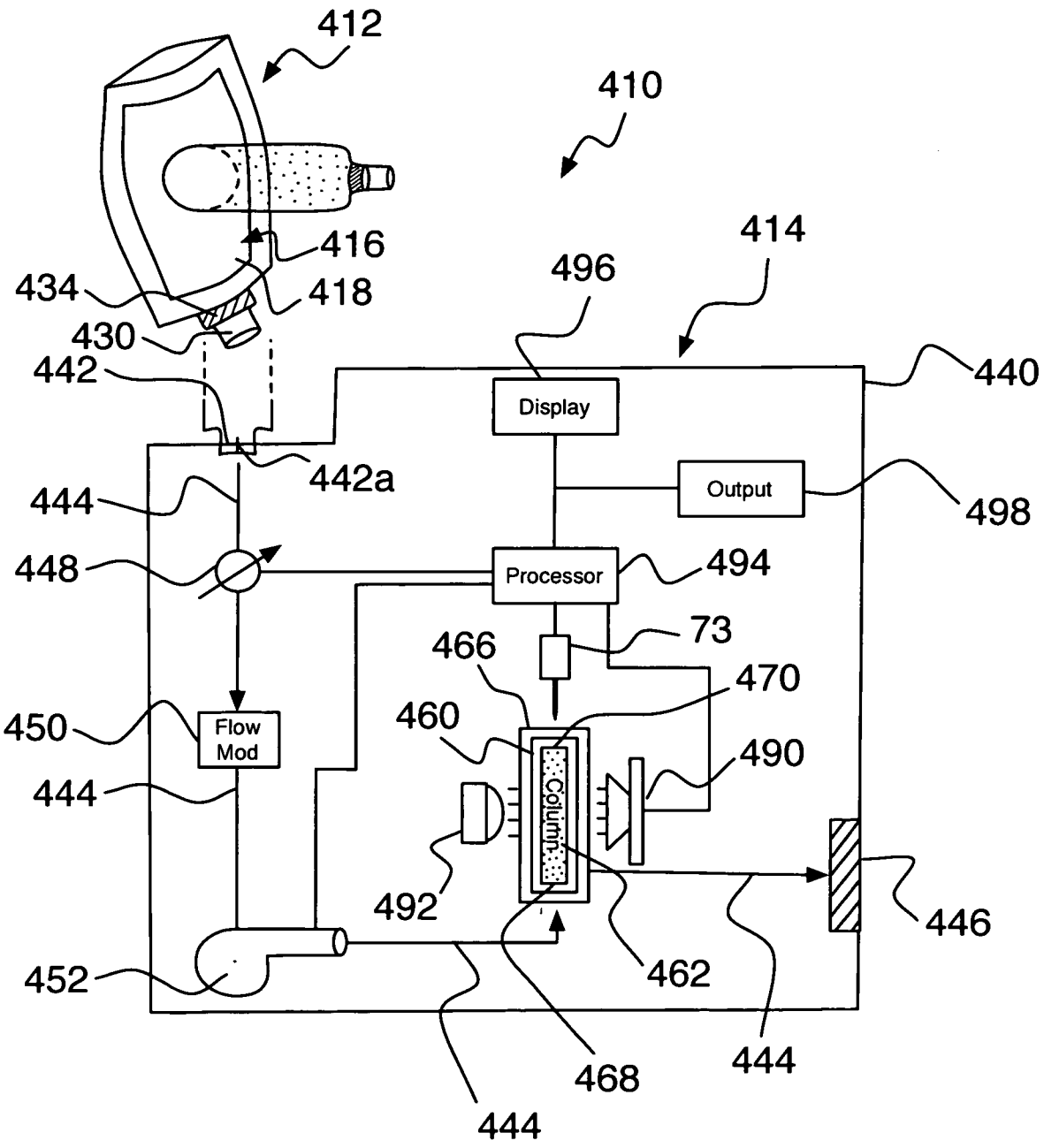

412
410
414
416
496
434
418
430
442
440
Display
442a
444
Output
498
448
Processor
494
73
466
470
450
Flow Mod
460
490
444
Column
492
446
452
462
468
444
444

FIG. 10

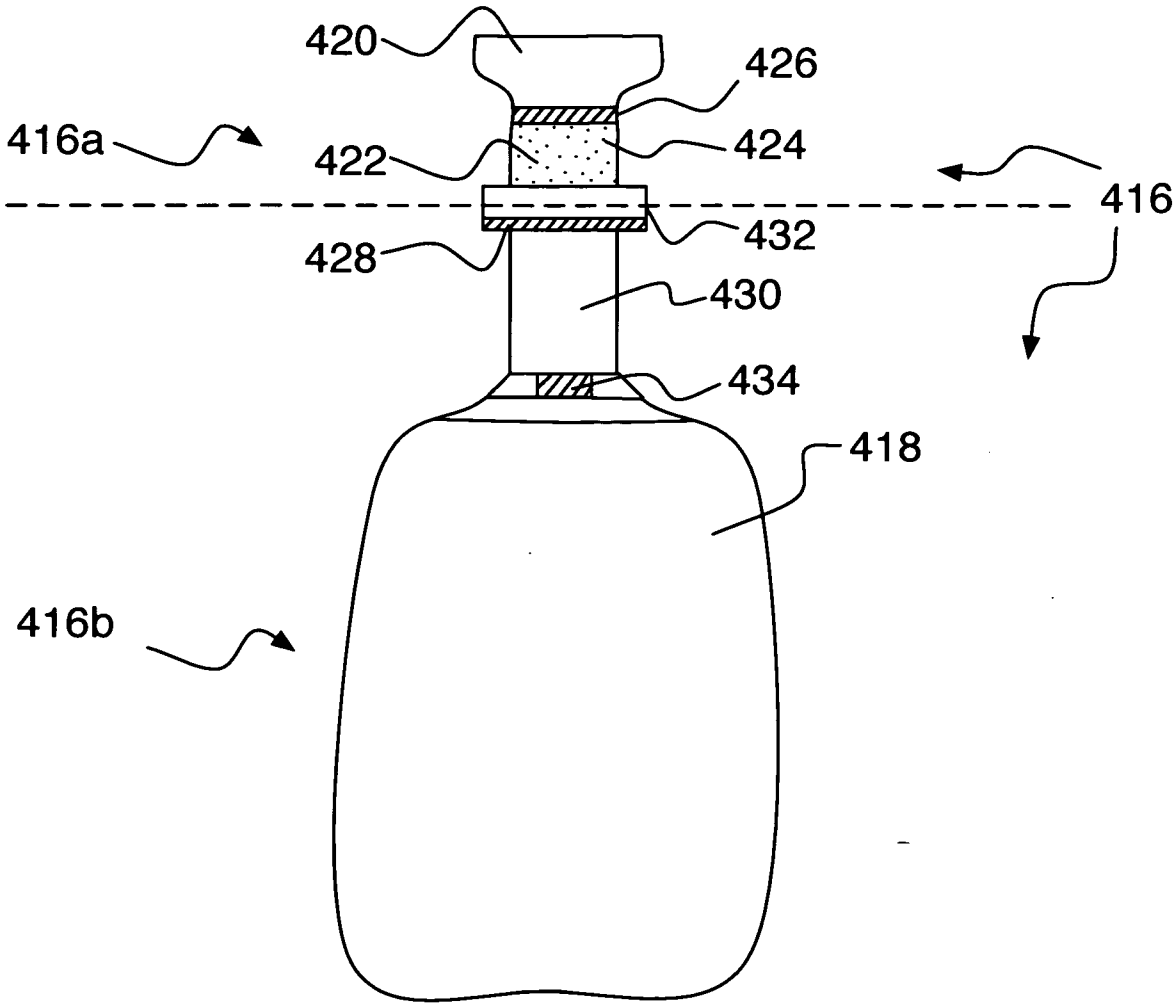


FIG. 11

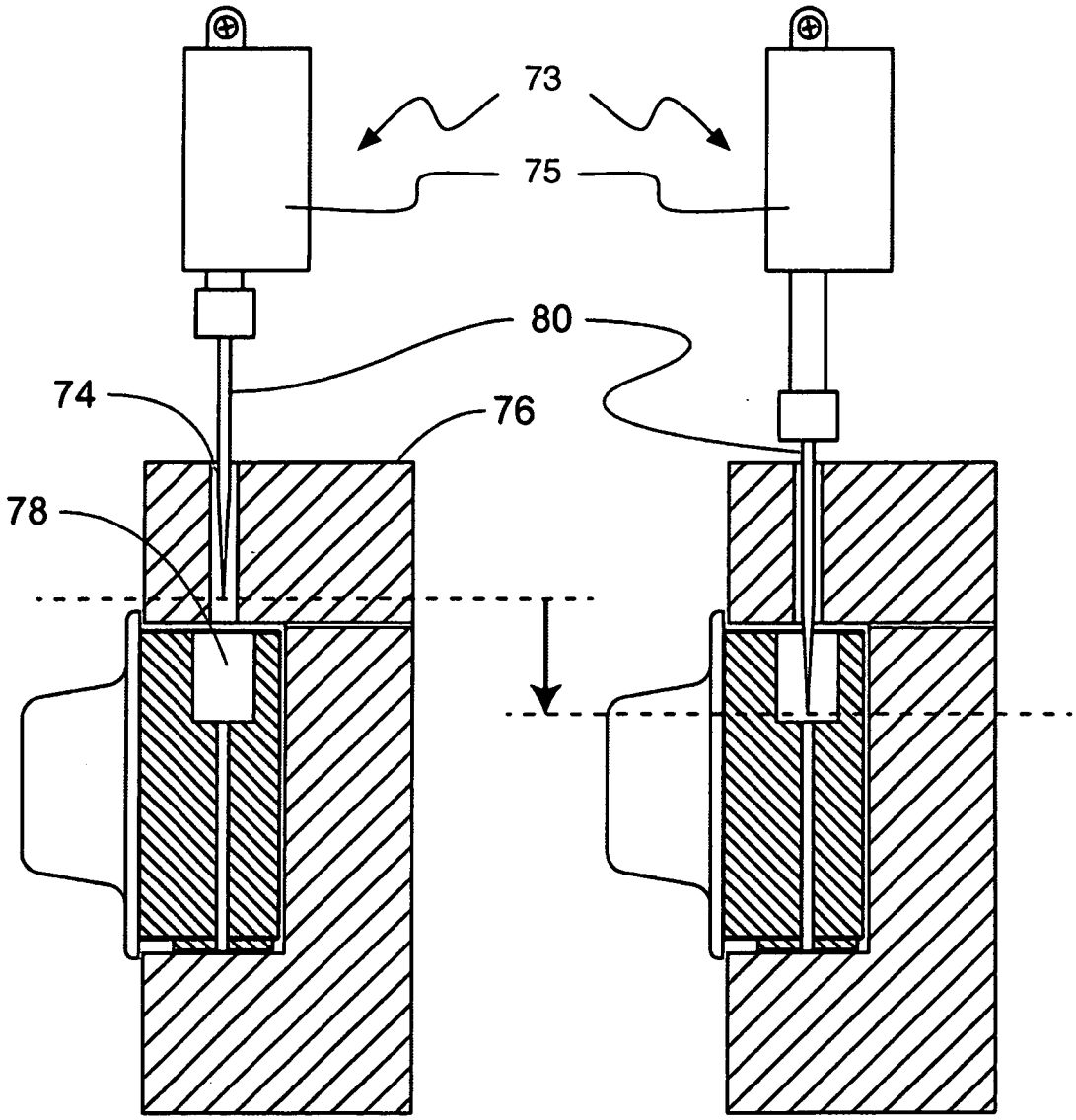


FIG. 12

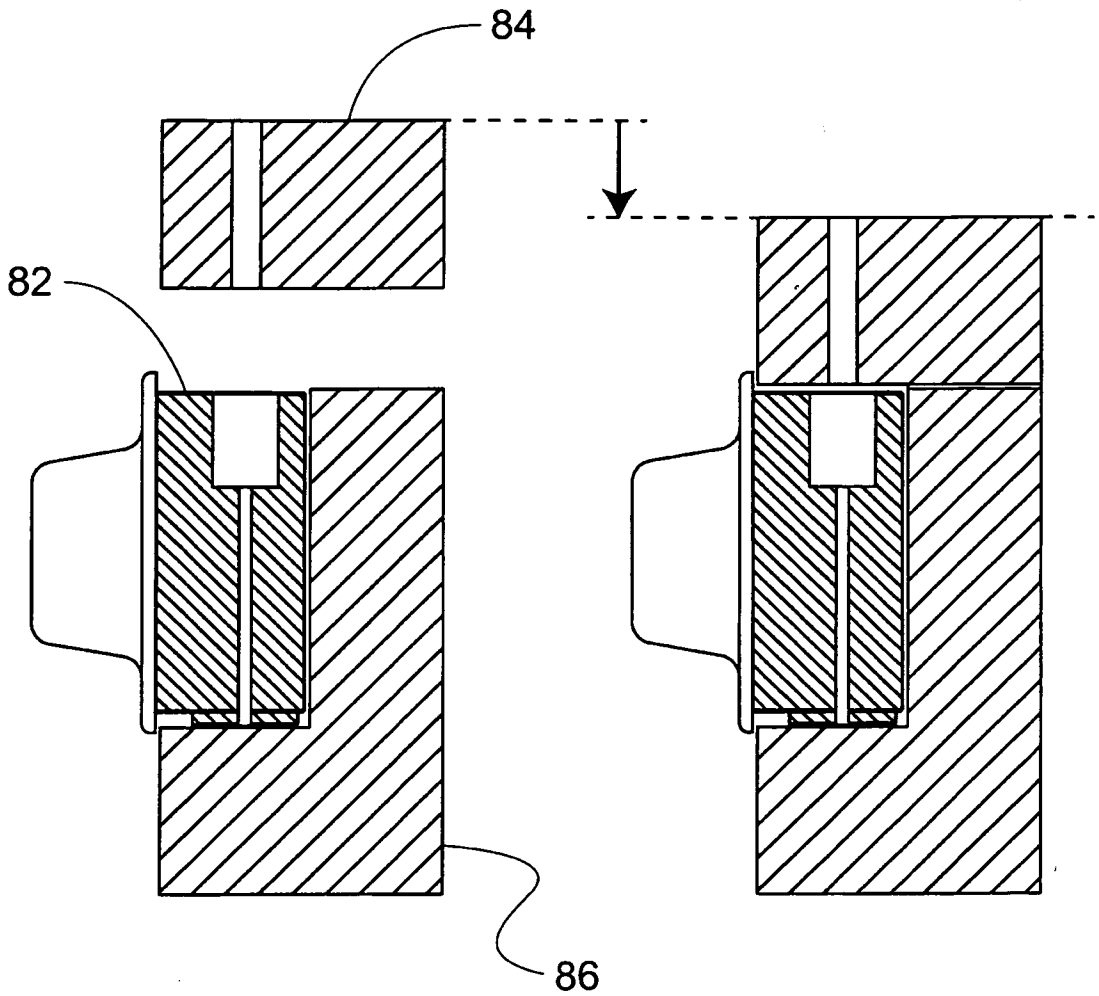


FIG. 13

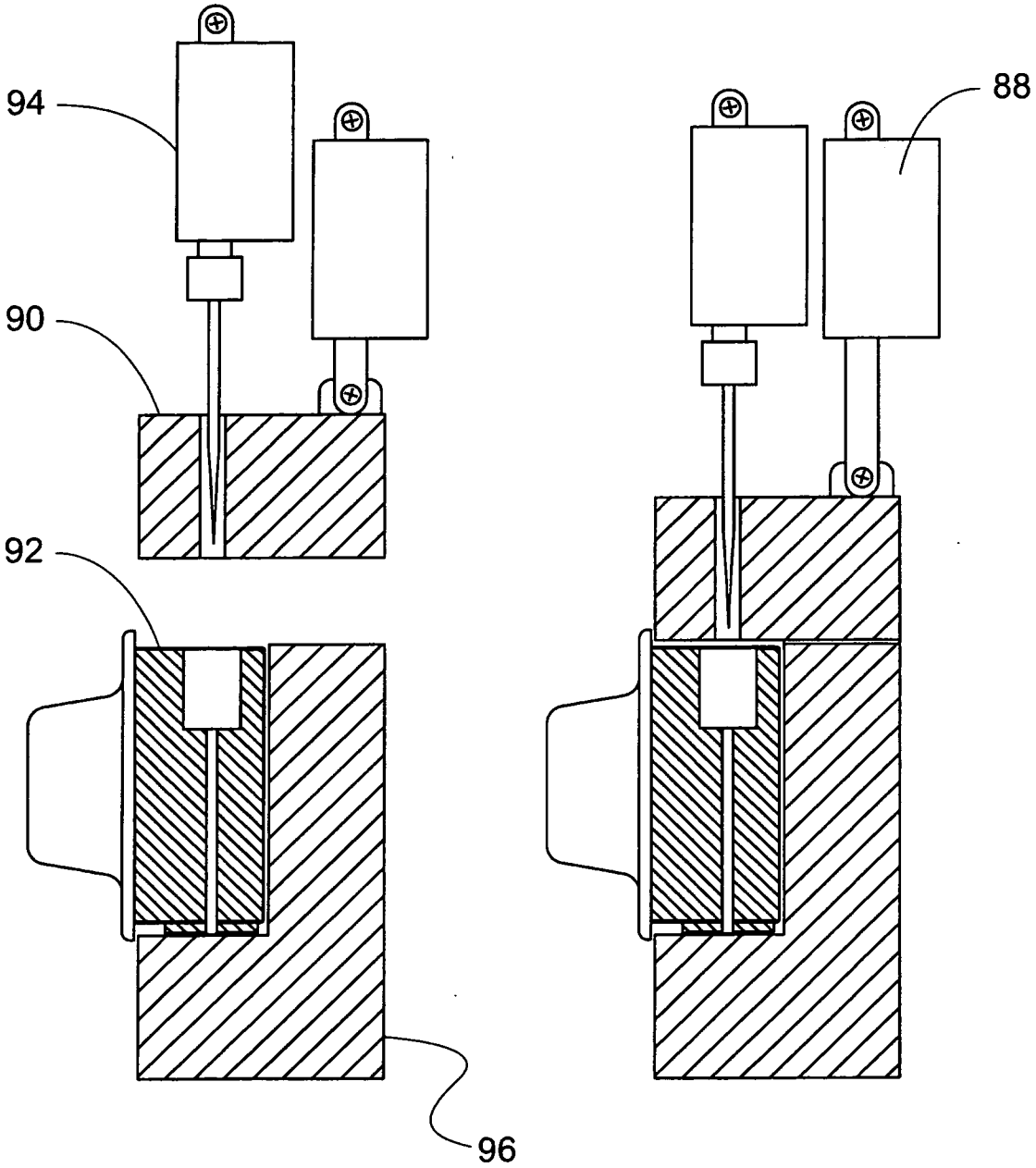


FIG. 14

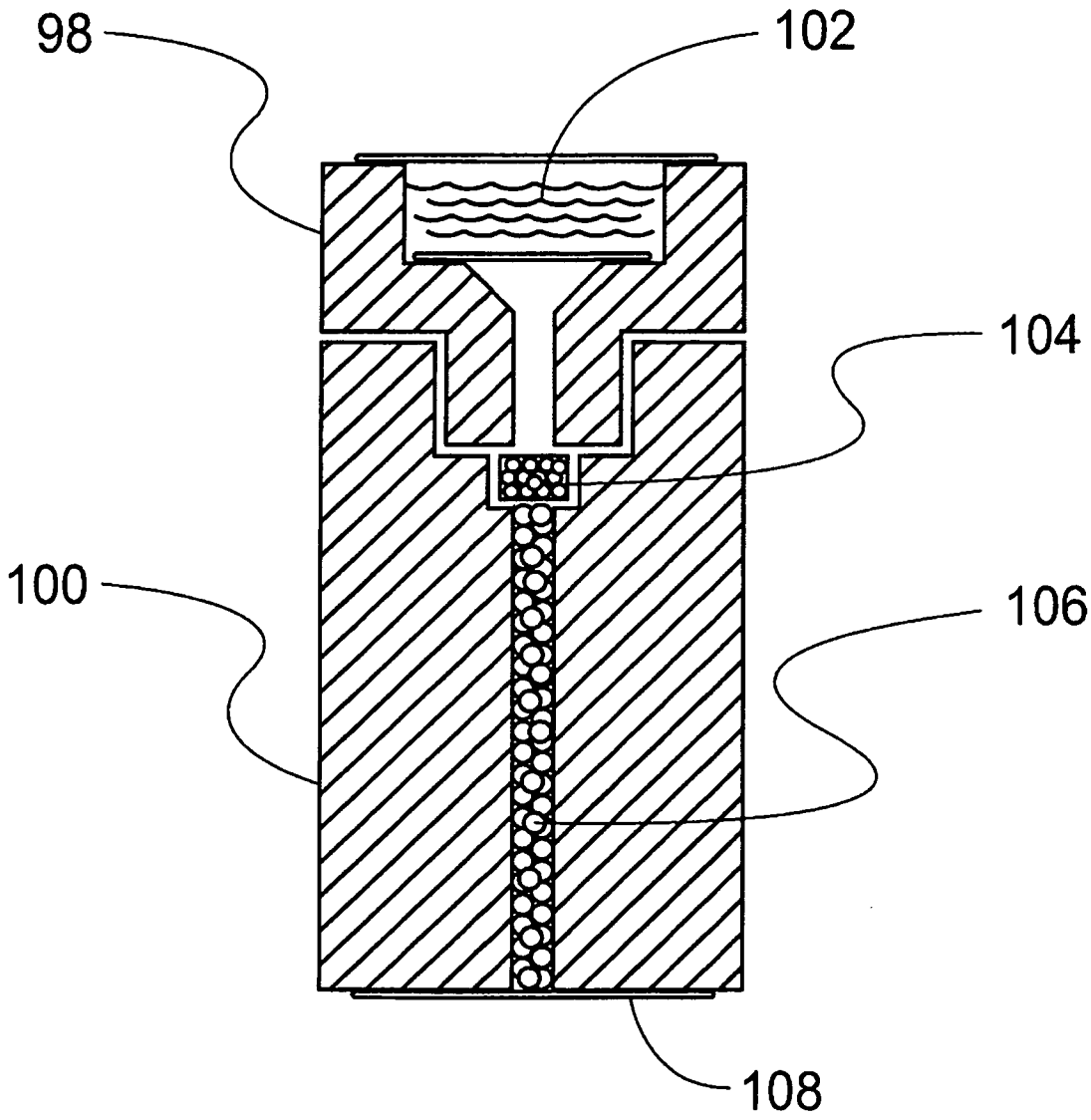


FIG. 15

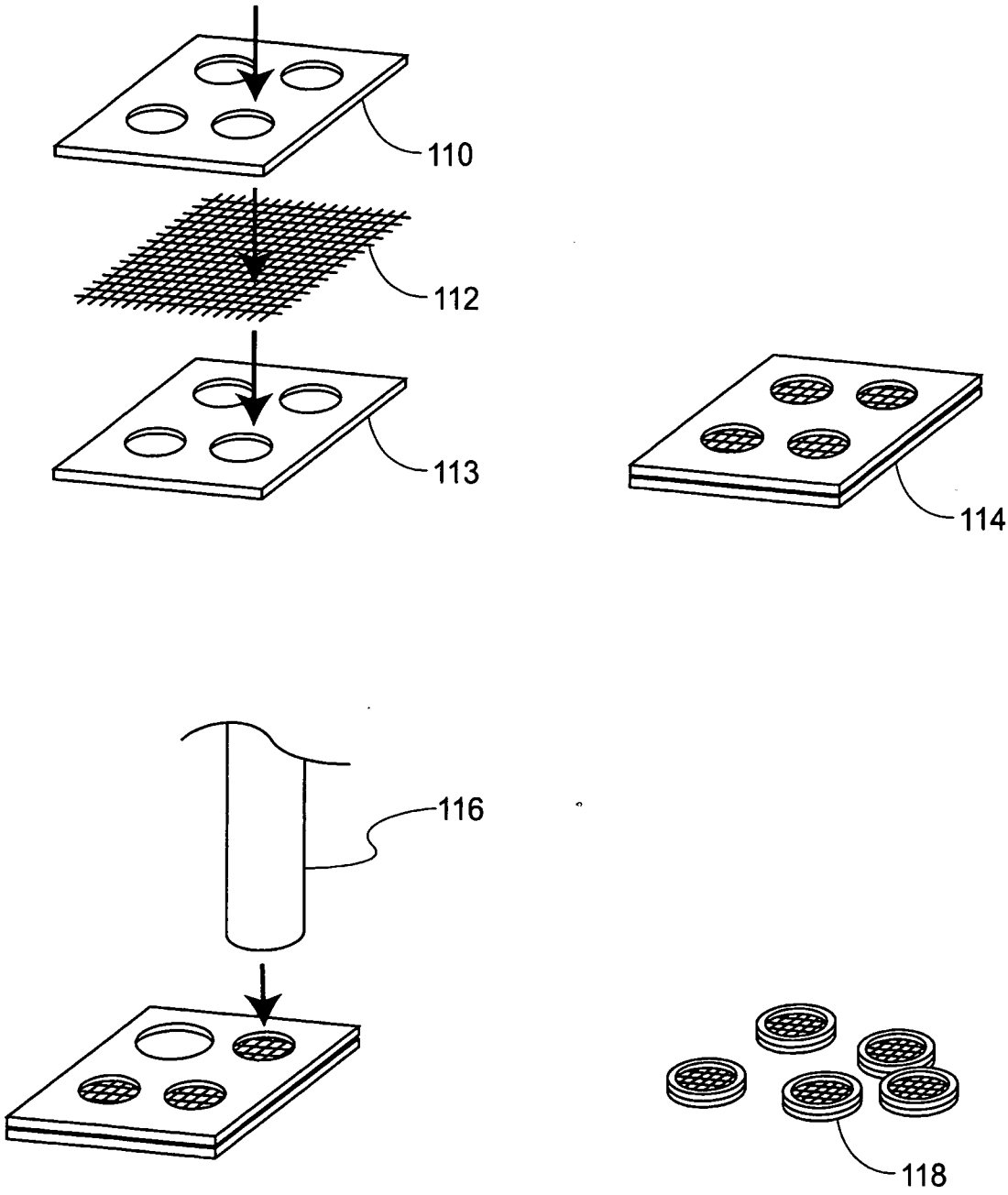


FIG. 16

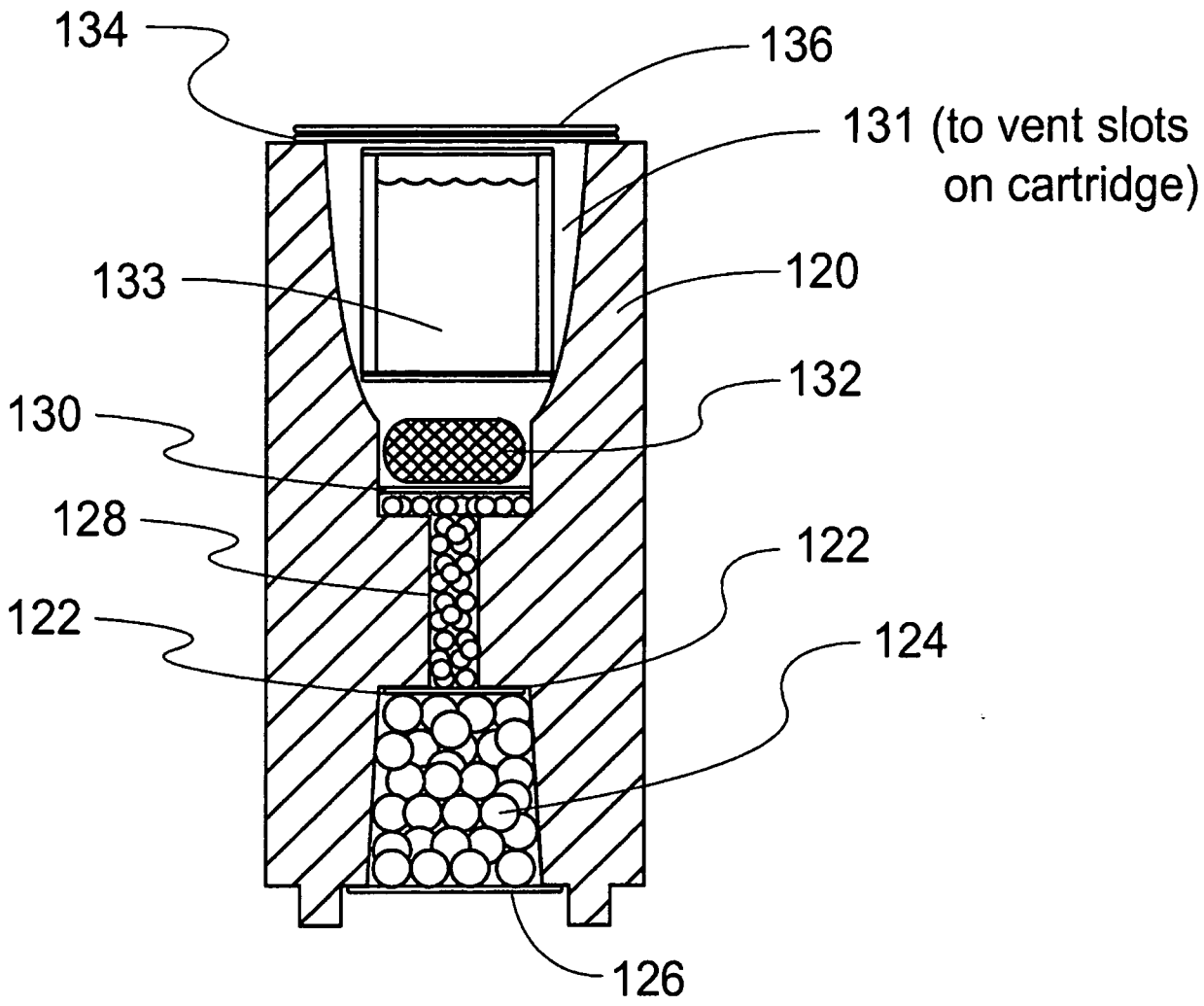

134
136
131 (to vent slots on cartridge)
133
120
132
130
128
122
122
124
126

FIG. 17

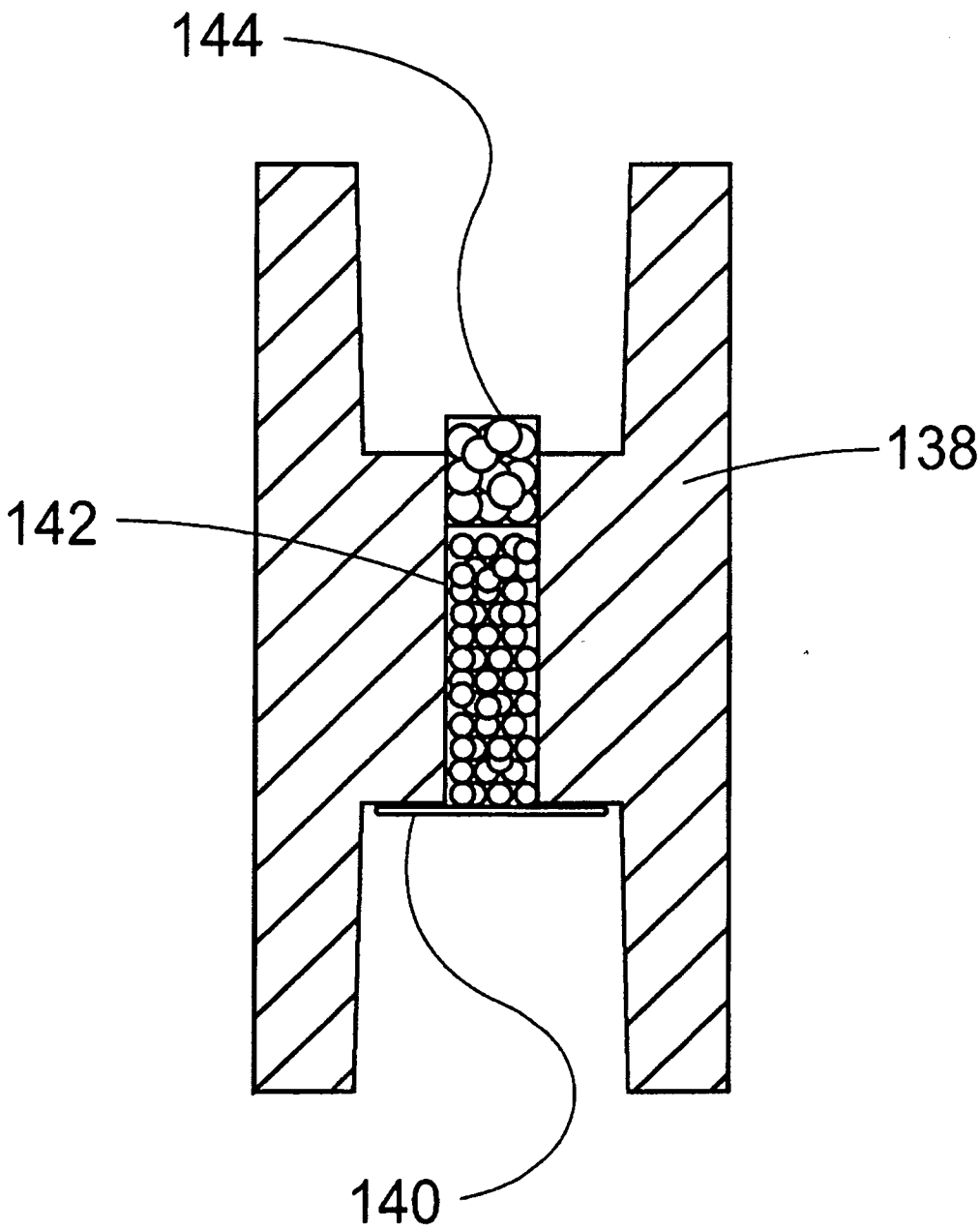


FIG. 18

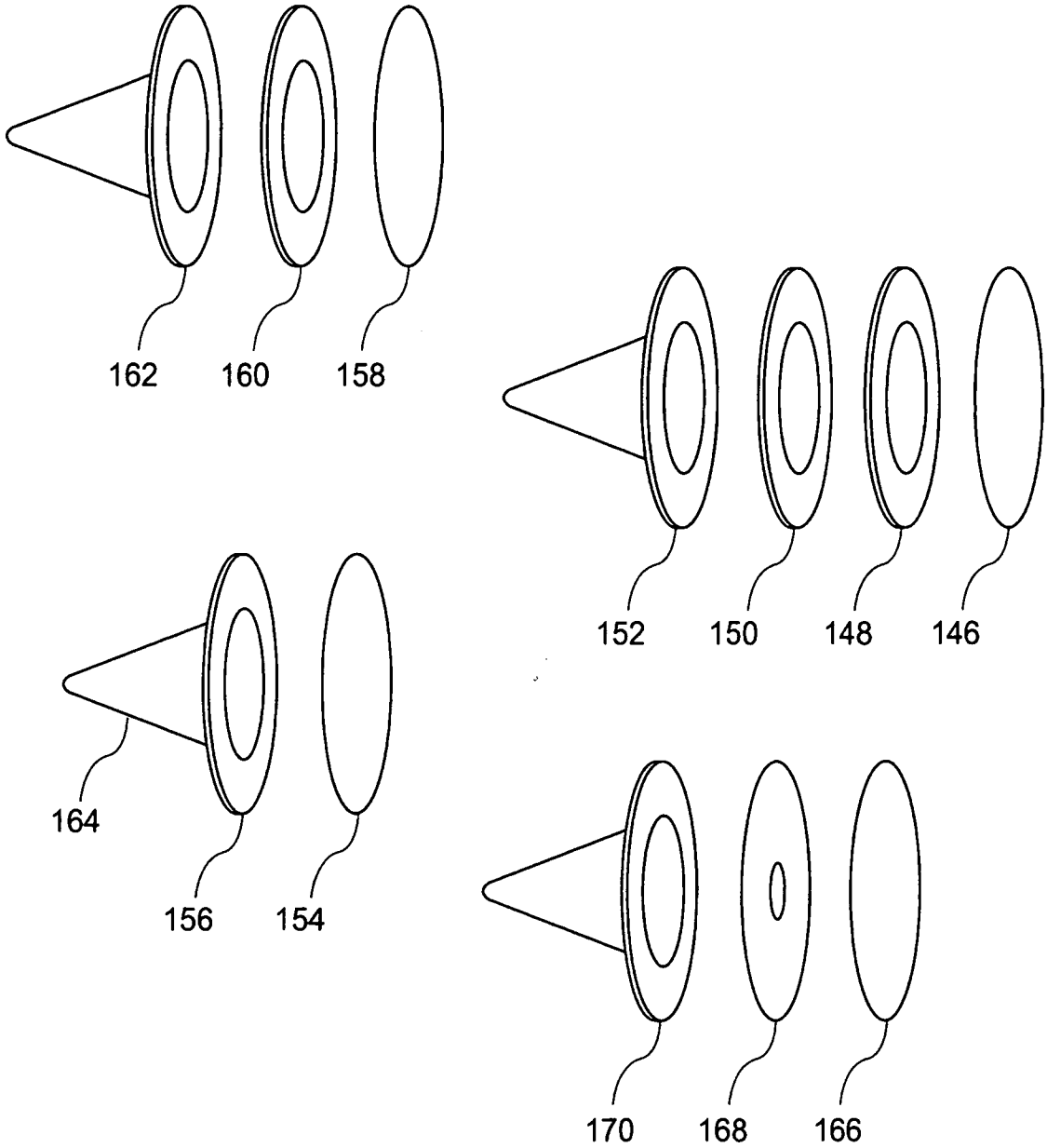


FIG. 19

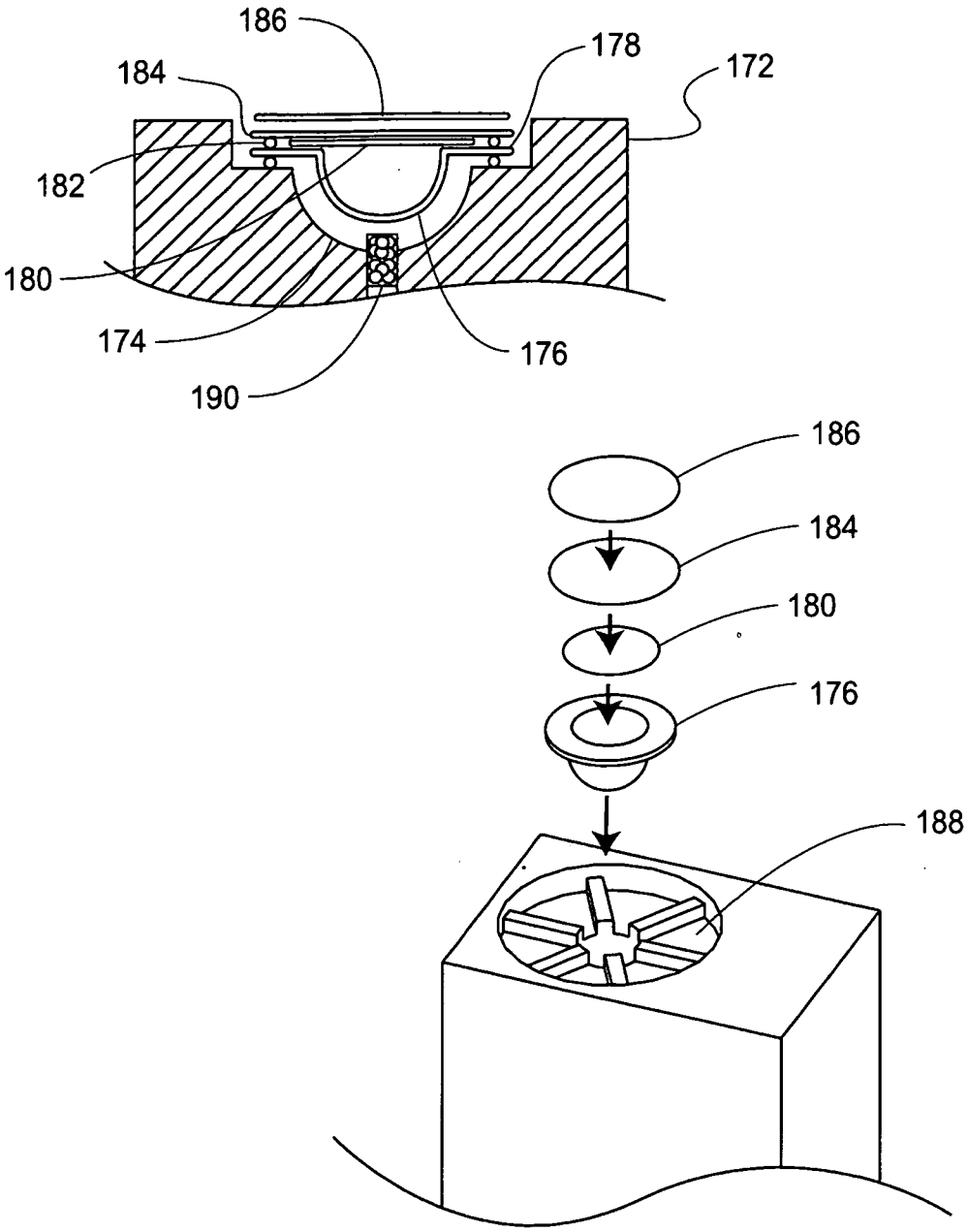


FIG. 20

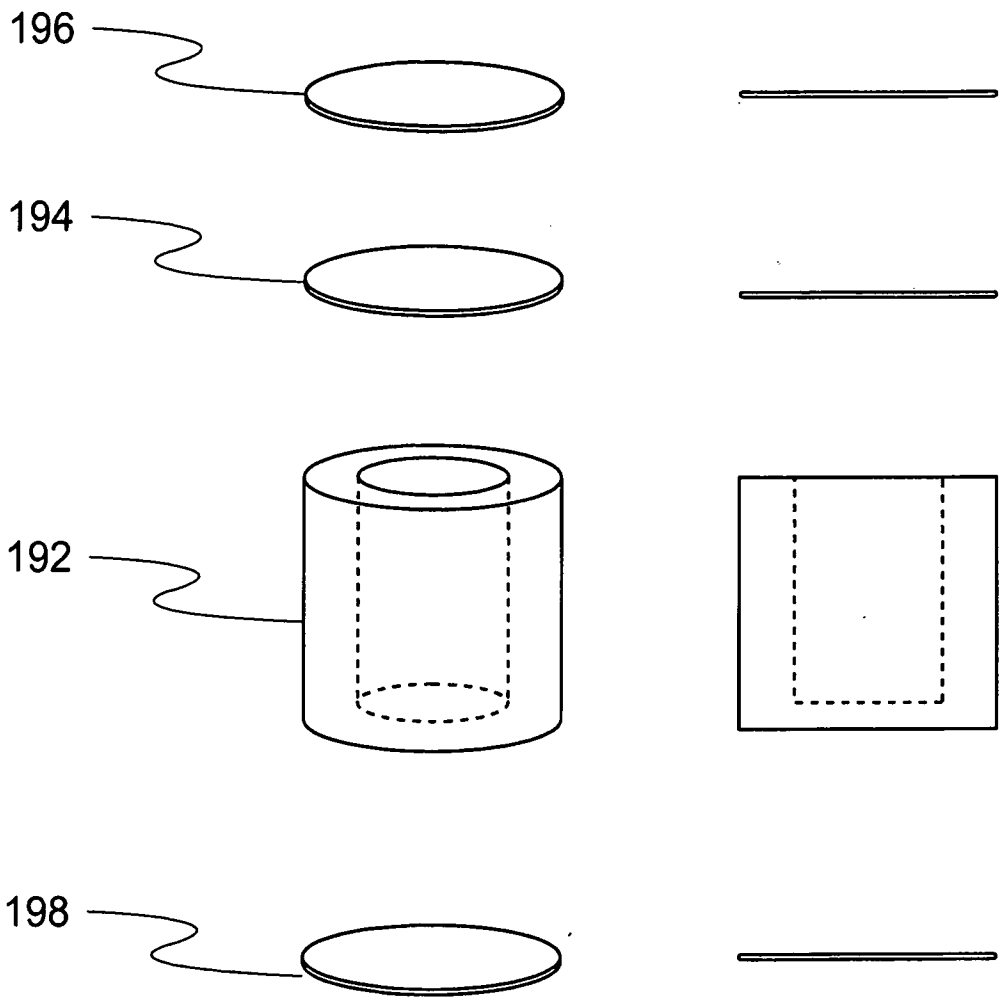


FIG. 21

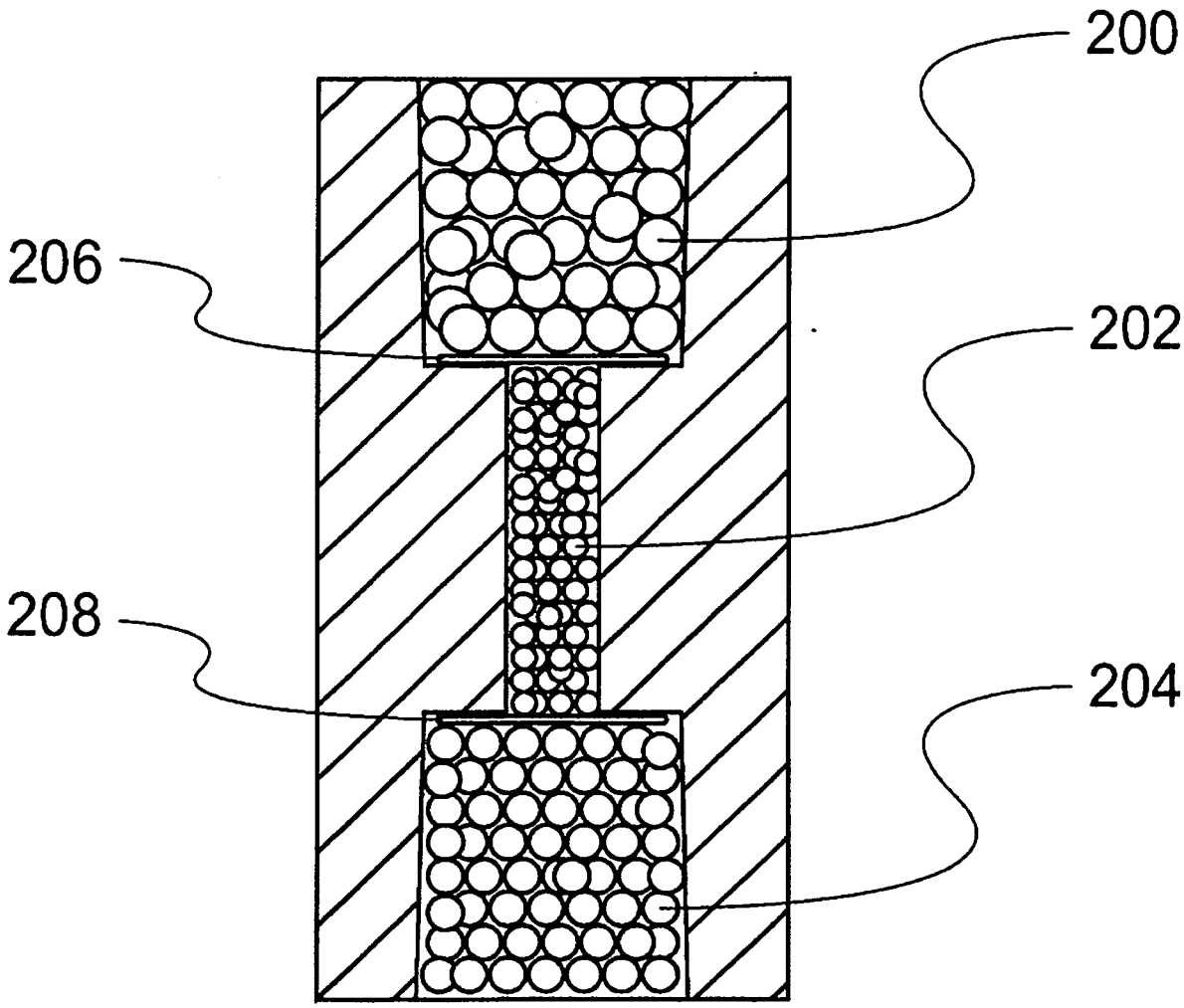


FIG. 22

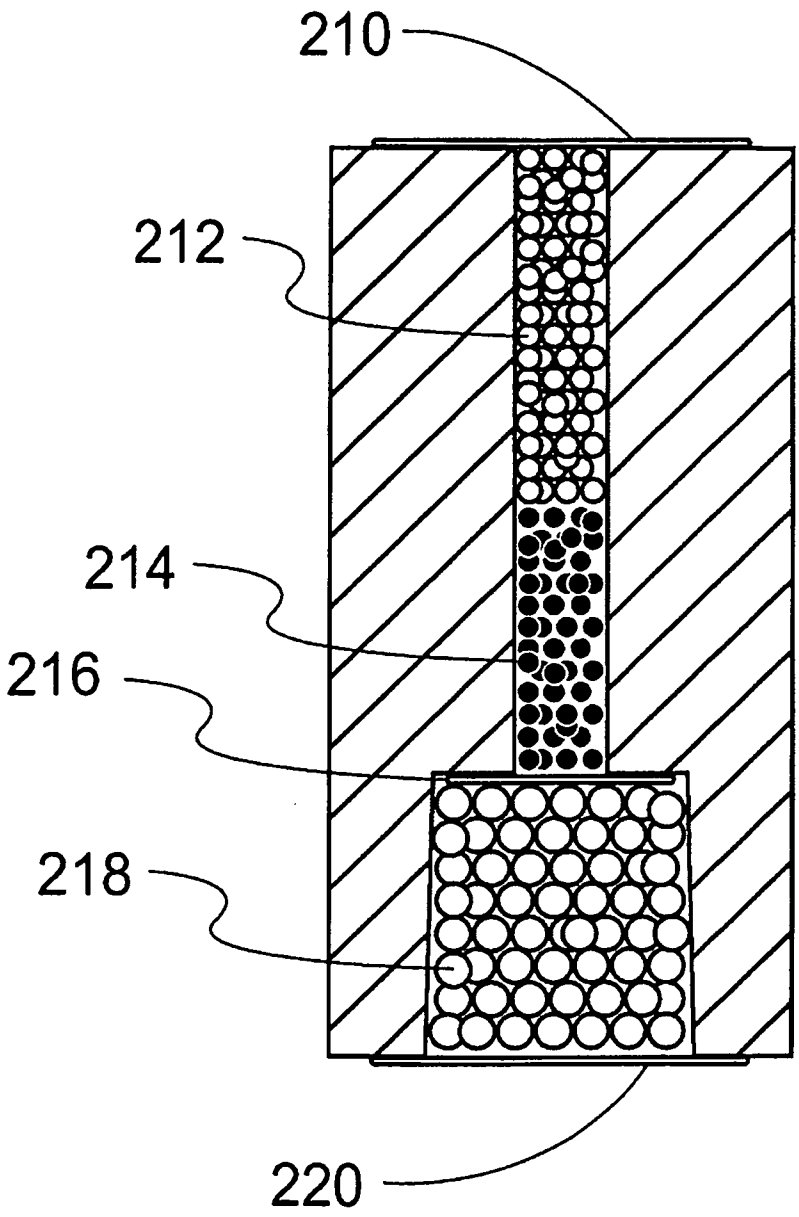


FIG. 23

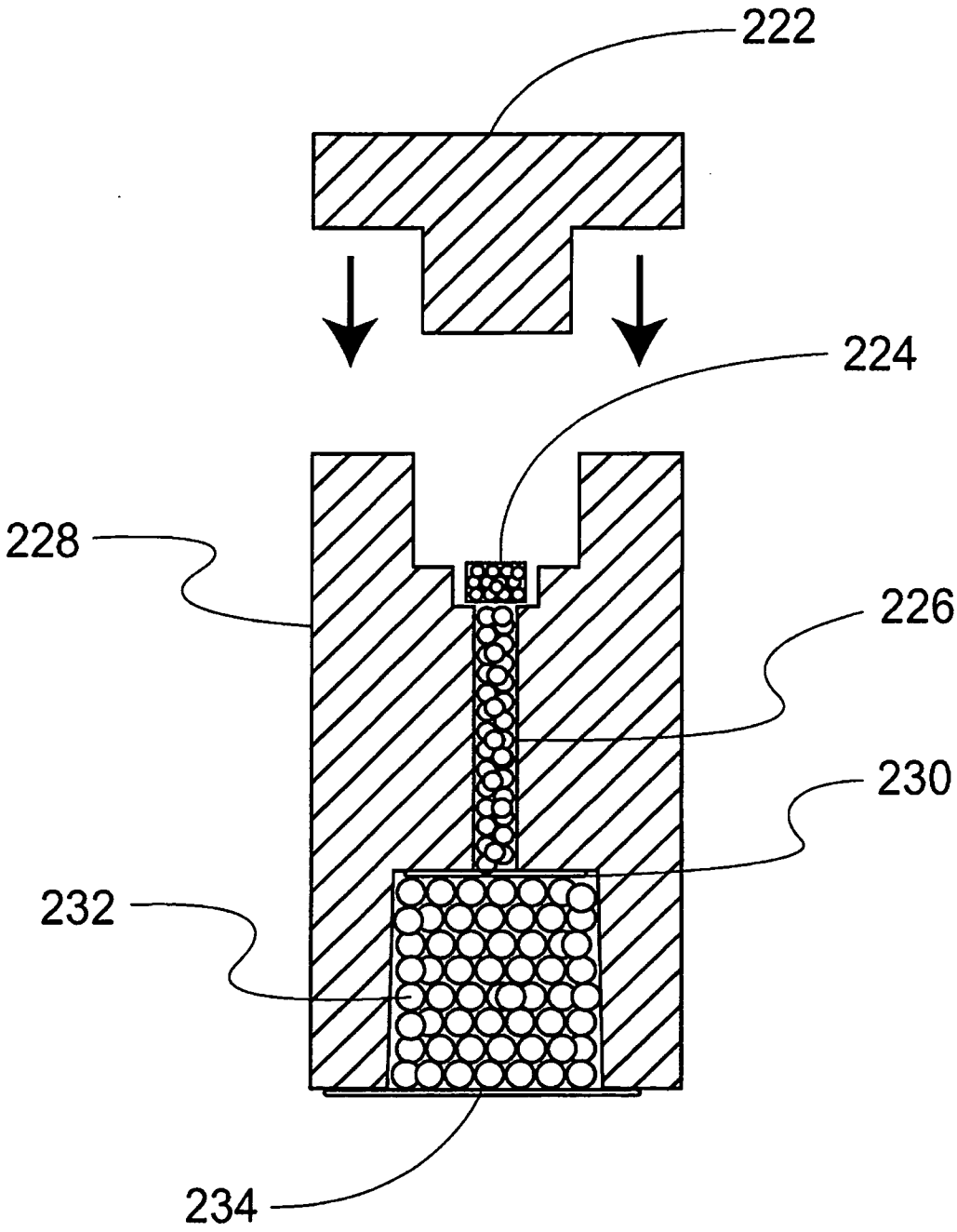


FIG. 24

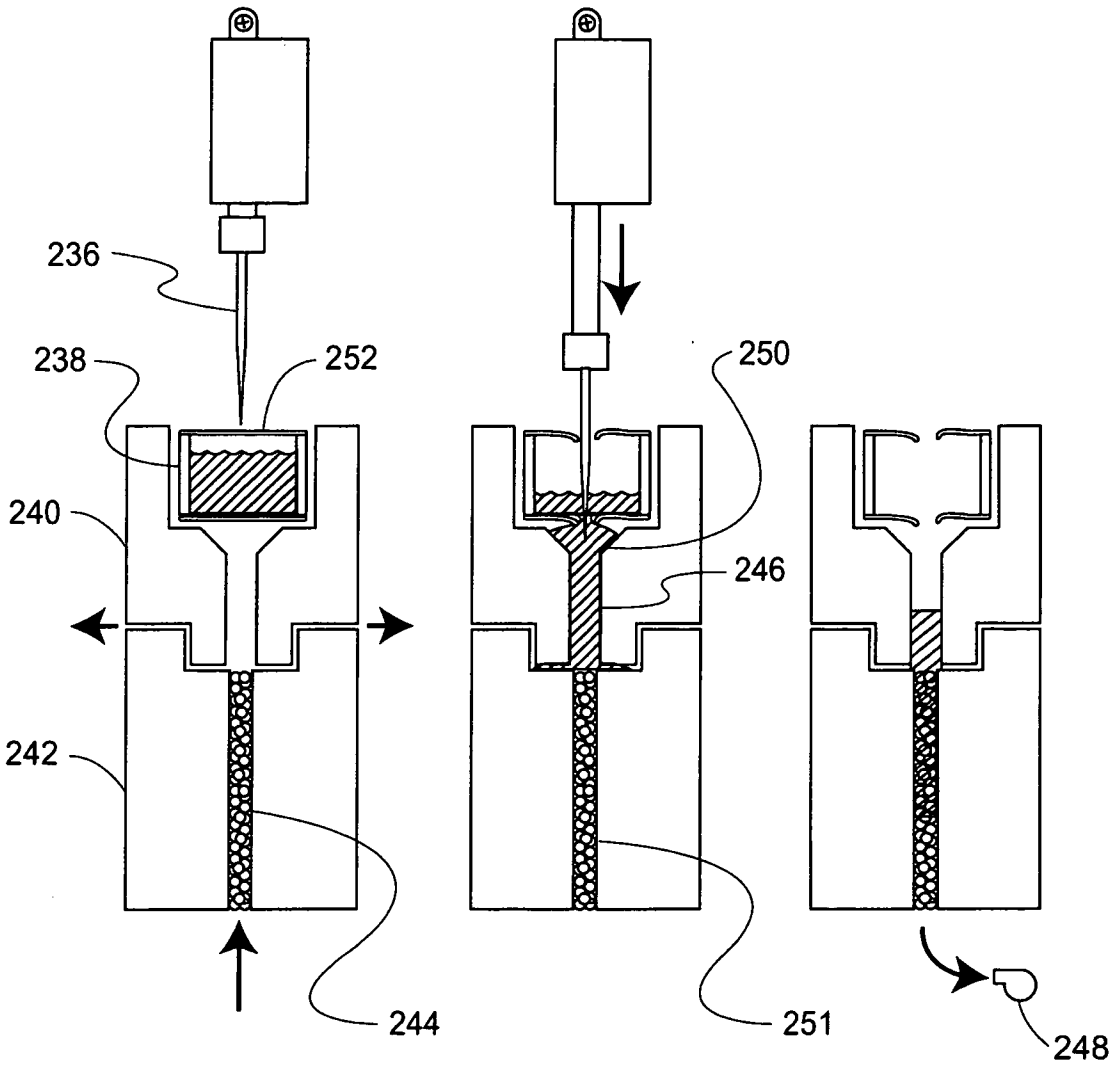


FIG. 25

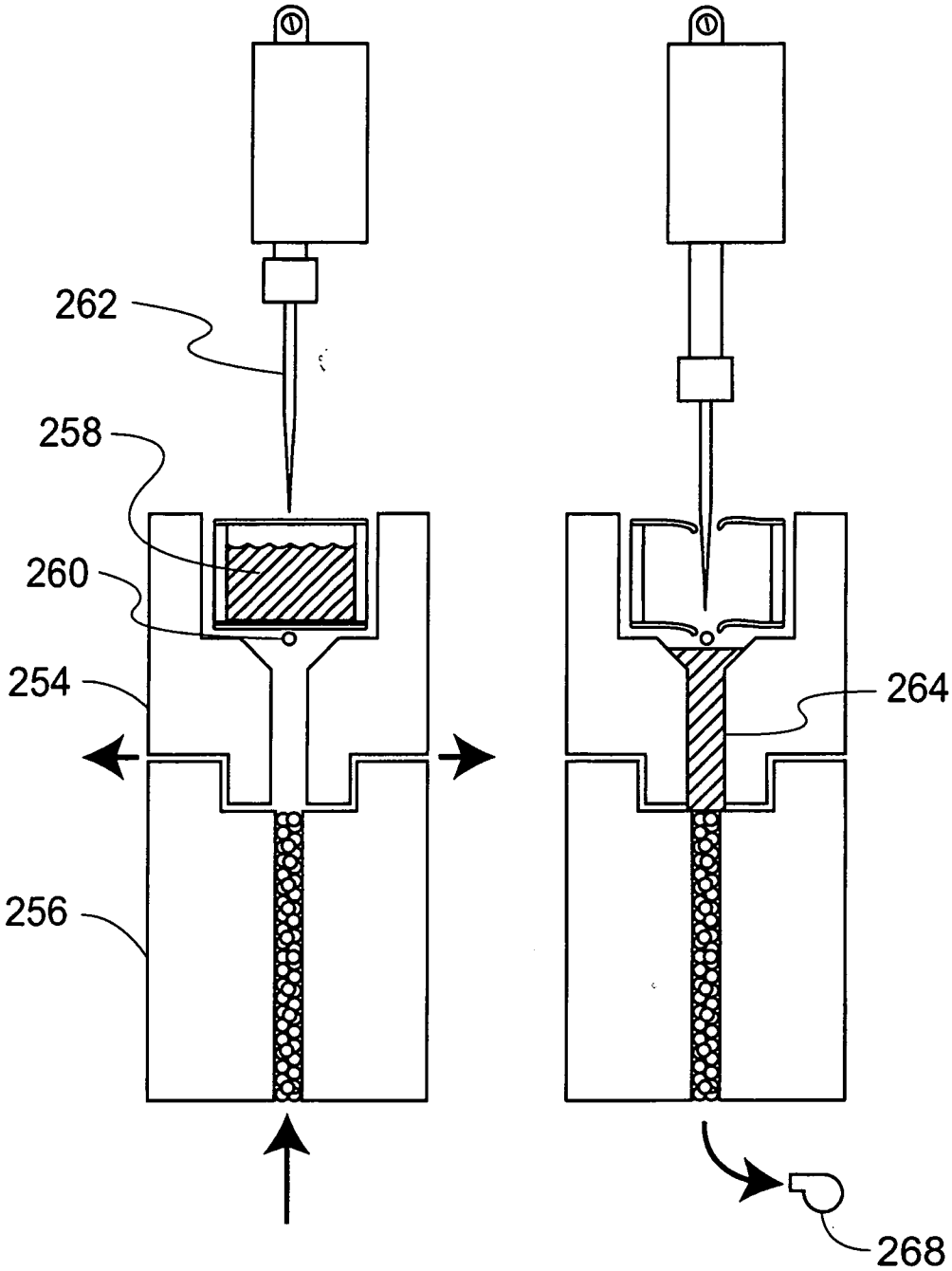


FIG. 26

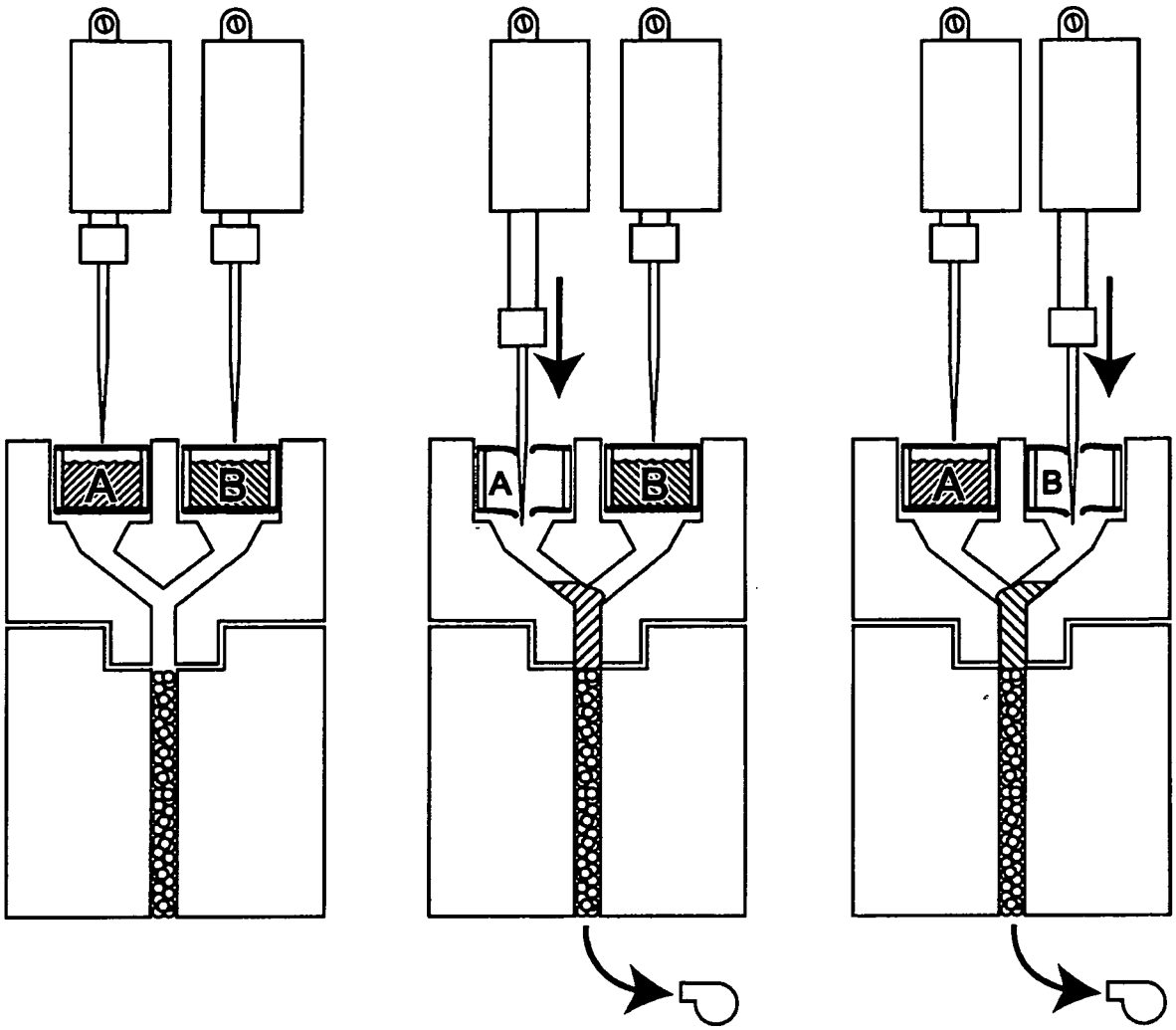
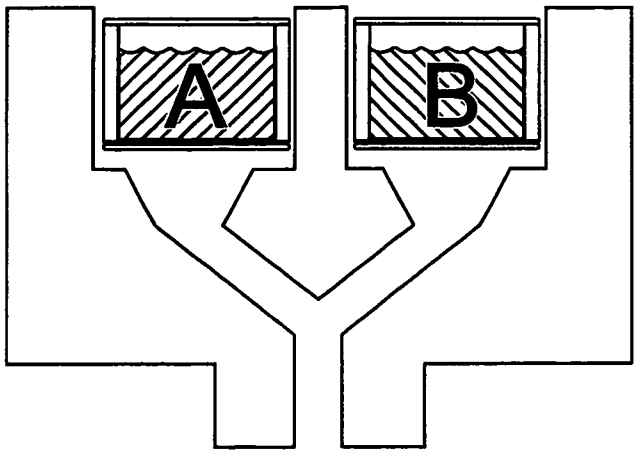


FIG. 27



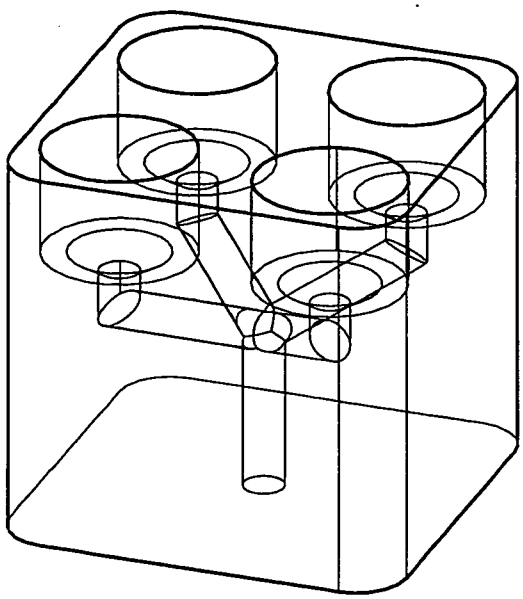
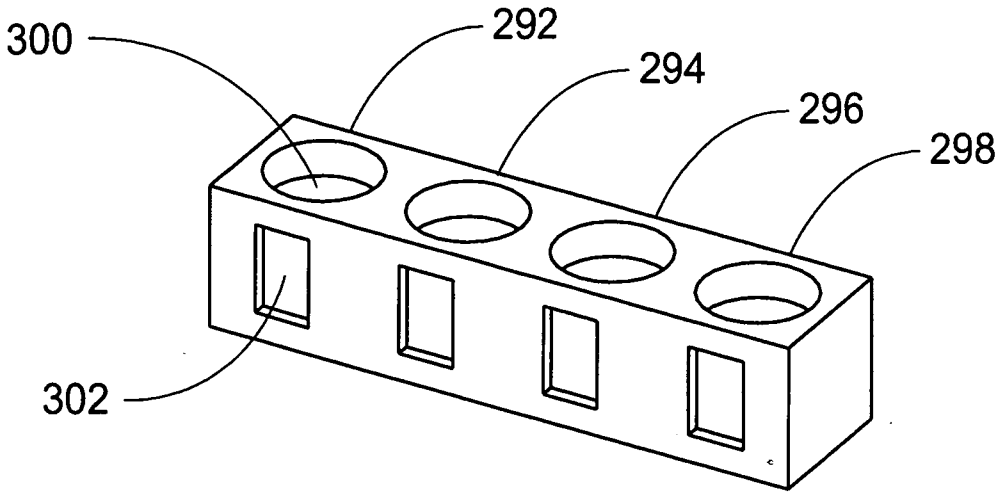


FIG. 28



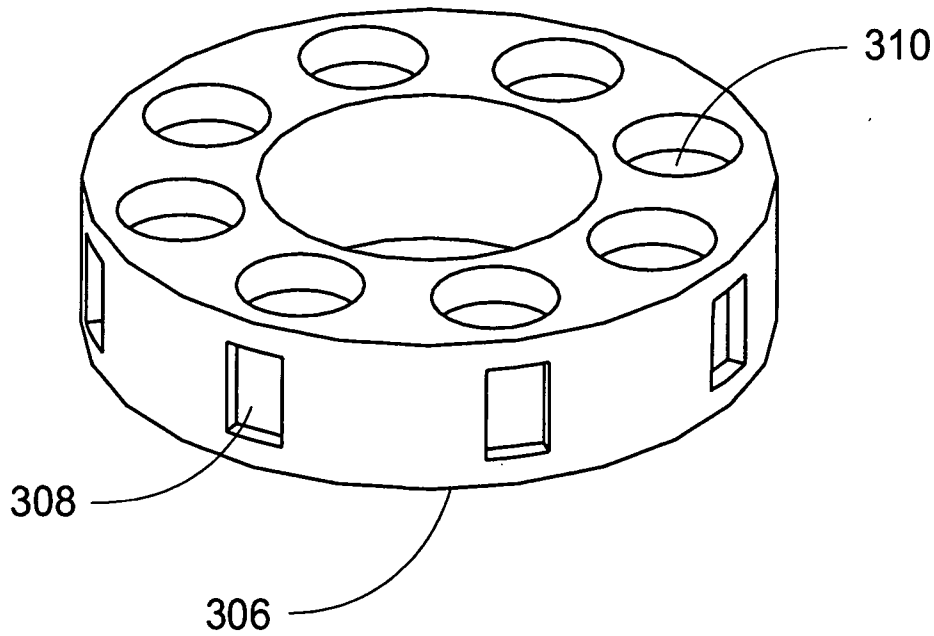


FIG. 29

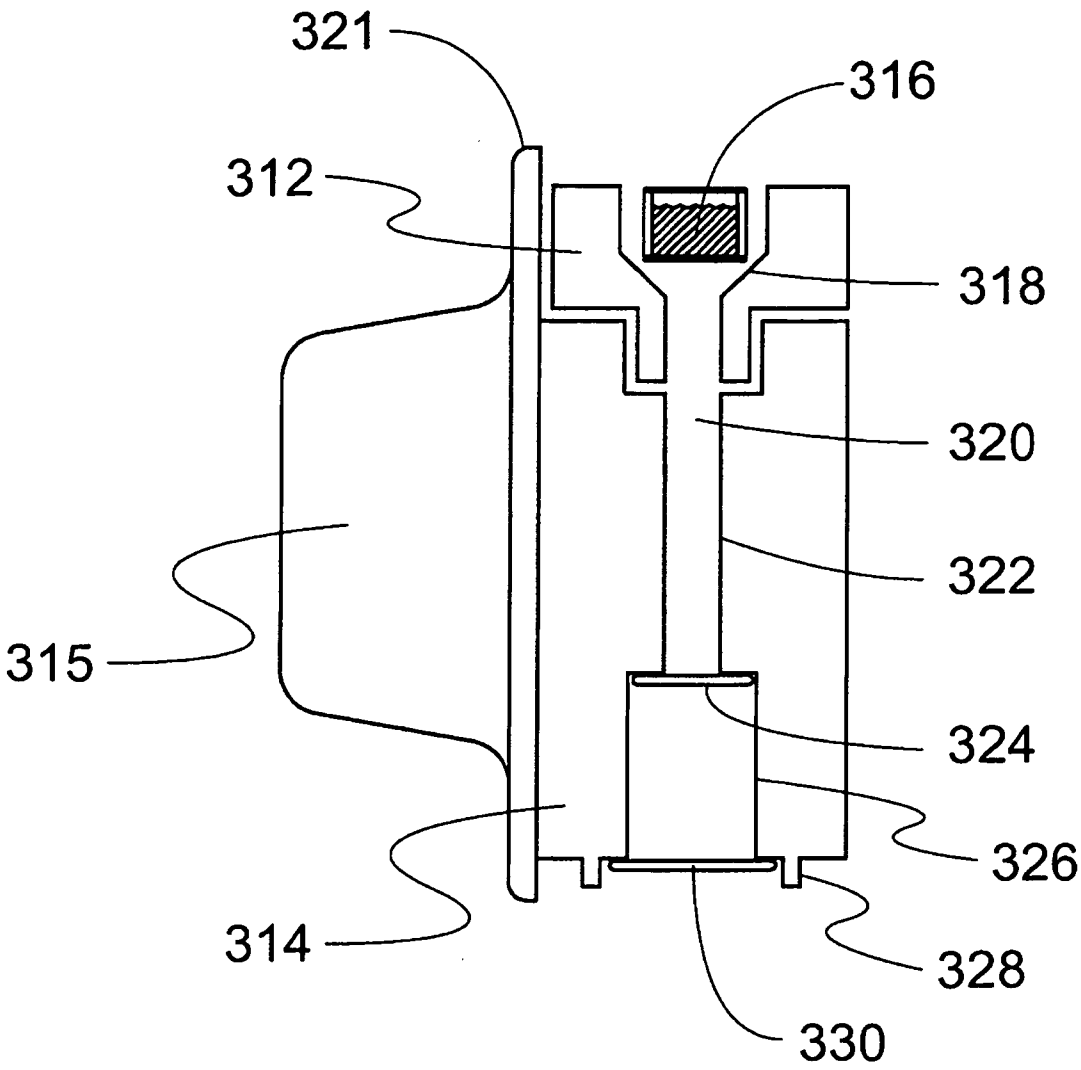


FIG. 30

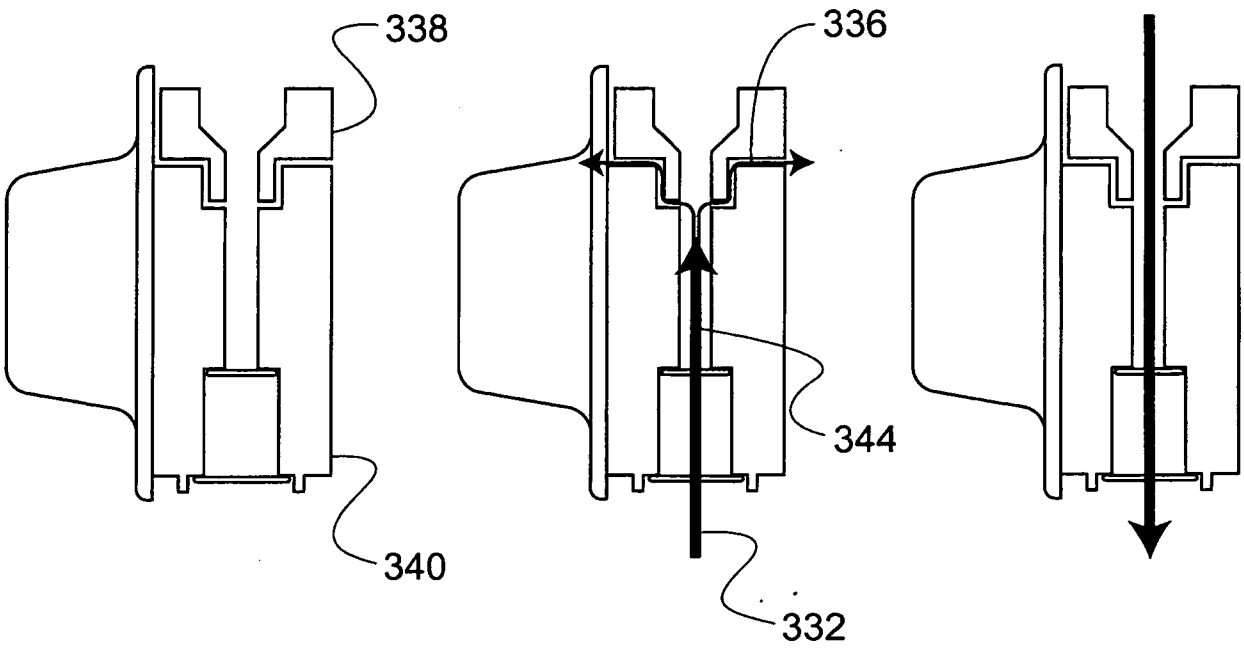


FIG. 31

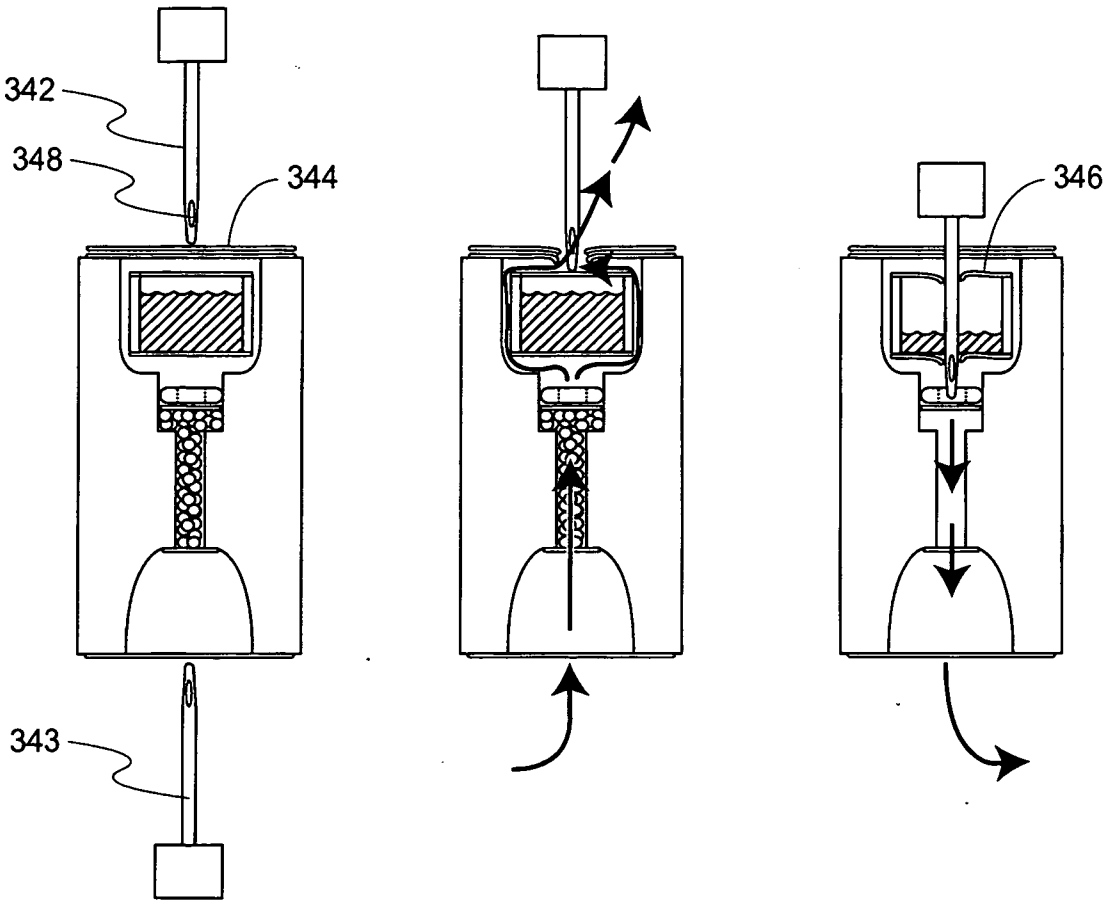


FIG. 32

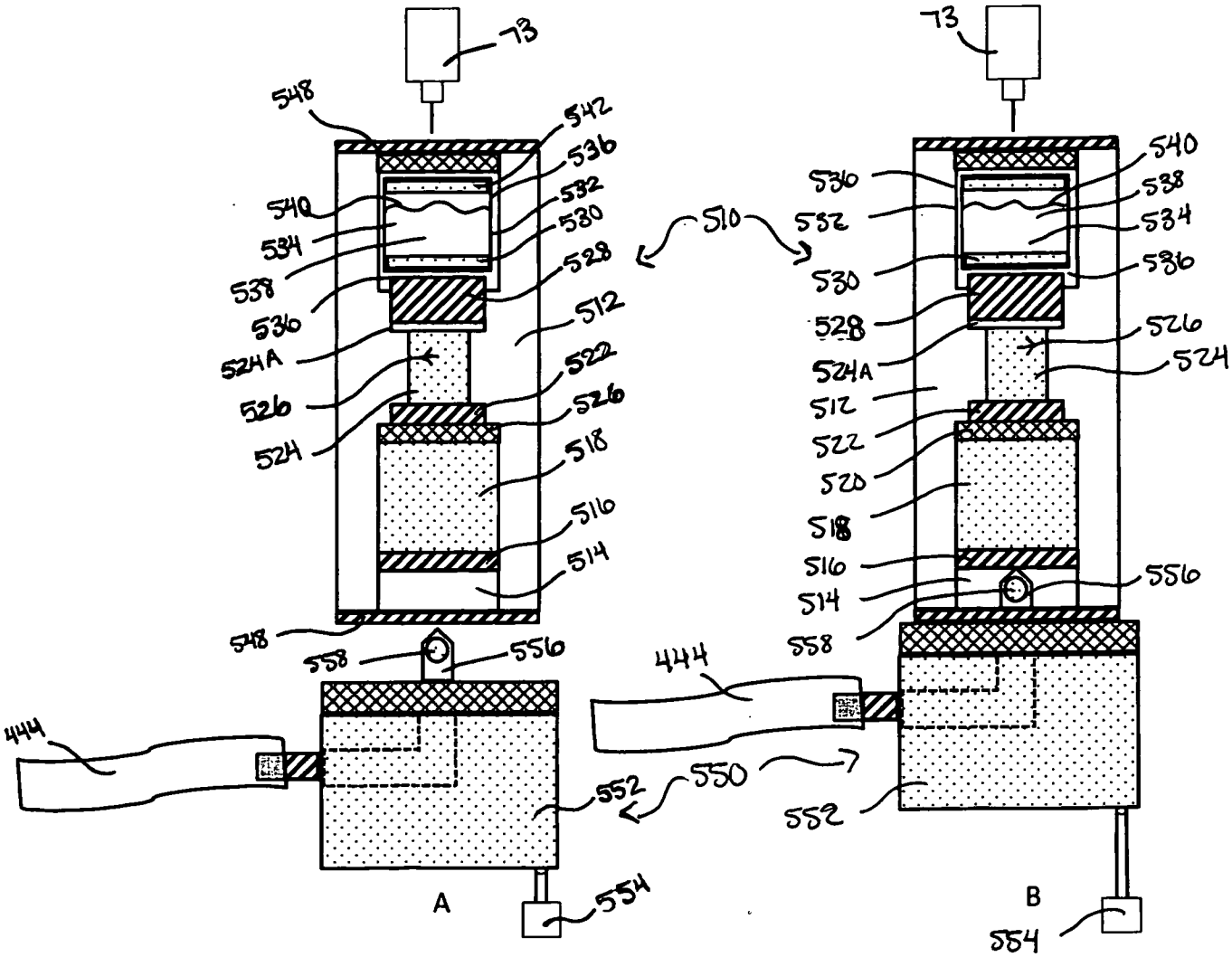

73
548
542
536
540
532
534
538
530
528
524A
526
524
512
522
518
516
514
558
556
444
552
550
554
A
B
510

FIG. 33

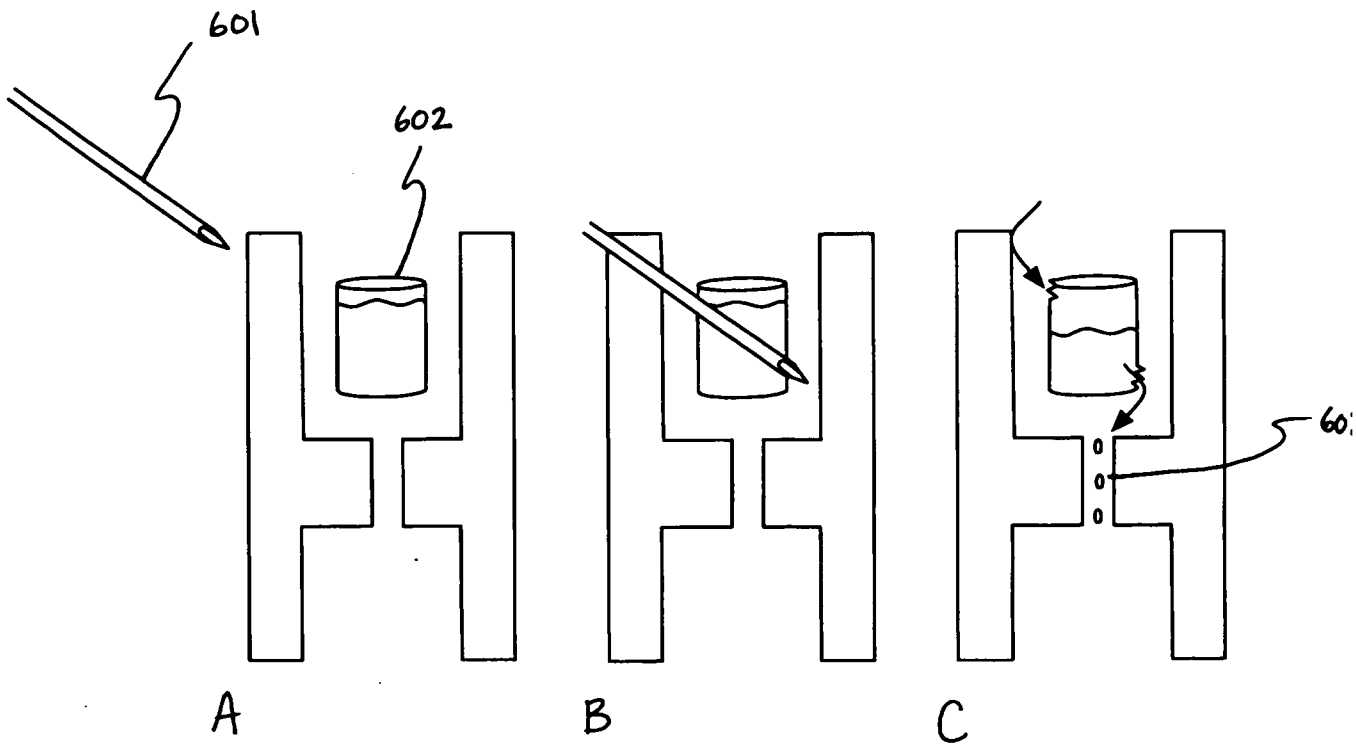


FIG. 34

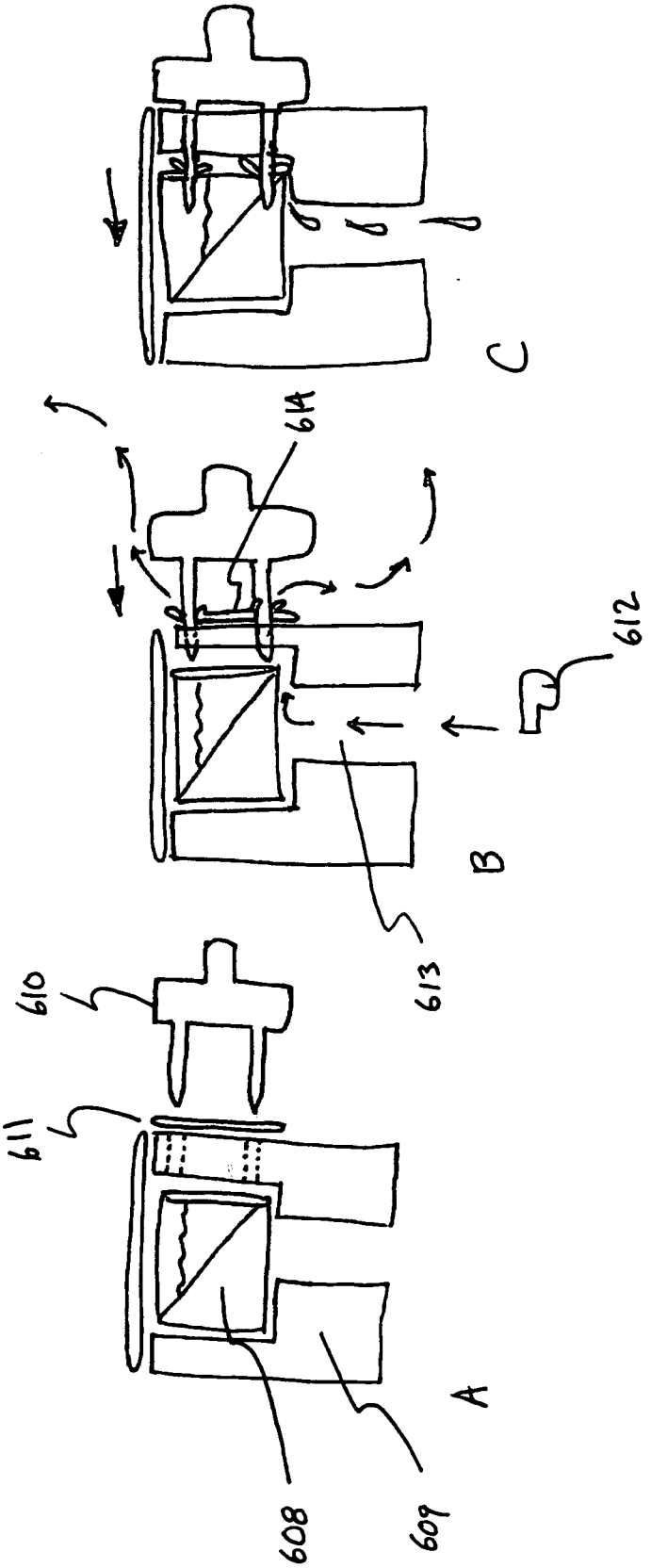


FIG. 35

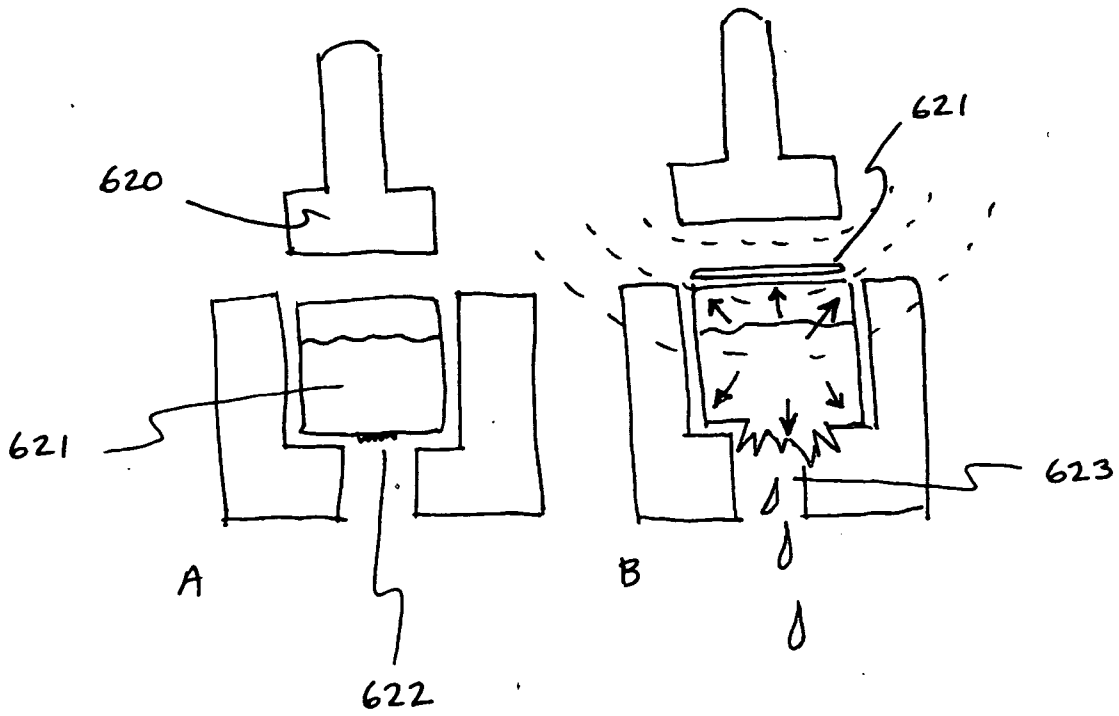


FIG. 36

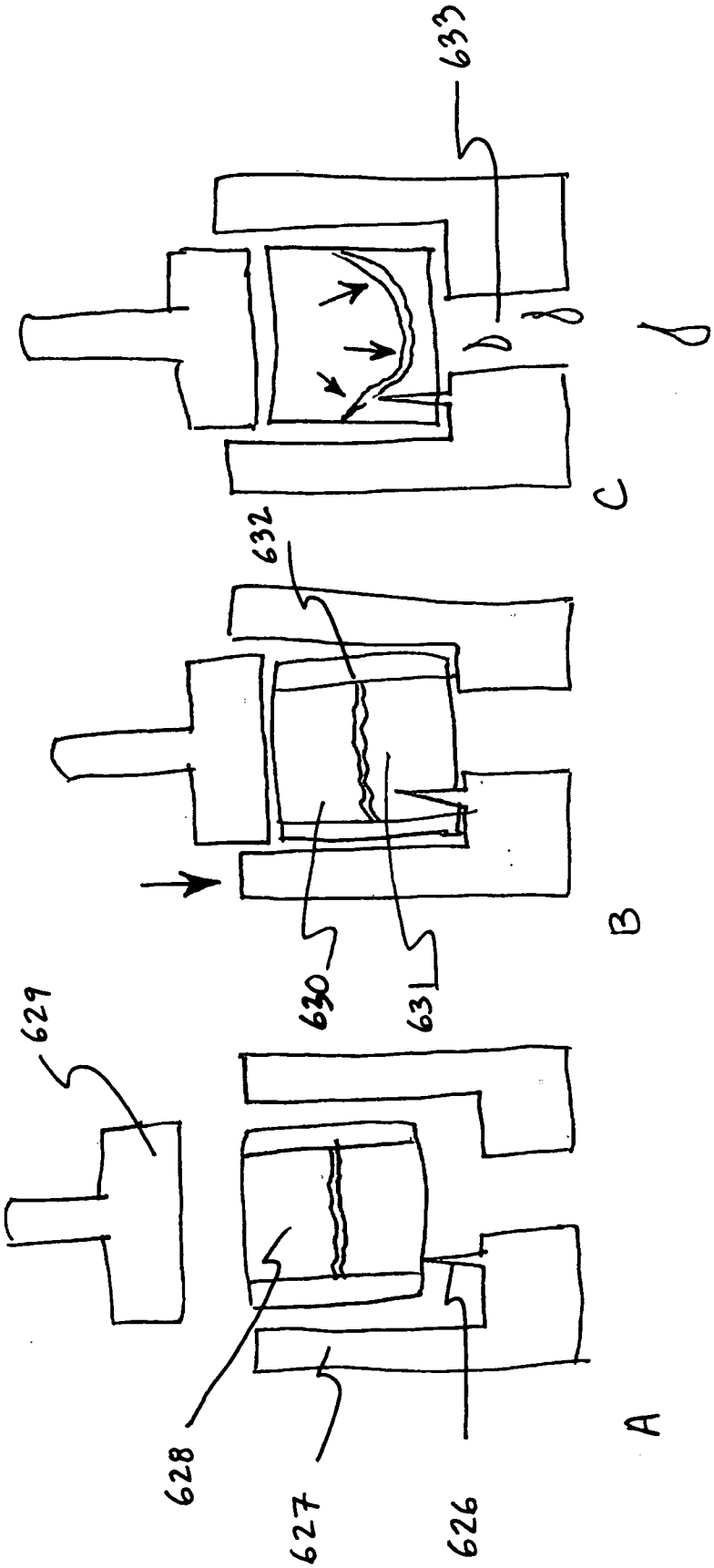


FIG. 37

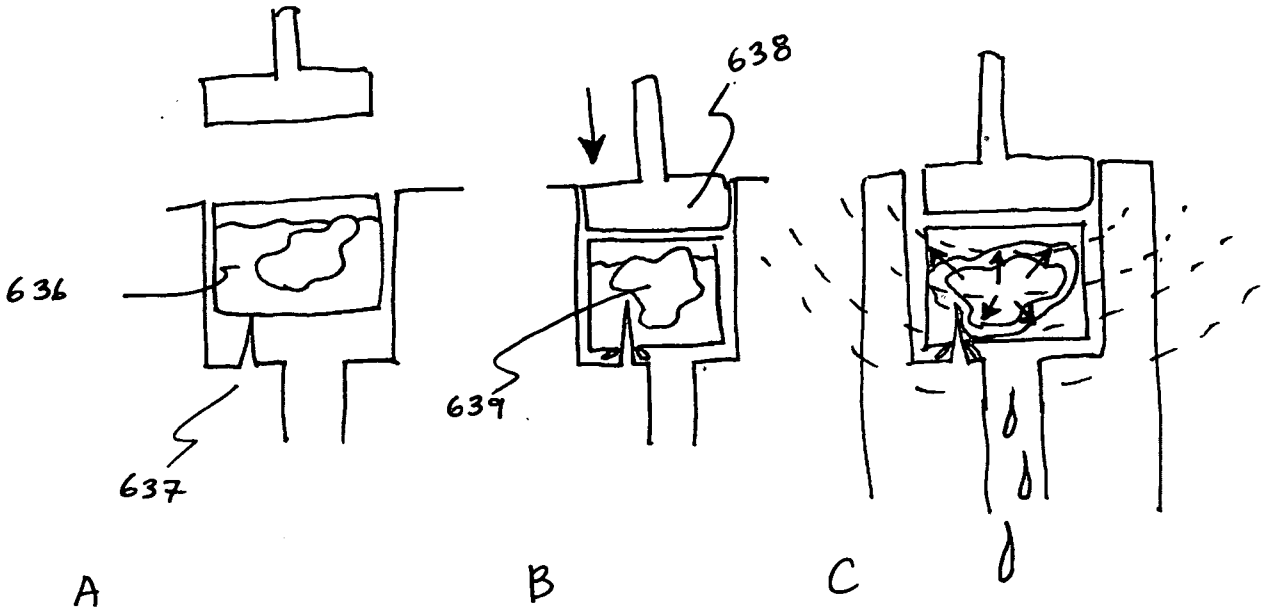


FIG. 38

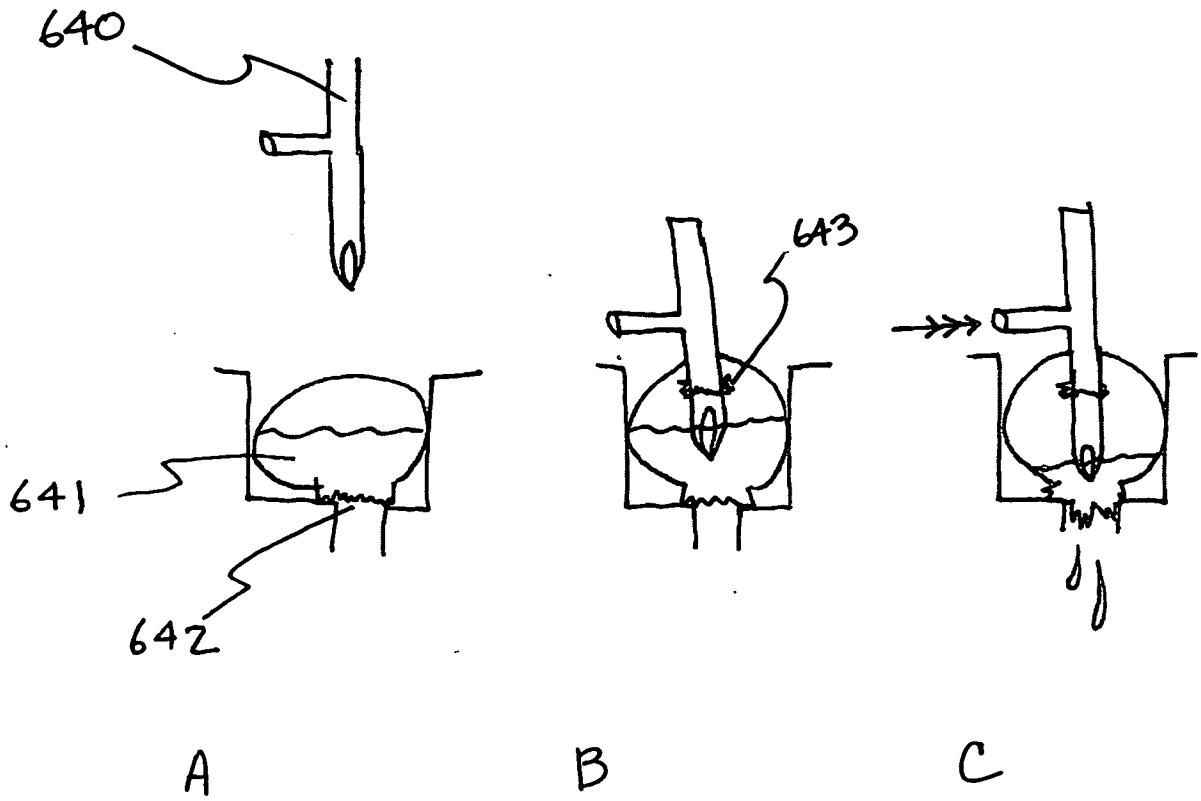


FIG. 39

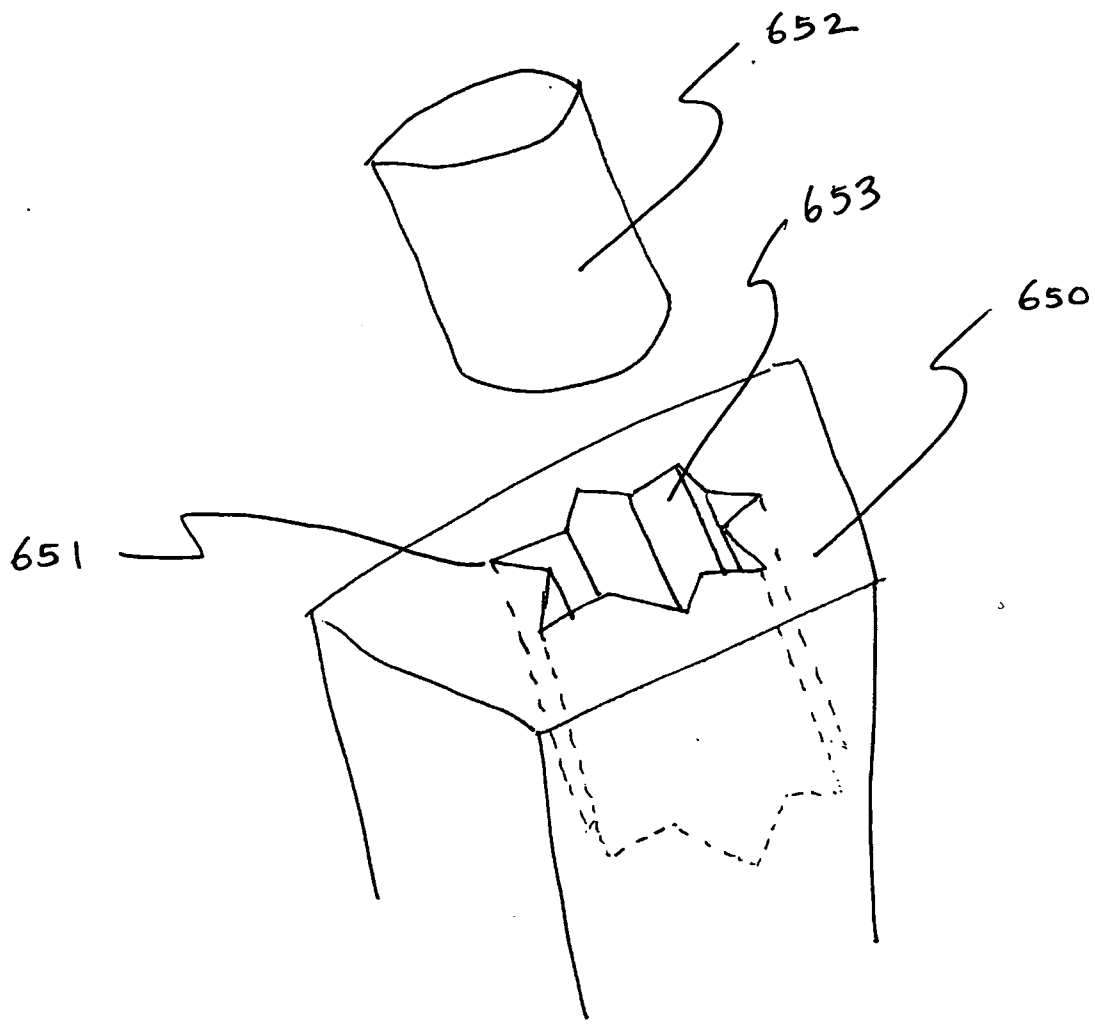


FIG. 40

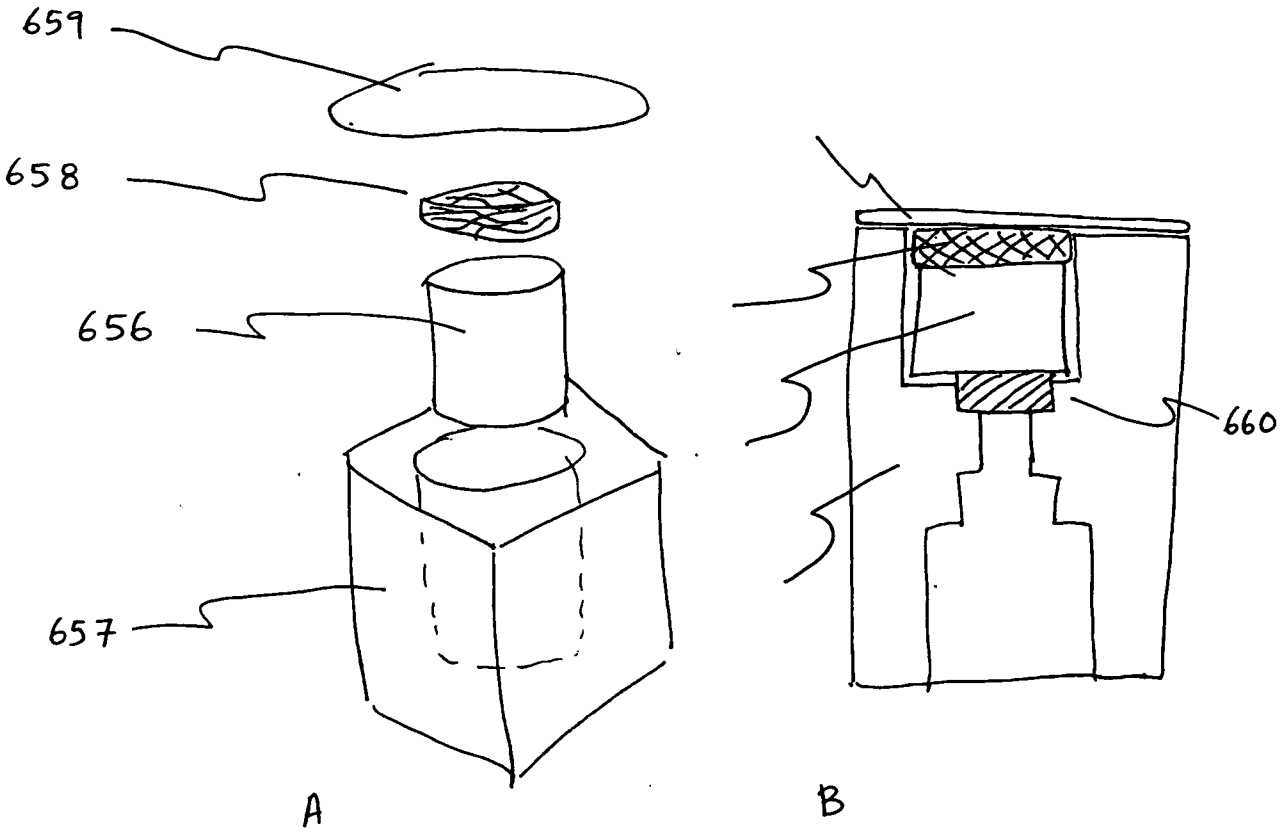


FIG. 41

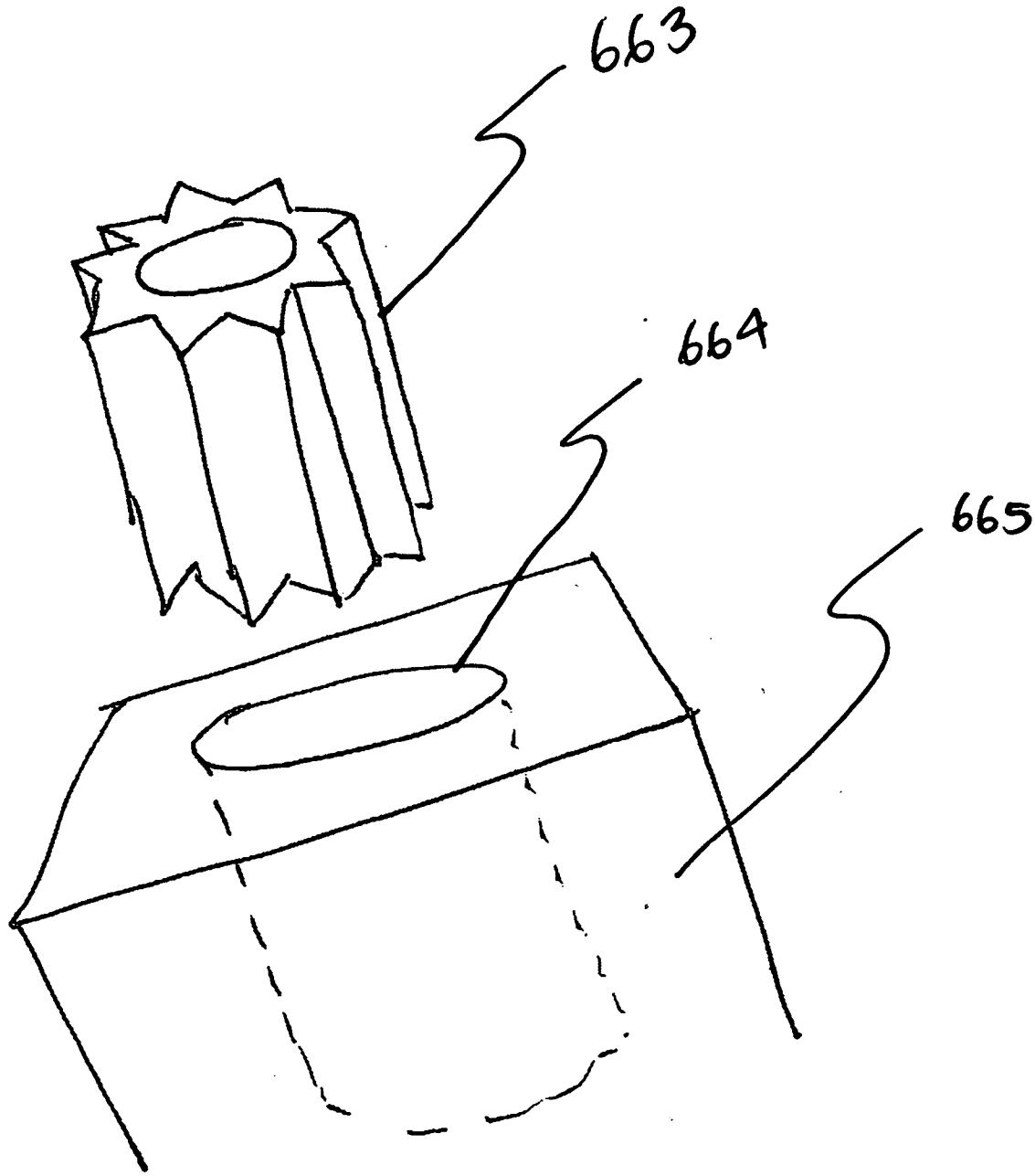


FIG. 42

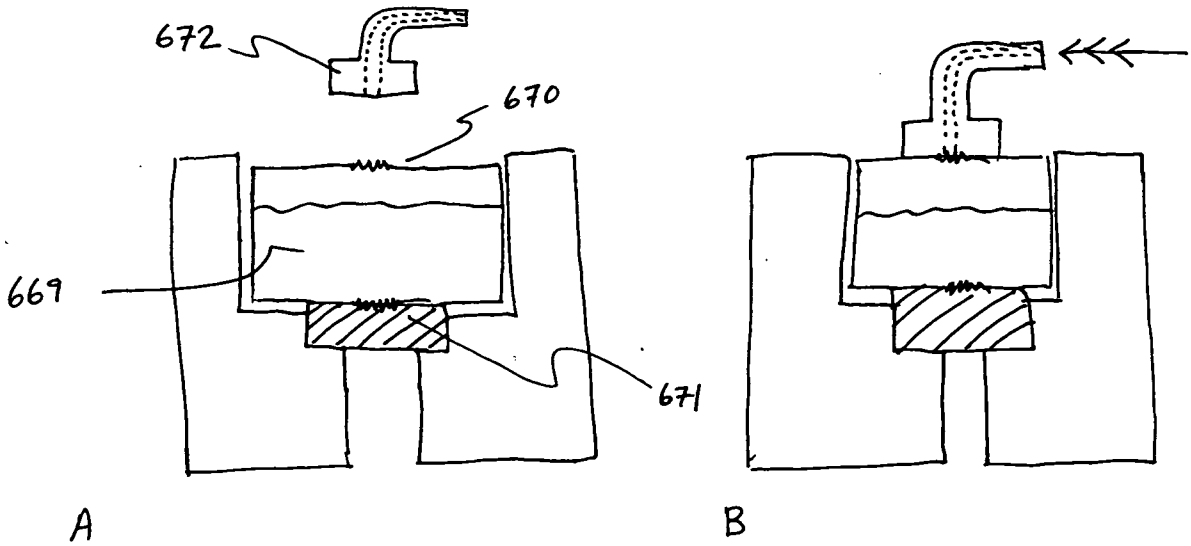


FIG. 43

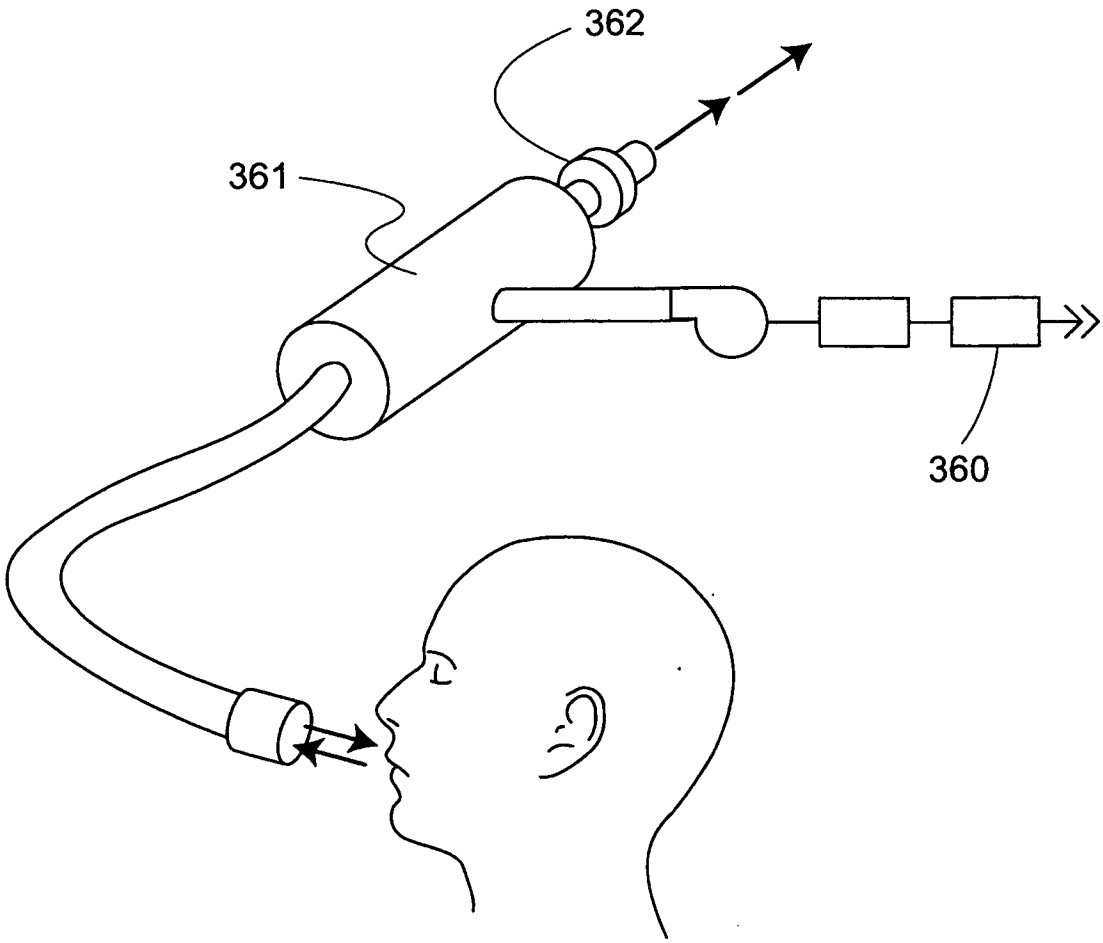
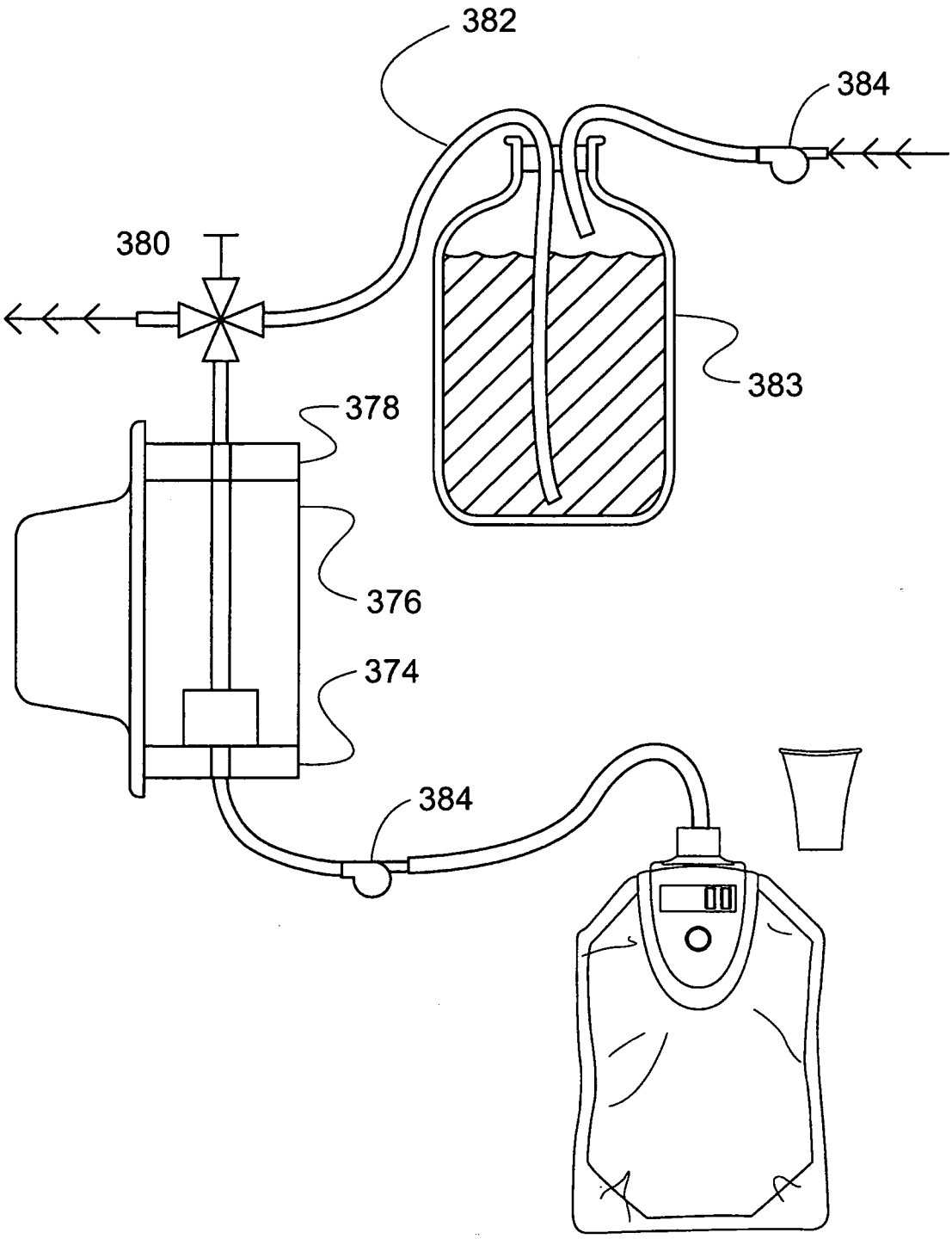


FIG. 44



INTERNATIONAL SEARCH REPORT

013/000026 17.06.2013

International application No.
PCT/US2013/000026

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61B 5/08 (2013.01)
USPC - 422/85
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) - A61B 5/08, 5/097; G01N 33/483, 33/497 (2013.01)
USPC - 73/1.02, 1.06, 23.3; 422/83, 84, 85, 86; 600/529, 532

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC - A61B 5/08, 5/082; G01N 33/483, 33/497, 33/4972 (2013.01)

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2011/0098590 A1 (GARBUTT et al) 28 April 2011 (28.04.2011) entire document	1-31
A	US 2008/0004542 A1 (ALLEN et al) 03 January 2008 (03.01.2008) entire document	1-31
A	WO 2005/082234 A1 (FLAHERTY et al) 09 September 2005 (09.09.2005) entire document	1-31

☐ 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
"E" earlier application or patent but published on or after the international filing date
"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
23 May 2013	17 JUN 2013
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: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774