

APPARATUS FOR DETERMINATION OF DIFFUSION OR PERMEATION THROUGH A  
SPECIMEN, METHOD OF FORMING THE SAME AND METHOD FOR CONTROLLING  
THE SAME

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**Technical Field**

[0001] Various embodiments relate to an apparatus for determination of diffusion or permeation through a specimen, a method of forming an apparatus for determination of diffusion or permeation through a specimen, and a method for controlling an apparatus for determination of  
10 diffusion or permeation through a specimen.

**Background**

[0002] For measurements relating to skin absorption or skin permeation, temperature control and  
15 flow rate are closely related to the accuracy of the testing results.

[0003] There are a number of skin diffusion systems available in the market. They can be divided into two groups: manual systems and automated systems.

[0004] Known automated systems generally use a peristaltic pump for fluid control, where the pump controls the flow rate of the receptor fluid used. However, peristaltic pumps may not offer  
20 sufficiently high precision in the control of the flow rate, which thus may compromise the results of measurements conducted using such known automated systems.

[0005] Further, in some known automated systems, the infusion pump and tubings of the systems produce small bubbles that have a big impact on the final volumes in each tubing, which may affect the results of measurements conducted using such known automated systems.

[0006] Also, in some known automated systems, for temperature control, the heating system  
25 employs water jacketed circulator/water bath/dry block to control the temperature. A water jacket is a water-filled casing surrounding the diffusion device, to allow water to be pumped through and circulated. The flow of water to an external heating device allows temperature control of the device. Hence, an extra pump and a water container are needed, which make the design  
30 complicated and increase the size of the instrument. Also, most importantly, water is a source of contamination. Further, a water bath and dry block causes an uneven heat distribution.

[0007] Further, in known automated systems, there are three to six diffusion cells for testing purposes, resulting in a low throughput for the known systems.

[0008] Further, in known automated systems, only one type of receptor fluid can be investigated per run.

5 [0009] There is therefore need for systems/apparatus and/or methods that address one or more of the problems associated with known systems.

### **Summary**

10 [0010] The invention is defined in the independent claims. Further embodiments of the invention are defined in the dependent claims.

[0011] According to an embodiment, an apparatus for determination of diffusion or permeation through a specimen is provided. The apparatus may include a fluid transport arrangement configured to deliver a fluid, a sampling arrangement configured to receive at least one specimen  
15 and the fluid to interact with the at least one specimen to collect material diffused or permeated through the at least one specimen, and a collection arrangement configured to receive and move at least one container to collect the fluid after interaction with the at least one specimen.

[0012] According to an embodiment, a method of forming an apparatus for determination of diffusion or permeation through a specimen is provided. The method may include arranging a  
20 fluid transport arrangement in fluid communication with a sampling arrangement configured to receive at least one specimen and a fluid to be delivered from the fluid transport arrangement for interacting with the at least one specimen to collect material diffused or permeated through the at least one specimen, and arranging the sampling arrangement in fluid communication with a collection arrangement configured to receive and move at least one container to collect the fluid  
25 after the interaction with the at least one specimen.

[0013] According to an embodiment, a method for controlling an apparatus for determination of diffusion or permeation through a specimen is provided. The method may include providing at least one specimen in a sampling arrangement of the apparatus, delivering a fluid from a fluid transport arrangement of the apparatus to the at least one specimen to interact with the at least  
30 one specimen to collect material diffused or permeated through the at least one specimen, collecting, in at least one container of a plurality of containers received by a collection

arrangement of the apparatus, a portion of the fluid after the interaction with the at least one specimen, and moving the plurality of containers, by means of the collection arrangement, to at least one different position to collect, in at least one other container of the plurality of containers, at least one other portion of the fluid after the interaction with the at least one specimen.

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### **Brief Description of the Drawings**

[0014] In the drawings, like reference characters generally refer to like parts throughout the different views. The drawings are not necessarily to scale, emphasis instead generally being placed upon illustrating the principles of the invention. In the following description, various

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embodiments of the invention are described with reference to the following drawings, in which:

[0015] FIG. 1A shows a schematic block diagram of an apparatus for determination of diffusion or permeation through a specimen, according to various embodiments.

[0016] FIG. 1B shows a flow chart illustrating a method of forming an apparatus for

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[0017] FIG. 1C shows a flow chart illustrating a method for controlling an apparatus for determination of diffusion or permeation through a specimen, according to various embodiments.

[0018] FIG. 2A shows a simplistic schematic block diagram for the apparatus of various embodiments.

[0019] FIG. 2B shows a schematic block diagram for the apparatus of various embodiments.

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[0020] FIGS. 3A-3D show schematic perspective views of respective apparatus for determination of diffusion or permeation through a specimen, according to various embodiments.

[0021] FIG. 4A shows a schematic perspective view of a collection arrangement, according to various embodiments, while FIG. 4B shows a side view of a part of the apparatus of various

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embodiments incorporating the collection arrangement of FIG. 4A.

[0022] FIG. 5 shows a schematic perspective view of a diffusion device.

### **Detailed Description**

[0023] The following detailed description refers to the accompanying drawings that show, by way of illustration, specific details and embodiments in which the invention may be practiced.

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These embodiments are described in sufficient detail to enable those skilled in the art to practice the invention. Other embodiments may be utilized and structural, logical, and electrical changes may be made without departing from the scope of the invention. The various embodiments are not necessarily mutually exclusive, as some embodiments can be combined with one or more other embodiments to form new embodiments.

**[0024]** Embodiments described in the context of one of the methods or devices are analogously valid for the other methods or devices. Similarly, embodiments described in the context of a method are analogously valid for a device, and vice versa.

**[0025]** Features that are described in the context of an embodiment may correspondingly be applicable to the same or similar features in the other embodiments. Features that are described in the context of an embodiment may correspondingly be applicable to the other embodiments, even if not explicitly described in these other embodiments. Furthermore, additions and/or combinations and/or alternatives as described for a feature in the context of an embodiment may correspondingly be applicable to the same or similar feature in the other embodiments.

**[0026]** In the context of various embodiments, the articles “a”, “an” and “the” as used with regard to a feature or element include a reference to one or more of the features or elements.

**[0027]** In the context of various embodiments, the term “about” as applied to a numeric value encompasses the exact value and a reasonable variance.

**[0028]** As used herein, the term “and/or” includes any and all combinations of one or more of the associated listed items.

**[0029]** As used herein, the phrase of the form of “at least one of A or B” may include A or B or both A and B. Correspondingly, the phrase of the form of “at least one of A or B or C”, or including further listed items, may include any and all combinations of one or more of the associated listed items.

**[0030]** Various embodiments may provide a diffusion system or apparatus, for example, for determination (or analysis or measurement) of diffusion or permeation of at least one material (e.g., chemical, drug, etc.) through a specimen. The diffusion system or apparatus may be an automated diffusion system (ADS) or apparatus. Use of the ADS allows measurements to be conducted in an automated way.

**[0031]** The ADS of various embodiments may be an automatic, integrated system for use for skin permeation study. The ADS may serve as a ‘vehicle’ for a diffusion device, for example, of the

type as disclosed in US patent application number 14/051,720. Generally, a diffusion device needs to be connected to a set of equipment to be functional, for example, for skin permeation determination or measurement, and the ADS of various embodiments may be utilised to replace such a set of equipment. Using the ADS, skin permeation measurement or determination or study may be performed in a high throughput, high precision manner.

**[0032]** Various embodiments may provide a system or apparatus (e.g., an automated (integrated) system) for skin permeation measurement or study, having a syringe pump and an arrangement of multiple syringes that may be actuated by the syringe pump to draw a receptor fluid (e.g., phosphate buffer saline (PBS)) from a storage arrangement and to deliver the receptor fluid to a distribution manifold (which, however, may be optional). The receptor fluid may then be split or divided via the manifold into a plurality of channels that may then flow into and through respective receptor chambers (for example, each may contain a specimen (e.g., membrane, biomembrane, skin) under test) of a diffusion device (or permeation device), where the material permeated through the specimens may be carried away with the receptor fluid to be collected. As a non-limiting example, two diffusion devices may be placed into a heated circulation box of the apparatus, where each diffusion device may include 6 diffusion cells or receptor chambers. Each diffusion device is a separate device that may be used as an insert into the apparatus. Air heating may be used within the heated circulation box to provide uniform heat distribution. A sample collection arrangement (e.g., an automated sample collection arrangement) may be used to collect the eluting samples (e.g., receptor fluid with the permeated material or permeant), having a pinch valve and a tray. In various embodiments, the tray may be a (programmable) tray that may linearly slide at different time intervals for the eluting samples or fluids to be collected into containers/vials receivable by the tray. In other embodiments, a (programmable) rotary tray may be used for rotation at different time intervals for collection of the eluting samples. The automated integrated system of various embodiments may be arranged as a two-tiered system.

**[0033]** In various embodiments, a syringe pump may be used as it offers a higher precision in control of the flow rate and/or fluid volume, which may lead to a higher accuracy of test results, as compared to known systems using a peristaltic pump. Further, a syringe pump is easily sterilizable. The syringe pump may be a multi syringe pump with multiple syringes. The use of a syringe pump may address the challenges of precision control of the flow rate of the receptor fluid, and/or bubbles, as mentioned above, that are associated with known systems.

[0034] In various embodiments, an air heating system may be employed. The use of air heating may allow the heated air to surround the diffusion device or diffusion cell completely, allowing uniform distribution of heat, as compared to known systems using a water-based method. Air heating may enable a more precise temperature control, may simplify the operations involved and/or eliminate the possibility of contamination from water.

[0035] The apparatus or system of various embodiments may enable a high throughput, allowing a higher number of specimen testing per sampling run. For example, a plurality or higher number of diffusion devices, each having a predefined number of diffusion cells or receptor chambers, and/or, a plurality or higher number of receptor/diffusion chambers (or diffusion cells) per diffusion device, may be employed with the system of various embodiments, as compared to known systems. Further, the utilisation of a plurality of receptor chambers may enable parallel processing of specimens. Each diffusion cell or receptor chamber may hold one specimen. As a non-limiting example, the number of diffusion cells or receptor chambers employed per sampling run may be 12 in the system of various embodiments, thereby, enabling a higher throughput compared to known systems. Nevertheless, it should be appreciated that more than 12 diffusion cells or receptor chambers per sampling run may be accommodated.

[0036] The type of receptor fluid to be used generally varies with the type of material to be tested or measured due to differences in the physicochemical properties of different materials to be diffused through one or more specimens. The system of various embodiments may allow the use of different types of receptor fluids per sampling run. For example, a plurality of syringes may be employed in cooperation with the syringe pump for delivery of different types of receptor fluids from respective syringes during one sampling run. The number of different types of receptor fluids may correspond to the number of syringes used. Using two different receptor fluids as a non-limiting example, a user of the apparatus or system of various embodiments may be able to screen two types of receptor fluids for one material, or to test two materials with two different types of receptor fluid, according to the difference(s) in their physicochemical properties. For example, phosphate buffer saline (PBS) is the most commonly used receptor fluid in permeation study. However, when testing hydrophobic drugs, one or more solubilizers (e.g., polyethylene glycol (PEG), ethanol), may be needed in the receptor fluid. Hence, for the apparatus or system of various embodiments, a user may, for example, use PBS, and PBS plus one or more

solubilizers to test two different materials with different water solubility in the same sampling run.

[0037] The apparatus or system of various embodiments may have a smaller footprint, for example, about  $\frac{1}{2}$  to  $\frac{3}{4}$  of the smallest known systems.

5 [0038] The apparatus or system of various embodiments may employ an auto-sampler, for automated sample collection, which may include a programmable linear (or linearly movable/slidable) tray or a programmable rotary (or rotatable) tray. The programmable tray may be used to control sample collection. A pinch valve may be provided in cooperation with the tray to control sample collection.

10 [0039] FIG. 1A shows a schematic block diagram of an apparatus 100 for determination of diffusion or permeation through a specimen, according to various embodiments. The apparatus 100 includes a fluid transport arrangement 102 configured to deliver a fluid (represented by arrow 103a), a sampling arrangement 104 configured to receive at least one specimen 105 and the fluid 103a to interact with the at least one specimen 105 to collect material  
15 diffused or permeated through the at least one specimen 105, and a collection arrangement 106 configured to receive and move at least one container to collect the fluid 103b after the interaction with the at least one specimen 105.

[0040] In other words, an apparatus 100 may be provided, having a fluid transport arrangement 102, a sampling arrangement 104, and a collection arrangement 106. The fluid  
20 transport arrangement 102 may deliver or transport a fluid 103a. The fluid transport arrangement 102 may include or may be part of an infusion system.

[0041] The sampling arrangement 104 may be arranged in fluid communication (represented by line 110a) with the fluid transport arrangement 102 to receive the fluid 103a. The sampling arrangement 104 may receive at least one specimen 105 to interact with the fluid 103a received,  
25 for diffusion or permeation determination of at least one material through the specimen 105.

[0042] In various embodiments, the at least one material may be provided in contact with the specimen 105. The at least one material may be provided via one or more pipettes to the at least one specimen 105. As a non-limiting example, the at least one material may be provided on or onto the specimen 105 on a side of the specimen 105 that may be opposite to the side of the  
30 specimen 105 that may interact with the fluid 103a. The at least one material may diffuse or

permeate (e.g., permeant) through the specimen 105 to be subsequently collected or carried away by the fluid 103a.

**[0043]** In the context of various embodiments, the at least one material may include, but not limited to, a drug or chemical, e.g., in the form of liquid, cream, gel, etc.

5 **[0044]** In various embodiments, an interaction of the at least one specimen 105 and the fluid 103a may include contact between the at least one specimen 105 and the fluid 103a such that a material (or substance or composition) provided to or on the at least one specimen 105 and diffusing or permeating through the at least one specimen 105 may pass or flow into the fluid 103a interacting with the at least one specimen 105. The resulting fluid 103b, after  
10 interaction with the at least one specimen 105, may include at least part or some of the material that has diffused or permeated through the at least one specimen 105. This may mean that, in the sampling arrangement 104, during operation, the at least one specimen 105 and the fluid 103a may come into contact with each other. For example, the fluid 103a may just about contact a lower surface of the at least one specimen 105. After the interaction, the fluid 103b may contain  
15 the material permeated (i.e., permeant) through the at least one specimen 105. However, it should be appreciated that, until the material has diffused through the specimen 105 and be collected by the fluid 103a, the fluid 103b after the interaction may be the fluid 103a.

**[0045]** A collection arrangement 106 may be arranged in fluid communication (represented by line 110b) with the sampling arrangement 104 to receive the fluid 103b after the interaction with  
20 the at least one specimen 105. The collection arrangement 106 may receive at least one container (e.g., a vial) to collect the fluid 103b. The collection arrangement 106 may further move the at least one container to collect the fluid 103b. In various embodiments, a portion (e.g., collection unit) of the collection arrangement 106 may be movable to move the at least one container. In the context of various embodiments, the phrase “at least one container” may include a reference to a  
25 plurality of containers.

**[0046]** In various embodiments, the collection arrangement 106 may be or may include an auto-sampler.

**[0047]** In various embodiments, the sampling arrangement 104 may be arranged in between the fluid transport arrangement 102 and the collection arrangement 106.

30 **[0048]** In various embodiments, the at least one container may be removable from the collection arrangement 106. At the end of the collection or sampling run, the at least one container

containing the fluid (e.g., with permeant) 103b may be removed for analysis or processing, for example, to determine the diffusion or permeation rate of a material (or substance or composition) provided to or on the at least one specimen 105, through the specimen 105.

**[0049]** In various embodiments, the collection arrangement 106 may receive a plurality of containers. A portion of the fluid 103b may be collected in at least one container of the plurality of containers. The collection arrangement 106 may then move the plurality of containers to at least one different position to collect, in at least one other container of the plurality of containers, at least one other portion of the fluid 103b.

**[0050]** In various embodiments, the sampling arrangement 104 may further include a diffusion device (or receptor device) configured to receive the at least one specimen 105 (and the fluid 103a for interaction with the at least one specimen 105). The diffusion device may be removable and may be provided as an insert in the apparatus 100. The diffusion device may be the device to be described in the context of FIG. 5. In various embodiments, a plurality of diffusion devices may be employed.

**[0051]** The diffusion device or each diffusion device may include at least one diffusion cell or receptor chamber to receive the at least one specimen 105 (and the fluid 103a for interaction with the at least one specimen 105). A plurality of diffusion cells or receptor chambers may be provided with the diffusion device or each diffusion device, for example, 2, 3, 4, 5, 6, 7, 8, or any higher number of diffusion cells or receptor chambers.

**[0052]** In various embodiments, the apparatus 100 may further include a controller arrangement configured to control the collection arrangement 106 to move the at least one container to a plurality of different positions at respective intervals. In other words, the controller arrangement may be configured to control movement of the at least one container at intervals. For example, a portion (e.g., receiving portion or collection unit) of the collection arrangement 106 may be movable, and the portion may be controlled to move at intervals. The controller arrangement may include a processor, for example, a central controller unit or a central processor for controlling such movement.

**[0053]** In various embodiments, the fluid transport arrangement 102 may include a syringe pump configured to deliver (or configured for delivery of) the fluid 103a, and the controller arrangement may be further configured to control the syringe pump to control at least one flow parameter of the fluid 103a (to be delivered to the sampling arrangement 104). This may mean

that the syringe pump may be under the control of the controller arrangement to regulate at least one flow parameter of the fluid 103a to be delivered by the fluid transport arrangement 104. The at least one flow parameter may include a flow rate and/or a flow volume. In various embodiments, a user may set the value for the at least one flow parameter using the controller arrangement. In this way, the syringe pump may be programmable or automated.

**[0054]** The fluid transport arrangement 102 may further include at least one syringe, and the syringe pump may be configured to actuate the at least one syringe to deliver the fluid 103a. It should be appreciated that a plurality of syringes may be used in cooperation with the syringe pump, for example, 2, 3, 4, 5 or any higher number of syringes. The syringe pump may be a multi-channel syringe pump, capable of actuating a plurality of syringes. The plurality of syringes may be actuated individually or independently.

**[0055]** In various embodiments, the number of syringes may correspond to the number of diffusion cells (or receptor chambers) for a 1-to-1 relationship. Providing a 1-to-1 relationship may enable a better control of the at least one flow parameter (e.g., flow rate and/or flow volume) of the fluid 103a that may be provided to the associated diffusion cell.

**[0056]** In various embodiments, the fluid transport arrangement 102 may be further configured to withdraw a content from at least one storage vessel (or container or bottle) to be delivered by the fluid transport arrangement 102 as the fluid 103a. The fluid transport arrangement 102 may be configured to withdraw a (predefined) volume of the content from the at least one storage vessel.

The syringe pump may cooperate with the at least one syringe to withdraw the content from the at least one storage vessel. As a non-limiting example, the at least one syringe may be actuated by the syringe pump to withdraw the content from the at least one storage vessel, prior to being further actuated by the syringe pump to deliver the content as the fluid 103a. In various embodiments, the at least one storage vessel may be provided, for example, integrally, with the apparatus 100, the at least one storage vessel being adapted to receive the fluid 103a as the content therewithin to be withdrawn by the fluid transport arrangement 102. It should be appreciated that a plurality of storage vessels (or containers or bottles) may be used with or provided within the apparatus 100. Different types of fluids may be received or stored in different respective storage vessels. The number of the plurality of storage vessels may correspond to the number of the plurality of syringes. For example, each syringe of the plurality of syringes may be in fluid communication with a respective storage vessel of the plurality of storage vessels.

[0057] In various embodiments, the collection arrangement 106 may include a collection unit configured to receive the at least one container, the collection arrangement 106 being configured to move the collection unit to move the at least one container. This may mean that the collection unit may receive at least one container (e.g., a vial) to collect the fluid 103b. The collection unit may be movable so as to move the at least one container to collect the fluid 103b. In various embodiments, the at least one container may be removable from the collection unit.

[0058] In various embodiments, the controller arrangement may be configured to control the collection unit to move at intervals. This may mean that the collection unit may move at intervals under control of the controller arrangement.

[0059] As non-limiting examples, the collection unit may first be positioned at a home position (e.g., for collecting the fluid 103b at the home position), then move for a predefined distance to a first position, pause at the first position at least temporarily (e.g., for collecting the fluid 103b at the first position), then move for a predefined distance to a second position (e.g., for collecting the fluid 103b at the second position), and so on. Each predefined distance may be of the same distance or may be of a different distance. Each pause of the collection unit may be of the same duration or may be of a different duration. In some embodiments, the fluid 103b may first be collected at the first position, rather than at the home position.

[0060] In various embodiments, a user may set the value for the intervals using the controller arrangement (or the central controller unit), and the collection unit may subsequently move, under control of the controller arrangement, at intervals as defined by the user. In this way, the collection unit may be programmable so that the collection unit may be moved at intervals, or movement of the collection unit may be automated. In general, the collection arrangement 106 may be programmable or may be automated.

[0061] In various embodiments, the collection arrangement 106 may be configured to move the collection unit in a linear motion or a rotary motion. In other words, the collection unit may be movable in a linear motion (or linearly movable) or in a rotary motion (or rotatably movable), for example, relative to a home position of the collection unit. The collection unit may be movable to a plurality of different positions relative to the home position. As non-limiting examples, the collection unit may be movable successively further relative to the home position. This may mean that each successive position of the plurality of different positions may be increasingly further from the home position.

[0062] In various embodiments, the apparatus 100 may further include a sensor (e.g., a position or location sensor) for determining (or indicating) a home position of the collection unit. The home position of the collection unit may be a starting position or a rest position or an initial position of the collection unit. For example, the collection unit may be at the home position for the start of a sampling run. The home position may provide a reference position. For example, movement or a position of the collection unit may be determined or measurable relative to the home position. As a non-limiting example, the home position may be at position  $X = 0$  (based on a Cartesian coordinate system) for a collection unit that is linearly movable, or  $\theta = 0$  (angle) for a collection unit that is rotatably movable.

[0063] In one example, the collection unit may move in or along a linear or straight path. The collection unit may be linearly movable along a horizontal plane (e.g., along an X-axis based on a Cartesian coordinate system).

[0064] In various embodiments, the collection arrangement 106 may include a linear slide assembly, and the collection arrangement 106 may be configured to move the collection unit in the linear motion along the linear slide assembly. The linear slide assembly may include a linear slide track (or guide) and the collection unit may be linearly movable along the linear slide track. The linear slide assembly may include an actuator, for example, a motor (e.g., stepper motor), to drive or move the collection unit linearly along the linear slide track. In various embodiments, the sensor associated with the collection arrangement 106 (for determining the home position of the collection unit) may be positioned at the linear slide assembly or at the linear slide track.

[0065] In various embodiments, the collection unit may include a mounting support adapted to receive a removable tray configured to receive the at least one container. The mounting support may include a recess to receive the removable tray. The removable tray may be provided as part of the collection unit.

[0066] In various embodiments, the collection unit may be or may include a tray configured to receive the at least one container. The tray may be a linear motion tray, meaning that the tray may be movable in a linear motion. The tray may be removable.

[0067] In another example, the collection unit may rotate about an axis. The collection unit may be or may include a tray. The tray may be a rotary motion tray, meaning that the tray may be movable in a rotary motion. The tray may be removable. An actuator, for example, a motor (e.g., stepper motor), may be provided to drive or move the tray in the rotary motion.

[0068] In various embodiments, the collection unit may include at least one opening or aperture adapted to receive the at least one container. As a non-limiting example, the collection unit may include a tray (e.g., as described above) capable of receiving or configured to receive the at least one container, e.g., a tray having at least one opening or aperture adapted to receive the at least one container. The tray may be removable.

[0069] In various embodiments, the apparatus 100 may further include a dispenser arrangement configured to dispense the fluid 103b after the interaction to the at least one container to be received by the collection arrangement 106 (e.g., received by the collection unit).

[0070] In various embodiments, the dispenser arrangement may include at least one dispenser, and the dispenser arrangement may be configured to move the at least one dispenser between a home position and a dispensing position proximal to the collection arrangement 106 (e.g., or proximal to the collection unit). The at least one dispenser may be configured to dispense the fluid 103b after the interaction to the at least one container to be received by the collection arrangement 106. This may mean that the at least one dispenser may receive the fluid 103b for dispensing to the at least one container. The at least one dispenser may be configured to dispense the fluid 103b at the dispensing position. The apparatus 100 may include one or more mount supports or brackets to support the dispenser arrangement. The at least one dispenser may be arranged in fluid communication with the sampling arrangement 104.

[0071] It should be appreciated that a plurality of dispensers may be employed. The number of the plurality of dispensers may correspond to the number of the plurality of containers available to collect the fluid 103b at any one time.

[0072] In various embodiments, the at least one container for collecting the fluid 103b may be covered or sealed (e.g., at the top of the container), and the at least one dispenser may puncture the cover or seal to dispense the fluid 103b into the container.

[0073] In various embodiments, the at least one dispenser may be or may include a needle. The needle may puncture a seal or cover of the container to dispense the fluid 103b into the container.

[0074] In various embodiments, the dispenser arrangement may be configured to move the at least one dispenser in a linear motion. This may mean that the at least one dispenser may be linearly movable between the home position and the dispensing position proximal to the collection arrangement 106. The home position may be distal to the collection arrangement 106. The dispensing position may be at a lower location relative to the home position. In various

embodiments, the at least one dispenser may move from the home position in a downwardly direction to the dispensing position, and may move from the dispensing position in an upwardly direction to the home position.

[0075] The home position of the at least one dispenser may be a starting position or a rest position or an initial position of the at least one dispenser. For example, the at least one dispenser may be at the home position for the start of a sampling run. The home position may provide a reference position. For example, movement or a position of the at least one dispenser may be determined or measurable relative to the home position. As a non-limiting example, the home position of the at least one dispenser may be at position  $Z = 0$  (based on a Cartesian coordinate system) for the at least one dispenser that is linearly movable.

[0076] The at least one dispenser may be movable along a vertical plane (e.g., along a Z-axis based on a Cartesian coordinate system). For example, the at least one dispenser may be positioned at the home position over the collection unit and may be moved in a direction towards the collection unit to the dispensing position to dispense the fluid 103b into the at least one container.

[0077] In various embodiments, after dispensing the fluid 103b, the at least one dispenser may move or return to the home position to await the subsequent dispensing action, e.g., where the collection unit is moved to allow at least one new (or fresh or unused) container to be in position to receive the fluid 103b for said subsequent dispensing action. Thereafter, the at least one dispenser may move to the dispensing position again to dispense the fluid 103b during said subsequent dispensing action. For example, the at least one dispenser may first be positioned at the home position (e.g., for receiving the fluid 103b after interaction with the at least one specimen 105), then move for a predefined distance to the dispensing position, pause at the dispensing position at least temporarily (e.g., for dispensing the fluid 103b to the at least one container), then move for the predefined distance in the reverse direction to the home position (e.g., for receiving the fluid 103b after interaction with the at least one specimen 105 for the subsequent dispensing action), and so on. In various embodiments, the at least one dispenser may be moved at intervals from the home position to the dispensing position. Each pause at the dispensing position may be of the same duration or may be of a different duration.

[0078] In various embodiments, movement of the at least one dispenser may be under the control of the controller arrangement. A user may set the value for the intervals using the controller arrangement.

[0079] In various embodiments, the dispenser arrangement may include a dispenser actuator arrangement, for example, including a linear slide assembly, and a motor (e.g., stepper motor), to drive or move the at least one dispenser between the home position and the dispensing position along the linear slide assembly. The at least one dispenser may be received or supported by a support structure of the dispenser actuator arrangement.

[0080] In various embodiments, the apparatus 100 may further include a sensor (e.g., a position or location sensor) for determining (or indicating) the home position of the at least one dispenser. The sensor may be positioned at a mount support or bracket supporting the dispenser arrangement.

[0081] In various embodiments, the apparatus 100 may be arranged as a two-tiered arrangement, and the collection arrangement 106 may be arranged at a lower tier of the two-tiered arrangement. This may mean that the collection arrangement 106 may be arranged proximal to a floor of the apparatus 100. At least one of the sampling arrangement 104, the fluid transport arrangement 102, or the dispenser arrangement may be arranged at an upper tier of the two-tiered arrangement. This may mean that the collection arrangement 106 may be arranged lower than that of at least one of the sampling arrangement 104, the fluid transport arrangement 102, or the dispenser arrangement.

[0082] In various embodiments, the sampling arrangement 104 may include an enclosure for receiving the at least one specimen 105, the enclosure adapted to allow heating of air within the enclosure (for example, for heating the at least one specimen 105). The enclosure may be configured to contain or seal in heated air therewithin. The diffusion device or each diffusion device may be received within the enclosure. Air within the enclosure may be heated to a temperature in the range of between about 30°C and about 40°C, for example, between about 30°C and about 35°C, between about 35°C and about 40°C, between about 30°C and about 32°C, or between about 32°C and about 35°C. As a non-limiting example, the temperature of the air within the enclosure may be heated to about 32°C to simulate human skin temperature.

[0083] In various embodiments, a heating element may be provided within the enclosure for heating the air therewithin. Heated air may be circulated within the enclosure.

[0084] In various embodiments, an air circulator or a fan may be provided within the enclosure, for example, to circulate air (e.g., heated air) within the enclosure and/or to cool the air within the enclosure. In some embodiments, the air circulator or the fan may be maintained powered on, for circulating heated air, once the apparatus 100 is activated and in operation.

5 [0085] In various embodiments, a temperature sensor (e.g., a thermocouple) may be provided to monitor the temperature within the enclosure, e.g., the air temperature within the enclosure. The temperature sensor may be provided within the enclosure.

[0086] In various embodiments, the controller arrangement may receive a signal or reading from the temperature sensor, where the signal is indicative of or represents the temperature within the enclosure, and may then compare the temperature against the user-defined temperature. Where  
10 necessary, in response thereto, the controller arrangement may control heating or cooling of the air within the enclosure. For example, where the temperature may be lower than the desired temperature or the user-defined temperature, the controller arrangement may cause heating of the air to bring the temperature up to the desired temperature (e.g., by increasing power supplied to  
15 the heating element, and/or deactivating the fan). Where the temperature may be higher than the desired temperature or the user-defined temperature, the controller arrangement may cause cooling of the air to bring the temperature down to the desired temperature (e.g., by reducing power supplied to the heating element, or cutting off power supplied to the heating element at least temporarily, and/or activating the fan). In some embodiments, the fan may be left operating  
20 continuously during measurement.

[0087] In various embodiments, the apparatus 100 may further include a (distribution) manifold in fluid communication with the fluid transport arrangement 102 and the sampling arrangement 104 to transport the fluid 103a delivered from the fluid transport arrangement 102 to the sampling arrangement 104. The manifold may be arranged in between the fluid transport  
25 arrangement 102 and the sampling arrangement 104. This may mean that the fluid 103a that is delivered from the fluid transport arrangement 102 may be transported through the manifold to the sampling arrangement 104, and subsequently received by the sampling arrangement 104.

[0088] As may be appreciated, a manifold may mean an element that may include a main conduit (or path) that then splits or divides into a plurality of branch conduits (or paths). The manifold  
30 may include a single main conduit that may then be divided into several branch conduits. For example, the manifold may be a 1-to-8 manifold (i.e., a manifold having a single input to 8

outputs). Nevertheless, it should be appreciated that other configurations may be possible, including but not limited to, a 1-to-4 manifold, a 1-to-5 manifold, a 1-to-6 manifold, etc.

[0089] In the context of various embodiments, each of the fluid transport arrangement 102, the sampling arrangement 104, the collection arrangement 106, the controller arrangement and the dispenser arrangement may be a separate or independent arrangement, or, a part of one of the arrangements may be incorporated into another arrangement, or a combination thereof.

[0090] The apparatus 100 of various embodiments may be an integrated system (e.g., for skin permeation study). This may mean that the fluid transport arrangement 102, the sampling arrangement 104, and the collection arrangement 106 may be integrated or integrally provided in one (single) apparatus/system or platform. The control arrangement may also be integrated or integrally provided with the apparatus 100. The dispenser arrangement may also be integrated or integrally provided with the apparatus 100.

[0091] In various embodiments, the fluid 103a may flow or pass through the apparatus 100, in sequence, the fluid transport arrangement 102 (e.g., through the at least one syringe), the manifold (which may be optional), the sampling arrangement 104 (e.g., through the enclosure), the dispenser arrangement (e.g., through the at least one dispenser), and the collection arrangement 106. The fluid 103a may initially be withdrawn from at least one storage vessel.

[0092] In various embodiments, the apparatus 100 may be automated, for example, fully automated throughout the course of sampling or measurement after an initial user input (e.g., to set the various parameters such as flow parameter, interval, etc.).

[0093] It should be appreciated that the flow or propagation of fluid between different arrangements or devices may be by means of one or more tubings (e.g., chemical resistant tubing(s)).

[0094] FIG. 1B shows a flow chart 160 illustrating a method of forming an apparatus for determination of diffusion or permeation through a specimen, according to various embodiments.

[0095] At 162, a fluid transport arrangement is arranged in fluid communication with a sampling arrangement configured to receive at least one specimen and a fluid to be delivered from the fluid transport arrangement for interacting with the at least one specimen to collect material diffused or permeated through the at least one specimen.

[0096] At 164, the sampling arrangement is arranged in fluid communication with a collection arrangement configured to receive and move at least one container to collect the fluid after the

interaction with the at least one specimen. The at least one container may collect the fluid after the interaction with the at least one specimen. The at least one container may be removable from the collection arrangement. The collection arrangement may include a collection unit configured to receive the at least one container.

5 [0097] FIG. 1C shows a flow chart 170 illustrating a method for controlling an apparatus for determination of diffusion or permeation through a specimen, according to various embodiments.

[0098] At 172, at least one specimen is provided in a sampling arrangement of the apparatus.

[0099] At 174, a fluid is delivered from a fluid transport arrangement of the apparatus to the at least one specimen to interact with the at least one specimen to collect material diffused or  
10 permeated through the at least one specimen.

[0100] At 176, a portion of the fluid after the interaction with the at least one specimen is collected in at least one container of a plurality of containers received by a collection arrangement of the apparatus. The at least one container may be removable from the collection arrangement.

15 [0101] At 178, the plurality of containers are moved, by means of the collection arrangement, to at least one different position to collect, in at least one other container of the plurality of containers, at least one other portion of the fluid after the interaction with the at least one specimen. The at least one other container may be removable from the collection arrangement.

[0102] In various embodiments, the plurality of containers may be removable from the collection  
20 arrangement.

[0103] In various embodiments, at 174, a plurality of different fluids may be delivered from the fluid transport arrangement, for example, to a plurality of specimens. Each respective fluid of the plurality of different fluids may interact with a respective specimen of the plurality of specimens.

[0104] In various embodiments, the collection arrangement may include a collection unit  
25 configured to receive the plurality of containers. The plurality of containers may be moved, by means of the collection unit. The collection of fluid may be carried out at a home position of the collection unit. The plurality of containers may be removable from the collection unit.

[0105] In various embodiments, at 178, the plurality of containers may be moved in a linear motion or a rotary motion to the at least one different position. For example, the plurality of  
30 containers may be received in a collection unit, where the collection unit may be linearly

movable or rotatably movable to move the plurality of containers in a linear motion or a rotary motion.

**[0106]** In various embodiments, at least one material to be diffused or permeated through the at least one specimen may be provided, for example, at 172 and/or 174.

5 **[0107]** In various embodiments, the plurality of containers may be received by the collection unit, and, at 178, the plurality of containers may be moved to a plurality of different positions, each successive position of the plurality of different positions being increasingly further relative to a home position of the collection unit.

10 **[0108]** In various embodiments, the plurality of containers may be moved to a plurality of different positions at intervals (e.g., at 178), and a duration of the intervals may be controlled. This may mean that the plurality of containers may be moved to each of the plurality of different positions at respective intervals, and a duration of each respective interval may be controlled. The duration for each respective interval may be the same or may be different from one interval to another interval.

15 **[0109]** In various embodiments, the fluid may be delivered from the fluid transport arrangement to the at least one specimen by means of a syringe pump of the fluid transport arrangement (e.g., at 174), and the syringe pump may be controlled to control at least one flow parameter of the fluid. The at least one flow parameter may include a flow rate and/or a flow volume.

20 **[0110]** In various embodiments, the method may further include withdrawing, by means of the fluid transport arrangement, a content from at least one storage vessel, and, at 174, the content may be delivered as the fluid to the at least one specimen to interact with the at least one specimen.

25 **[0111]** In various embodiments, the method may further include receiving, with a dispenser arrangement, the fluid after the interaction, and dispensing the fluid from the dispenser arrangement to the at least one container received by the collection arrangement.

30 **[0112]** In various embodiments, the at least one dispenser of the dispenser arrangement may be moved from a home position to a dispensing position proximal to the collection arrangement to dispense the fluid, and, after dispensing the fluid, the at least one dispenser may be returned to the home position. Such movement of the at least one dispenser from the home position to the dispensing position to dispense the fluid and, thereafter, from the dispensing position returning to

the home position, may be carried out for each time the fluid is dispensed from the at least one dispenser.

[0113] In various embodiments, the at least one specimen may be provided in an enclosure of the sampling arrangement (e.g., at 172), and an air within the enclosure may be heated (for heating the at least one specimen). The air within the enclosure may be heated to a temperature in the range of between about 30°C and about 40°C, for example, between about 30°C and about 35°C, between about 35°C and about 40°C, between about 30°C and about 32°C, or between about 32°C and about 35°C. Preferably, the temperature of the air within the enclosure may be heated to about 32°C to simulate human skin temperature.

[0114] While the methods described above are illustrated and described as a series of steps or events, it will be appreciated that any ordering of such steps or events are not to be interpreted in a limiting sense. For example, some steps may occur in different orders and/or concurrently with other steps or events apart from those illustrated and/or described herein. In addition, not all illustrated steps may be required to implement one or more aspects or embodiments described herein. Also, one or more of the steps depicted herein may be carried out in one or more separate acts and/or phases.

[0115] In the context of various embodiments, the at least one specimen (e.g., 105) may be or may include a membrane or a biomembrane, e.g., a skin portion, or may include skin cells.

[0116] In the context of various embodiments, the fluid (e.g., 103a) may be or may include a receptor fluid or a buffer solution. The receptor fluid may include, but not limited to, phosphate buffer saline (PBS)).

[0117] In the context of various embodiments, the container or each container receivable or to be received by the collection arrangement 106 or the collection unit may be a storage container. The container or each container may retain or store the fluid 103b collected therewithin. In various embodiments, the container may be a vial, e.g., a HPLC vial (or a vial suitable for high-performance liquid chromatography applications).

[0118] In the context of various embodiments, the term “arrangement” may include a reference to a “component” or “module” or “unit”.

[0119] It should be appreciated that descriptions in the context of the apparatus 100 may correspondingly be applicable in relation to the method of forming an apparatus for determination of diffusion or permeation through a specimen described in the context of the flow chart 160 and

the method for controlling an apparatus for determination of diffusion or permeation through a specimen described in the context of the flow chart 170, and vice versa.

[0120] FIG. 2A shows a simplistic schematic block diagram for the apparatus 200a of various embodiments, illustrating a representative flow diagram of the system of various embodiments. A diffusion device incorporating at least one diffusion cell 272 having a donor chamber 274 and a receptor chamber 276, is an individual device, and which may be provided as an insert in the apparatus 200a. This may mean that the diffusion device may be a device separate from and removable from the apparatus 200a. The donor chamber 274 may be received by or within the receptor chamber 276. The diffusion device may be of the type disclosed in US patent application number 14/051,720, and illustratively shown in FIG. 5 to be described below. A specimen, such as a skin sample 205, and a material, such as test chemical 290, for determination of diffusion or permeation through the skin sample 205, may be provided in the diffusion cell 272.

[0121] The apparatus 200a may include a syringe pump 220a for delivering a receptor fluid (e.g., phosphate buffer saline (PBS)) 203a to the diffusion cell 272, for example, to and through the receptor chamber 276. After interaction with the skin sample 205 and passing through the diffusion cell 272, the receptor fluid with chemical concentration (collectively represented by 203b) of the test chemical that diffuses or permeates through the skin sample 205 may be collected by a sample collection arrangement 206a of the apparatus 200a.

[0122] FIG. 2B shows a schematic block diagram for the apparatus 200b of various embodiments. FIG. 2B may be a more detailed representation of the apparatus 200a. The apparatus 200b may include a syringe pump 220b that may be employed to withdraw a receptor fluid or buffer solution 203a, for example, from a storage vessel. The syringe pump 220b may further deliver or dispense the buffer solution 203a, through one or more manifolds 224 that may provide a 1-to-6 fluid split, to one or more multichannel diffusion devices or kits 270 (containing specimen(s)) that may be provided within an enclosure 226 in which heated air may be provided. Preferably, there may be two multichannel diffusion devices 270 provided in the enclosure 226. Fluid containing permeant, after interaction with the specimen(s) and flowing out of the multichannel diffusion device(s) 270 may be received by a dispenser arrangement 230 with a needle actuator arrangement which may then dispense the received fluid to an auto-sampler 206b for collection of the dispensed fluid. The different arrangements or elements may be arranged into the order or sequence as described above in the context of FIG. 2B to enable a functional

apparatus 200b. It should be appreciated that such sequence may be applicable to any apparatus of various embodiments. The manifold(s) 224 may be optional.

[0123] The syringe pump 220a, 220b may be part of a fluid transport arrangement (e.g., 102). The enclosure 226 may be part of a sampling arrangement (e.g., 104). The auto-sampler 206b may be part of a collection arrangement (e.g., 106, 206a). The auto-sampler 206b may include a collection unit.

[0124] FIGS. 3A-3C show schematic perspective views of respective apparatus 300a, 300b, 300c, for determination of diffusion or permeation through a specimen, according to various embodiments. Like elements in the apparatus 300a, 300b, 300c are denoted by the same reference numeral. It should be appreciated that any description, or an element or feature, or a method step or process described in the context of one apparatus 300a, 300b, 300c, may similarly be applicable to another apparatus 300a, 300b, 300c, either in an identical form or configuration, or suitably modified to be employed with the other apparatus 300a, 300b, 300c.

[0125] Referring to FIG. 3A, the apparatus 300a may include a raised dual channel syringe pump (a type of infusion pump) 320a. By the term “raised”, it is meant that the syringe pump 320a may be elevated from a floor of the apparatus 300a, for example, positioned at an upper tier of the apparatus 300a. By the term “dual channel”, it is meant that the syringe pump 320a may be able to support and actuate two syringes (as represented by 322a for one syringe). Control or actuation of the two syringes 322a may be independent from each other. It should be appreciated that any n-channel syringe pump may be employed, for example, “n” may be 1, 2, 3, 4, 5 or any higher number. The syringe pump 320a and the syringes 322a may form part of a fluid transport arrangement 302a.

[0126] The apparatus 300a may further include a sampling arrangement 304a including an enclosure 326a suitable for heating of air therewithin. The sampling arrangement 304a may further include a support structure, e.g., a clamp 342a, to support or hold one or more diffusion or permeation devices 370a. The clamp 342a may include a pair of plates to hold the diffusion device(s) 370a therebetween. Each diffusion device 370a may include one or more diffusion cells. As a non-limiting example, there may be provided two diffusion devices 370a.

[0127] A respective dual check valve 340a may be provided in fluid communication with a respective one syringe 322a for controlling transport or flow of fluid through the syringe 322a. A manifold (e.g., a 1-to-8 manifold) 324a may be provided in fluid communication with a

respective dual check valve 340a and the sampling arrangement 304a (e.g., with a respective diffusion device 370a). For example, a tubing (not shown) may be provided for fluid communication between a dual check valve 340a and the corresponding manifold 324a, and tubing(s) (not shown) may be provided for fluid communication between a manifold 324a and the corresponding diffusion device 370a. As a non-limiting example, there may be provided two dual check valves 340a and two manifolds 324a.

**[0128]** A respective dual check valve 340a may also be in fluid communication with a respective one storage vessel 344a. For example, a tubing (not shown) may be provided for fluid communication between a dual check valve 340a and the corresponding storage vessel 344a. As a non-limiting example, there may be provided two storage vessels 344a. A PBS solution may be stored or contained in one or more of the storage vessels 344a.

**[0129]** For each respective dual check valve 340a, the dual check valve 340a may be switched to a first position or setting to allow fluid flow between the respective syringe 322a and the corresponding storage vessel 344a, and to a second position or setting to allow fluid flow between the respective syringe 322a and the corresponding manifold 324a. Accordingly, each respective dual check valve 340a may act as a switch to allow one fluid flow at any one time.

**[0130]** The apparatus 300a may further include a collection arrangement 306a including a collection unit 308a. The collection arrangement 306a may include a linear slide assembly 346a with a linear slide track (or guide) and the collection unit 308a may be movable along the linear slide track, for example, along a horizontal plane in an X-axis direction. The linear slide assembly 346a may further include a motor (e.g., a motorised linear slide assembly) to drive the collection unit 308a along the linear slide track.

**[0131]** The collection unit 308a may include a mounting support 348a adapted to receive a removable tray 350a configured to receive one or more (storage) containers, e.g., HPLC vial(s) 352a. For example, one or more openings may be provided with the tray 350a for receiving the container(s)/vial(s) 352a. The removable tray 350a may be part of the collection unit 308a. The mounting support 348a may include a recess to receive the removable tray 350a. The tray 350a may be a linear motion tray, movable (together with the mounting support 348a) along the linear slide assembly 346a. As illustrated in FIG. 3A, the collection arrangement 306a may be arranged at a lower tier relative to the position of the syringe pump 320a and the enclosure 326a.

[0132] The tray 350a may include a receptacle or container 354a for priming purposes, for example, to receive a priming solution. A priming process may be considered as a blank or dry run before loading the test ingredient and is designed to remove bubbles within all connecting tubings. The eluted buffer or priming solution may be collected by the rectangular receptacle 354a. For example, a priming solution may be initially provided through the apparatus 300a, including through the various tubings, and then finally collected by the receptacle 354a.

[0133] The apparatus 300a may further include a dispenser arrangement 330a having one or more dispensers (e.g., needle(s)) (not shown). The dispenser arrangement 330a may include a dispenser actuator arrangement 331a, which may include a linear slide assembly (or track) 356a, a support structure (or dispenser shelf) 358a to support or receive the one or more dispensers, and a motor (e.g., stepper motor), to drive or move the dispenser(s) and support structure 358a along the linear slide assembly 356a. The dispenser(s) may be movable along the linear slide assembly 356a, for example, along a vertical plane in a Z-axis direction. The dispenser actuator arrangement 331a may be supported by a pair of mount supports or brackets (as represented by 360a for one mount support).

[0134] In various embodiments, each dispenser may be a needle, for example, a (commercial/off-shelf) syringe needle. The needle has a sharp tip and may be used as a consumable. The needle may be removed from the apparatus 300a and replaced with a new needle for another sampling run or experiment to avoid cross-contamination. The puncture force of a needle may be determined or measured by simulating a membrane and using a force gauge to measure the force when the needle penetrates the membrane. The force may then be multiplied by the number or amount (e.g., 12) of the needles to be employed, a motor may then be selected to ensure that there is enough force for all employed needles to puncture simultaneously.

[0135] The apparatus 300a may further include a processor, such as a central controller unit (CCU) 362a for controlling operation of the apparatus 300a. As a non-limiting example, the CCU 362a may control at least one of the following: operation of the syringe pump 320a, the heating/cooling process within the enclosure 326a, operation of the dispenser actuator arrangement 331a, and operation of the collection arrangement 306a.

[0136] Two sensors or home sensors may be provided with the apparatus 300a. One sensor 364a may be positioned at a mount support 360a for the support structure 358a to monitor the movement or distance of the dispenser(s). The sensor 364a knows the home position, namely the

starting point, associated with the support structure 358a or the dispenser(s). The apparatus 300a employs the home position as a reference and guides the movement of the dispenser(s) for a consistent distance for pushing down the dispenser(s) to punch through the cover of the container (e.g., HPLC vial membrane) at each sampling interval. Another sensor 365a may be positioned at the side of the linear slide track of the linear slide assembly 346a (e.g., auto-sampler) to monitor the position or movement of the collection unit 308a or the tray 350a. The apparatus 300a employs the home position as a reference and moves the tray 350a for a certain distance to the next sampling position or location. If the user pauses the sampling process or experiment, the support structure 358a and the tray 350a may be moved back to the respective home positions until the experiment resumes.

**[0137]** Referring now to FIG. 3B, the apparatus 300b may be similar to the apparatus 300a, and having a dual channel syringe pump 320b that may support and actuate two syringes (as represented by 322b for one syringe). A circulation enclosure or box 326b suitable for heating of air therewithin may be provided. Two diffusion devices (as represented by 370b for one diffusion device) and two respective manifolds (as represented by 324b for one manifold) may be provided within the enclosure 326b. Two storage vessels 344b may also be provided. The apparatus 300b may further include a linear slide assembly 346b with a linear slide track (or guide). A tray 350b (e.g., as part of a collection unit 308b) configured to receive one or more (storage) containers (e.g., vial(s)) 352b may be provided and may be movable along the linear slide track, for example, along a horizontal plane in an X-axis direction. The apparatus 300b may further include a processor, such as a controller box 362b for controlling operation of the apparatus 300b. An outlet bracket 366b may also be provided for safety purposes to minimise or prevent accidental contact by a user with the slide assembly 346b, for example, during operation of the apparatus 300b.

**[0138]** For the apparatus 300b, the various elements and/or the arrangement of these elements and/or the operations of these elements, and/or the general operation of the apparatus 300b as a whole, may be similar to that described in the context of the apparatus 300a and hence are omitted herein for conciseness and clarity purposes. Further, although not illustrated in FIG. 3B nor described, it should be appreciated that one or more elements or features described in the context of the apparatus 300a may nevertheless be present in the apparatus 300b, such as dual check valve(s), home position sensor(s), dispenser(s), tubings, motor(s), etc.

[0139] Referring now to FIG. 3C, the apparatus 300c may be similar to the apparatus 300a, and having a dual channel syringe or infusion pump 320c that may support and actuate two syringes (as represented by 322c for one syringe). Two storage vessels 344c may be provided in fluid communication with the respective syringes 322c and the respective manifolds (as represented by 324c for one manifold) via respective dual check valves (as represented by 340c for one dual check valve). Each storage vessel 344c may be provided with a heating element 345c for heating the content of the storage vessel 344c.

[0140] A circulation enclosure 326c suitable for heating of air therewithin may be provided. Fluid that is provided to the manifolds 324c may be provided into the enclosure 326c via a plurality of tubings (as represented by 392c for one tubing). One or more diffusion devices (as represented by 370c for one diffusion device) may be provided within the enclosure 326c to receive fluid via the tubings 392c. A plurality of tubings (as represented by 394c for one tubing) may be provided for outflow of fluid from the diffusion device(s).

[0141] For apparatus 300c, rather than a linear motion tray 350a, 350b as part of a collection unit as provided with the apparatus 300a, 300b, a rotary motion tray 350c (e.g., as part of a collection unit 308c) may be employed for the apparatus 300c. A plurality of openings (as represented by 351c for one opening) may be defined in the tray 350c for receiving containers/vials (not shown).

[0142] One or more pinch valves (as represented by 396c for one pinch valve) may be provided to control collection of the fluid flowing out of the diffusion device(s). One or more volumetric flow sensors (as represented by 398c for one sensor) may be provided to monitor the flow of the fluid out of the diffusion device(s) to be collected.

[0143] For the apparatus 300c, the various elements and/or the arrangement of these elements and/or the operations of these elements, and/or the general operation of the apparatus 300c as a whole, may be similar to that described in the context of the apparatus 300a and hence are omitted herein for conciseness and clarity purposes. Further, although not illustrated in FIG. 3C nor described, it should be appreciated that one or more elements or features described in the context of the apparatus 300a may nevertheless be present in the apparatus 300c, such as dual check valve(s), home position sensor(s), motor(s), processor, etc.

[0144] FIG. 3D shows a schematic perspective view of an apparatus 300d for determination of diffusion or permeation through a specimen, according to various embodiments. The

apparatus 300d is similar to the apparatus 300a (FIG. 3A) and like elements in the apparatus 300a, 300d are denoted by the same reference numeral and letter, and the corresponding description for such like elements in the apparatus 300d may be as described in the context of the apparatus 300a and, therefore, omitted here for conciseness. Nevertheless, there are  
5 some differences between the two apparatus 300a, 300d as will be described below.

**[0145]** The apparatus 300d may include a multi-channel syringe pump (or infusion pump) 320d, which may be able to support and actuate multiple syringes (as represented by 322d for one syringe). The syringe pump 320d and the syringes 322d may form part of a fluid transport arrangement 302d. While 12 syringes 322d are shown in FIG. 3D, it should be appreciated that  
10 any number of syringes may be employed as long as the number of the syringes corresponds to the number of diffusion cells for a 1-to-1 relationship. As would be appreciated, as one syringe 322d is provided for one diffusion cell, a manifold such as the manifold 324a of the apparatus 300a is not required in the apparatus 300d. Further, it should be appreciated that the arrangement for 1-to-1 relationship between the syringes and the diffusion cells may also be  
15 employed for the apparatus 300b, 300c with suitable modification. Having a 1-to-1 relationship may enable a better control of the flow rate and/or the flow volume of the fluid to be provided from a respective syringe 322d to the associated diffusion cell.

**[0146]** A respective syringe 322d may be in fluid communication with a respective diffusion device provided in the enclosure 326a via a tubing (illustratively represented by the dashed  
20 line 380d for one such tubing). The tubing 380d may be connected to a dual check valve 340d of a respective syringe 322d. The apparatus 300d may further include a processor, such as a central controller unit (CCU) 362d for controlling operation of the apparatus 300d. The CCU 362d may be and/or perform the function as described in the context of CCU 362a (FIG. 3A). The CCU 362d may be positioned at the lower tier of the apparatus 300d, for example, at or towards  
25 the floor of the apparatus 300d.

**[0147]** For the apparatus of various embodiments, linear motion tray 350a, 350b (e.g., having a linear shape design) may be preferably employed compared to a rotary motion tray 350c (e.g., having a circular shape) for the following reasons: (1) a linear shape is more space saving; (2) if using a circular shape design, the tubing from each outlet of a multichannel diffusion device to  
30 the corresponding sampling vial is different in length, which may cause inconsistent volume collection, thereby potentially leading to error in the final results.

[0148] Using the apparatus 300a, 300b, 300c, 300d as examples, the apparatus 300a, 300b, 300c, 300d may be designed as a two-tiered system with a smaller footprint while known systems generally has one layer or tier only. Each apparatus 300a, 300b, 300c, 300d may include one or more of the following arrangements or sub-systems: an infusion system (e.g., a fluid transport arrangement having a syringe pump 320a, 320b, 320c, 320d), an enclosure 326a, 326b, 326c suitable for air heating therewithin and which may receive one or more diffusion devices 370a, 370b, 370c, a dispenser arrangement 330a with a dispenser actuator arrangement (e.g., 331a), and an auto-sampler (e.g., a collection arrangement 306a having a collection unit 308a, 308b, 308c). One or more or all of the arrangements or subsystems may be controlled by a processor (e.g., 362a, 362b, 362d).

[0149] Generally, the buffer solution (e.g., PBS), as the receptor fluid, may be stored in two storage vessels 344a, 344b, 344c, e.g., two brown colour bottles. At the start of the sampling or experiment, the syringe pump 320a, 320b, 320c, 320d may control the syringes 322a, 322b, 322c, 322d to draw the buffer solution from the storage vessels 344a, 344b, 344c. After the syringes 322a, 322b, 322c, 322d are loaded with the buffer solution, the syringe pump 320a, 320b, 320c, 320d may push or actuate the plunger of one or both or multiple syringes 322a, 322b, 322c, 322d to deliver the solution firstly to pass through tubings 380d or a manifold 324a, 324b, 324c that then splits the solution into channels/tubings (e.g., 392c), for example, 6 channels/tubings. The solution in each tubing 380d or channel may flow into a respective receptor chamber of one diffusion device 370a, 370b, 370c and the solution may then pass through the receptor chamber, just beneath the skin (specimen) positioned in the receptor chamber, and carry away test ingredient permeated through the skin. Then, the solution containing the permeant may flow out of the receptor chamber and pass through the connecting tubing (e.g., 394c) towards or to a collection port or unit 308a, 308b, 308c. A tray 350a, 350b, 350c may be used to collect the eluting sample (solution containing the permeant) at different time intervals. Containers (e.g., 352a, 352b), for example, HPLC vials, may be received or carried by the tray 350a, 350b, 350c for collection or storage of the solution containing the permeant. At different time intervals, for example, a linear motion tray 350a, 350b, may linearly move or slide, or a rotary tray 350c may rotate, to an array of empty containers (e.g., 352a, 352b) for collection. Each apparatus 300a, 300b, 300c, 300d may be an automatic diffusion system (ADS).

[0150] The processor (e.g., CCU 362a, 362d) may control or allow one or more of the following functions: (1) Start, pause and stop sampling run or experiment; (2) Priming system or operation; (3) Access or define settings for at least one of flow rate, enclosure temperature, or sampling time intervals. In various embodiments, with the help of the processor, the apparatus or system of various embodiments may be fully automated throughout the course of sampling or experiment after an initial user input.

[0151] The operating temperature, or the internal air temperature of the heated enclosure 326a, 326b, 326c may be adjustable within the range of of 30-40°C. Preferably, a temperature of about 32°C may be employed to simulate human skin temperature.

[0152] In various embodiments, at least one of a fan or a temperature sensor may be provided in the enclosure 326a, 326b, 326c. Generally, the diffusion device 370a, 370b, 370c may need to be maintained at a specific temperature (preferably 32°C  $\pm$  1°C) throughout the sampling or experiment process. To achieve this, the air within the enclosure 326a, 326b, 326c may be heated up and regulated with temperature feedback control. This in turn may cause the permeation device(s) 370a, 370b, 370c to warm up to the user-defined temperature. Heated air inside the enclosure 326a, 326b, 326c may be generated by using a heating element that is attached to a heatsink and a fan assembly. As cool air is drawn by the fan, it passes through the hot fins of the heatsink, heating up in the process. The warmed air passes over an upper portion of the enclosure 326a, 326b, 326c through a ventilation wall and contacts a thermocouple located above the diffusion device(s) 370a, 370b, 370c. The thermocouple provides air temperature feedback to the processor (e.g., CCU 362a, 362d) which may compare the measured temperature against the user-defined temperature. If the measured temperature is too low, the heating element may remain on, otherwise, the heating element may be turned off. Air temperature may be regulated by consistent on-off switching of the heating element according to the feedback from the thermocouple.

[0153] In various embodiments, according to the user-defined sampling intervals, the movement of the sampling dispensers (or needles) may be controlled by the processor (e.g., CCU 362a, 362d).

[0154] In various embodiments, a Z-axis dispenser actuator arrangement may be designed to allow the fluid (containing permeant) to be delivered into covered sampling containers or vials through dispenser (or needle) penetration.

[0155] Chemical resistant tubings (e.g., 392c, 394c, 380d) may be used to deliver fluid within the apparatus (e.g., 300a, 300b, 300c, 300d). In contrast, in known systems, the fluid flows in microchannels made of polydimethylsiloxane (PDMS).

[0156] In one non-limiting example, the working steps for the apparatus (e.g., 300a, 300b, 300c, 300d) of various embodiments may include one or more or all of the following:

1. Set or define (e.g., by a user) the flow rate of the syringe pump 320a, 320b, 320c, 320d, the temperature for the enclosure 326a, 326b, 326c and the sampling time points (e.g., intervals) at the processor (e.g., 362a, 362b, 362d). Real time temperature and progress of each sampling/experiment may be monitored and displayed at the processor.
2. After initiating the setting, the syringe pump 320a, 320b, 320c, 320d may begin to withdraw solution or content, via the syringes 322a, 322b, 322c, 322d, from the buffer bottles 344a, 344b, 344c (e.g., PBS bottles) to a certain volume.
3. Then, the heating element within the enclosure 326a, 326b, 326c may be activated to work so as to increase the temperature within the enclosure 326a, 326b, 326c to the defined value. The dispenser actuator arrangement (e.g., 331a) controlling the movement of the dispenser(s), and the tray 350a, 350b, 350c (e.g., a removable tray) may be moved to the target position (e.g., the home position, or a first position away from the home position).
4. The syringe pump 320a, 320b, 320c, 320d may start to deliver or dispense the solution from the syringes 322a, 322b, 322c, 322d at the defined flow rate, to two manifolds 324a, 324b, 324c, or to tubings 380d. Each manifold 324a, 324b, 324c may split one inlet flow into 6 equal outlet flows to then be delivered by chemical resistant tubings (e.g., 392c).
5. The fluid from each tubing (e.g., 392c, 380d) may then be delivered to one end of a diffusion device 370a, 370b, 370c (as inlet flow) located in the heated enclosure 326a, 326b, 326c. The fluid may interact with one or more specimens received in the diffusion device 370a, 370b, 370c. There may be two sets of multichannel diffusion devices or kits 370a, 370b, 370c in the heated enclosure 326a, 326b, 326c. Each device 370a, 370b, 370c may include 6 diffusion cells or receptor chambers.
6. The fluid containing test ingredients permeated through a specimen (e.g., a membrane) may be delivered by another tubing (e.g., 394c) connecting to the other end of the diffusion device 370a, 370b, 370c (as outlet flow). The tubing (e.g., 394c) crosses or passes through the heated enclosure 326a, 326b, 326c and extends to a rack or support structure

(e.g., 358a) where dispensers (e.g., needles) with luer lock ends may be suspended. A Z-axis dispenser actuator arrangement (e.g., 331a), for example having an actuator located below the support structure (e.g., 358a), may allow the fluid (after interaction with specimen and containing permeant) to be delivered into covered sampling vials (e.g., 352a, 352b) through dispenser (needle) penetration.

7. The fluid from each respective tubing (e.g., 394c) may be delivered to a corresponding dispenser, and the droplets from the dispenser may drip down to a sampling vial (e.g., 352a, 352b).

8. At the defined sampling points, the syringe pump 320a, 320b, 320c, 320d may pause and the Z-axis needle actuator lifts up and then moves to the next target position for dispensing (i.e., dispensing position). After that, the syringe pump 320a, 320b, 320c, 320d continues dispensing the solution at the defined flow rate until the next defined sampling point. In some embodiments, the operation of the syringe pump 320a, 320b, 320c, 320d may be continuous (i.e., without a pause) throughout the entire process. There is no observable leakage from the dispensers (or needles) even when the dispensers are not in the dispensing position for dispensing into sampling vials (e.g., 352a, 352b).

**[0157]** FIG. 4A shows a schematic perspective view of a collection arrangement 406, according to various embodiments, while FIG. 4B shows a side view of a part of the apparatus 400 of various embodiments incorporating the collection arrangement 406. The collection arrangement 406 may be an auto-sampler. The collection arrangement 406 may be a linear motion auto-sampler designed to achieve a compact design with less complexity. The collection arrangement 406 may include a linear slide assembly 446 and a collection unit 408.

**[0158]** The linear slide assembly 446 may include a linear slide track (or precision linear slide actuator) 447 and a motor (e.g., a stepper motor) (not shown). The linear slide track 447 may have a length of about 400 mm. A home sensor (not shown) may be positioned at one side of the linear slide track 447. Accordingly, a motorised linear slide with a home sensor may be provided.

**[0159]** The collection unit 408 may include a tray mount (e.g., HPLC tray mount) 448, that may be (slidably) movable along the linear slide track 447. A removable tray (e.g., HPLC tray) 450 may be received in the mount 448. The tray 450 may be held in place through a recessed feature in the tray mount 448. Positioning of the tray mount 448 may be controlled by the motor driving the linear slide track 447 to move the tray mount 448, with a home sensor for positional accuracy.

[0160] The removable tray 450 may receive a plurality of (storage) containers (e.g., HPLC vials) (as represented by 452 for one container) so as to collect fluid. The plurality of containers 452 may be arranged in a plurality of rows and a plurality of columns, e.g., in a grid-like manner. The removable tray 450 may allow the user to arrange the containers 452 easily, away from the tray mount 448. It also allows the user to clean the tray 450 in case of spillage.

[0161] FIG. 4B shows the arrangement of the collection arrangement 406 in the apparatus 400. At the position shown in FIG. 4B, the sample vial tray (HPLC tray) 450 on or of the collection unit 408 may be easily removed and replaced. The collection arrangement 406 may be partially enclosed. While not shown, an optional access door may be provided to allow access to the collection arrangement 406 or the plurality of containers 452.

[0162] The position as shown in FIG. 4B may be the home position for the tray mount 448. Alternatively, at the home position, the first row of containers 452 may be positioned directly under the dispensers, e.g., distribution needles 459, allowing for the sampling process or experiment to start without additional positioning required. The fluid or solution containing material or test ingredient permeated through the specimen/membrane, after interaction with the specimen, may pass through the needles 459 and may be collected with the tray 450 having the containers 452 movable at the user configurable time intervals for further analysis.

[0163] FIG. 5 shows a schematic perspective view of a diffusion device (or permeation device) 570 suitable for use with the apparatus or system of various embodiments. The diffusion device 570 may be a 6-cell diffusion (or permeation) device, having 6 diffusion cells (represented by 572 for one cell). Each diffusion cell 572 may include a donor chamber 574 and a receptor chamber (not shown) that receives the donor chamber 574. Each diffusion cell 572 may receive or hold a specimen. The diffusion cells 572 may be supported on a support structure 578. A plurality of channels or fluid paths (represented by 580 for one channel) may be formed through the support structure 578. One respective channel 580 may be associated with a respective diffusion cell 572 for inflow of fluid to and outflow of fluid from the respective diffusion cell 572.

[0164] Table 1 below provides a comparison of the system or apparatus of various embodiments against known systems.

TABLE 1:

|                         | Known systems                              | Various embodiments                  |
|-------------------------|--------------------------------------------|--------------------------------------|
| Pump                    | Peristaltic pump (moderate precision 1-3%) | Syringe pump (high precision < 0.1%) |
| Heater/Circulator       | Water jacketed circulator                  | Air heating system                   |
| Throughput              | 3-6                                        | 12-24                                |
| Types of receptor fluid | 1                                          | 2                                    |
| Footprint               | Bulky (the smallest: 27" deep x 29" wide)  | Small (15" deep x 20" wide)          |

[0165] The system or apparatus of various embodiments may include one or more of the following features: (1) high precision due to the use of a syringe pump arrangement; (2) even heat distribution due to the use of an air heating system; (3) high throughput, where a number of replicates may be done within one sampling run, for example, using 12-24 diffusion chambers; (4) use of different receptor fluids, for example, per one sampling run; and (5) space saving due to its smaller footprint.

[0166] While the invention has been particularly shown and described with reference to specific embodiments, it should be understood by those skilled in the art that various changes in form and detail may be made therein without departing from the spirit and scope of the invention as defined by the appended claims. The scope of the invention is thus indicated by the appended claims and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced.

## CLAIMS

1. An apparatus for determination of diffusion or permeation through a specimen, the apparatus comprising:

5 a fluid transport arrangement configured to deliver a fluid;

a sampling arrangement configured to receive at least one specimen and the fluid to interact with the at least one specimen to collect material diffused or permeated through the at least one specimen; and

10 a collection arrangement configured to receive and move at least one container to collect the fluid after interaction with the at least one specimen.

2. The apparatus as claimed in claim 1, further comprising a controller arrangement configured to control the collection arrangement to move the at least one container to a plurality of different positions at respective intervals.

15 3. The apparatus as claimed in claim 2,

wherein the fluid transport arrangement comprises a syringe pump configured to deliver the fluid, and

20 wherein the controller arrangement is further configured to control the syringe pump to control at least one flow parameter of the fluid.

4. The apparatus as claimed in claim 3,

wherein the fluid transport arrangement further comprises at least one syringe, and

25 wherein the syringe pump is configured to actuate the at least one syringe to deliver the fluid.

5. The apparatus as claimed in any one of claims 1 to 4, wherein the fluid transport arrangement is further configured to withdraw a content from at least one storage vessel to be delivered by the fluid transport arrangement as the fluid.

6. The apparatus as claimed in any one of claims 1 to 5, wherein the collection arrangement comprises a collection unit configured to receive the at least one container, the collection arrangement being configured to move the collection unit to move the at least one container.

7. The apparatus as claimed in claim 6, further comprising a sensor for determining a home position of the collection unit.

8. The apparatus as claimed in claim 6 or 7, wherein the collection arrangement is configured to move the collection unit in a linear motion or a rotary motion.

9. The apparatus as claimed in claim 8,  
wherein the collection arrangement comprises a linear slide assembly, and  
wherein the collection arrangement is configured to move the collection unit in the linear motion along the linear slide assembly.

10. The apparatus as claimed in any one of claims 1 to 9, wherein the collection unit comprises a mounting support adapted to receive a removable tray configured to receive the at least one container.

11. The apparatus as claimed in any one of claims 1 to 10, further comprising a dispenser arrangement configured to dispense the fluid after the interaction to the at least one container to be received by the collection arrangement.

12. The apparatus as claimed in claim 11,  
wherein the dispenser arrangement comprises at least one dispenser, and  
wherein the dispenser arrangement is configured to move the at least one dispenser between a home position and a dispensing position proximal to the collection arrangement.

13. The apparatus as claimed in claim 12, further comprising another sensor for determining the home position of the at least one dispenser.

14. The apparatus as claimed in any one of claims 1 to 13, wherein the apparatus is arranged as a two-tiered arrangement, and wherein the collection arrangement is arranged at a lower tier of the two-tiered arrangement.

15. The apparatus as claimed in any one of claims 1 to 14, wherein the sampling arrangement comprises an enclosure for receiving the at least one specimen, the enclosure adapted to allow heating of air within the enclosure.

16. A method of forming an apparatus for determination of diffusion or permeation through a specimen, the method comprising:

arranging a fluid transport arrangement in fluid communication with a sampling arrangement configured to receive at least one specimen and a fluid to be delivered from the fluid transport arrangement for interacting with the at least one specimen to collect material diffused or permeated through the at least one specimen; and

arranging the sampling arrangement in fluid communication with a collection arrangement configured to receive and move at least one container to collect the fluid after the interaction with the at least one specimen.

17. A method for controlling an apparatus for determination of diffusion or permeation through a specimen, the method comprising:

providing at least one specimen in a sampling arrangement of the apparatus;

delivering a fluid from a fluid transport arrangement of the apparatus to the at least one specimen to interact with the at least one specimen to collect material diffused or permeated through the at least one specimen;

collecting, in at least one container of a plurality of containers received by a collection arrangement of the apparatus, a portion of the fluid after the interaction with the at least one specimen; and

moving the plurality of containers, by means of the collection arrangement, to at least one different position to collect, in at least one other container of the plurality of containers, at least one other portion of the fluid after the interaction with the at least one specimen.

18. The method as claimed in claim 17,  
wherein the plurality of containers are received by a collection unit of the collection arrangement, and

wherein moving the plurality of containers to at least one different position comprises moving the plurality of containers to a plurality of different positions, each successive position of the plurality of different positions being increasingly further relative to a home position of the collection unit.

19. The method as claimed in claim 17 or 18,

wherein moving the plurality of containers to at least one different position comprises moving the plurality of containers to a plurality of different positions at intervals, and wherein the method further comprises controlling a duration of the intervals.

20. The method as claimed in any one of claims 17 to 19,

wherein delivering a fluid comprises delivering the fluid from the fluid transport arrangement to the at least one specimen by means of a syringe pump of the fluid transport arrangement; and

wherein the method further comprises controlling the syringe pump to control at least one flow parameter of the fluid.

21. The method as claimed in any one of claims 17 to 20, further comprising withdrawing, by means of the fluid transport arrangement, a content from at least one storage vessel, and

wherein delivering a fluid comprises delivering the content as the fluid to the at least one specimen to interact with the at least one specimen.

22. The method as claimed in any one of claims 17 to 21, further comprising:

receiving, with a dispenser arrangement, the fluid after the interaction; and

dispensing the fluid from the dispenser arrangement to the at least one container received by the collection arrangement.

23. The method as claimed in claim 22,

wherein dispensing the fluid comprises moving at least one dispenser of the dispenser arrangement from a home position to a dispensing position proximal to the collection arrangement to dispense the fluid, and

5 after dispensing the fluid, the method further comprises returning the at least one dispenser to the home position.

24. The method as claimed in any one of claims 17 to 23,

wherein providing at least one specimen in a sampling arrangement comprises providing

10 the at least one specimen in an enclosure of the sampling arrangement, and

wherein the method further comprises heating an air within the enclosure.