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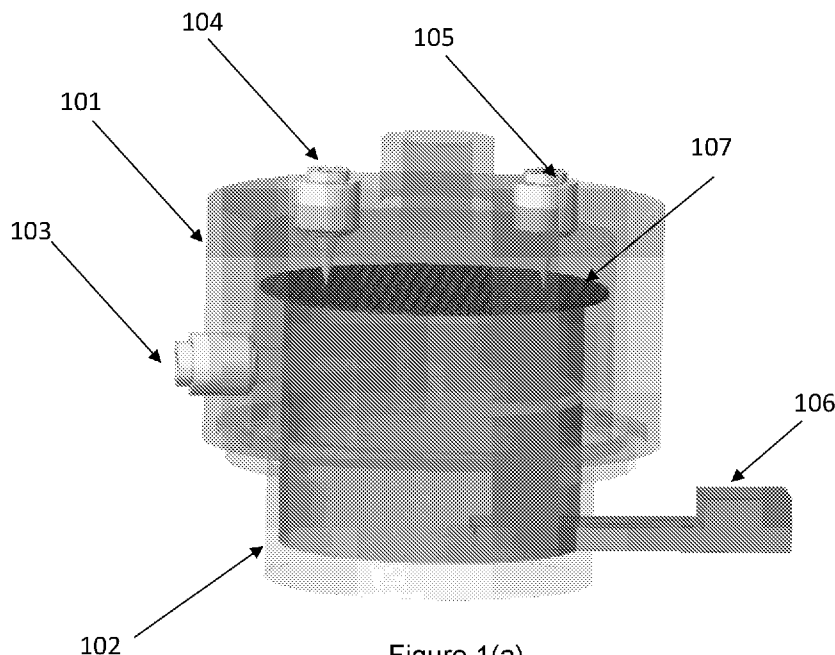


Figure 1(a)

(57) Abstract: The present invention relates to a particle analyser. In particular, the present invention relates to a device and a method for monitoring a dynamic profile of particles including deposition, and/or diffusion and/or dissolution rates of the particles.

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A PARTICLE ANALYSER

Related application

[0001] The present application claims priority to Australian Provisional Patent Application No. AU2023904149, filed 20 December 2023, which is incorporated by reference in its entirety.

Field of the Invention

[0002] The present invention relates to a particle analyser. In particular, the present invention relates to a device and a method for monitoring a dynamic profile of particles. However, it will be appreciated that the invention is not limited to these particular fields of use.

Background of the Invention

[0003] The following discussion of the prior art is provided to place the invention in an appropriate technical context and enable the advantages of it to be more fully understood. It should be appreciated, however, that any discussion of the prior art throughout the specification should not be considered as an express or implied admission that such prior art is widely known or forms part of the common general knowledge in the field.

[0004] The global market for pulmonary inhaled drug delivery systems is poised for robust expansion, with an anticipated value of \$91 billion USD by 2030. Drug formulation development involves extensive research, preclinical evaluations, stability assessments, and clinical trials. The cost of a single inhaler going through product development and clinical trial is of the order of tens of millions USD. Ensuring the success of clinical trials necessitates technologies that can bridge the gap between current *in-vitro* protocols (lab measurements) and *in-vivo* outcomes, i.e. technologies are required that are closer to the “physiological scenario”. In addition, technologies that are able to assess variability in aerosol behaviour as well as be able to identify the root cause of any batch to batch variability are highly valued in the industry. As part of the current drive to improve “*in-vitro-in-vivo*-correlation” (IVIVC) the inhaler research community needs to measure a range of processes, ranging from drug deposition to dissolution rate.

[0005] Dissolution rate is a critical feature of *in-vivo* performance as this relates to the ability of a drug to be dissolved in the body and be made bio-available. Dissolution rate defines how effectively a formulation is dissolved in a liquid medium after deposition to become available for cellular absorption, and therefore defines its bioavailability. Other than its chemical composition, the ability for a drug to dissolve depends on how distributed it is within the dissolution environment (e.g., how distributed it is across the filter paper making contact with the solvent in the *in vitro* measurement or how distributed across human tissue it is in reality).

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Dissolution will also depend on whether or not the powder forms a monolayer of particles, whether or not particle clusters are tightly packed or not, and what the size of the particles or agglomerates are. Currently such parameters cannot be easily measured in-situ. They are measured “off-line” rendering them far less useful as they do not represent the actual powder composition at the site of dissolution. Current methods of measuring the dissolution rate of drugs have been adopted from tablet testing procedures, and while they are robust enough to enable comparison between different benchmarks, they are not physiologically representative and do not enable an integrated measurement of the “full picture” of inhaled drug delivery (i.e. the delivery, deposition, dissolution and diffusion of the drug all in a singular measurement platform).

[0006] In addition to the desirability of IVIVC, new inhalers must meet the regulators’ lists of critical quality attributes (CQAs), which e.g. in the US are specified in documentation such as the FDA draft guidelines, with details provided in the United States Pharmacopeia (USP). Meeting quality attributes involves a series of laborious measurement protocols which aim to measure the particle size and deposition rate of drug particles in models of the human airway, as well as batch to batch repeatability testing of a particular inhaler.

[0007] US Patent No. 4,568,190 discloses an electrooptical system and technique for direct quantitative measurement of the mass concentration of monodisperse aerosols by means of filling an enclosed chamber with a cloud or a sequence of separate clouds of essentially transparent and spherical, aerosolized particles or droplets of known density and known or selectively controlled particle size.

[0008] US Patent No. 5,954,845 discloses an aerosol sampler. It discloses a method of abstracting a quantity of air through a curved porous plate, where the angle of curvature of the plate, and the size and number of the holes comprising the porosity are designed to allow accurate sampling of the particulate content over defined size ranges.

[0009] It is an object of the present invention to overcome or ameliorate at least one of the disadvantages of the prior art, or to provide a useful alternative.

[0010] Unless the context clearly requires otherwise, throughout the description and the claims, the words “comprise”, “comprising”, and the like are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense; that is to say, in the sense of “including, but not limited to”.

[0011] Although the invention will be described with reference to specific examples it will be appreciated by those skilled in the art that the invention may be embodied in many other forms.

Summary of the Invention

[0012] According to a first aspect of the present invention there is provided a device for monitoring a dynamic profile of particles, comprising:

a porous material for depositing the particles thereon, wherein the porous material is wetted with a dissolution medium; and

a first optical imaging module configured to obtain a deposition profile of the particles on the porous material to thereby obtain a diffusion rate of the particles through the porous material; wherein the dynamic profile of particles is a function of the obtained diffusion rate.

[0013] In some embodiments, the deposition profile of the particles comprises dynamic deposition thickness of the particles.

[0014] In some embodiments, the porous material comprises two portions, a first portion of the porous material being wetted with the dissolution medium and a second portion of the porous material not being wetted with any dissolution medium, the device further comprises a second optical imaging module configured to obtain a deposition profile of the particles on the second portion of the porous material to thereby obtain a deposition rate of the particles, and the dynamic profile of particles is a function of the obtained deposition rate and diffusion rate.

[0015] The inventors of the present invention have found that the device of the present invention advantageously enables both batch to batch testing of particle characteristics as well as measurements of a particle dynamic profile including simultaneous measurement of deposition, and/or diffusion, and/or dissolution rates in real time, all in the same apparatus, for the understanding of particle behaviours and inhaler performance.

[0016] The skilled person in the art would understand that the dissolution medium refers to a solvent that is capable of at least partially dissolving the particles. The skilled person would also appreciate that in some embodiments the first portion of the porous material is wetted with the dissolution medium and the second portion of the porous material is not wetted with the dissolution medium.

[0017] The skilled person would appreciate that in some embodiments, the first optical imaging module may be configured to measure the deposition rate and the diffusion rate. For example, the first optical imaging module may measure the deposition rate of the particles as they are being deposited on the porous material, and the skilled person would appreciate that the diffusion may be slower, or much slower, than the deposition. After the particles are deposited, the first optical imaging module may measure the diffusion rate.

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[0018] In some embodiments, the deposition profile comprises the thickness, area and/or volume of particles' deposition on the porous material. In certain embodiments, the deposition profile comprises changes in these parameters.

[0019] In some embodiments, the first optical imaging module is further configured to obtain the deposition rate of the particles from the second optical imaging module to thereby obtain the diffusion rate of the particles. The skilled person would appreciate that these embodiments may be useful when the diffusion and the deposition are at a similar rate, or when diffusion is faster than deposition.

[0020] In some embodiments, the first optical imaging module and/or the second optical imaging module are configured to provide light beams for obtaining the diffusion and/or deposition rate of particles. In a particular embodiment, the light beams are substantially parallel to each other.

[0021] In some embodiments, the device further comprises a compartment to contain the dissolution medium, wherein the dissolution medium is in contact with the wetted porous material. In some embodiments, the compartment is a first compartment.

[0022] In some embodiments, the device further comprises a third optical imaging module configured to obtain a dynamic optical path length through the dissolution medium to thereby obtain a dissolution rate of the particles through the dissolution medium, and wherein the dynamic profile of the particles is a function of the obtained deposition rate, and/or diffusion rate and/or dissolution rate.

[0023] In some embodiments, the optical path length is obtained by directing a light beam from the third optical imaging module through the dissolution medium to a mirror dispositioned on a wall of the compartment or the first compartment.

[0024] In some embodiments, the device further comprises a second compartment, wherein the second portion of the porous material is in contact with the second compartment; and wherein the second compartment is essentially devoid of any dissolution medium such that the second portion of the porous material is not wetted with any dissolution medium.

[0025] Advantageously, the device of the present invention is capable of measuring the dissolution rate of particles in the dissolution medium without the need for dose collection procedures employed in existing techniques (e.g., high performance liquid chromatography), which is a highly time consuming method commonly used for chemical assays. It also facilitates compatibility of the device with drug delivery devices and airway models, and mimicking aspects of *in vivo* deposition profiles.

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[0026] The skilled person would appreciate that the device may enable a real-time and in-situ correlation between dissolution and deposition profiles and deposition thickness, based on simultaneous monitoring of these parameters.

[0027] The skilled person would also appreciate that the optical path length measurement facilitates the quantification of a refractive index measurement of the dissolution medium.

[0028] A skilled person would also recognise that the alteration in optical attenuation within the dissolution medium can facilitate the assessment of solution concentration. The optical attenuation at the third optical imaging module changes as more particles dissolve in the medium.

[0029] The skilled person would also understand that the device enables the determination of diffusion rates through a porous material (for example, a membrane) via quantification of the change in thickness of powder deposition and is applicable in dissolution methods where dissolution occurs mainly by diffusion. For diffusion-controlled dissolution tests, accurate *in vitro* simulation of *in vivo* conditions necessitates high membrane diffusion and low retention, avoiding non-sink inaccuracies. Achieving a more accurate dissolution profile with the device requires diffusion coefficient determination, repeatability tests, and drug adsorption measurements on the porous material. Here, the device enables repetitive measurements in-situ and enables the study of the porous material attributes, especially regarding pore size effects, as well as the impact of drug properties (such as particle size, and powder layer characteristics and other physical characteristics) on dissolution rate.

[0030] In some embodiments, the first optical imaging module and the second optical imaging module are configured to provide light beams for obtaining the diffusion and deposition rate of particles, and the third optical imaging module is configured to provide the light beam substantially perpendicular to the light beams provided by the first and/or the second optical imaging modules. However, the skilled person would understand that the third optical imaging module can be positioned in any direction, as long as there is a dissolution medium present within a substantially fixed known length along the optical path before it reaches the mirror.

[0031] In some embodiments, the compartment or the first compartment comprises a protrusion that provides access to the dissolution medium through a window. In some embodiments, the protrusion is a rectangular protrusion. In some embodiments, the window is an optical window.

[0032] In some embodiments, the window is made from removal glass. In some embodiments, the window is affixed to the protrusion on both sides.

[0033] In some embodiments, the third optical imaging module is attached to the protrusion, aligning the light beam to the window.

[0034] In some embodiments, the third optical imaging module comprises a collimator. In some embodiments, the third optical imaging module is configured to provide a light beam that travels through the dissolution medium during its round trip between the collimator and the mirror.

[0035] In some embodiments, the device further comprises an electrochemical device operably connected with the compartment or the first compartment, the electrochemical device configured to measure the concentration of particles in the dissolution medium to thereby obtain a dissolution rate of the particles.

[0036] In some embodiments, the electrochemical device is any suitable device that involves electrical resistance measurement, similar to the process/device used for transepithelial electrical resistance measurement (TEER).

[0037] In some embodiments, the device is adapted to connect with an airway model to receive the particles. For example, the airway model may be a standard USP induction port, an Alberta idealized model or other idealized throat (e.g. VCU or OPC) or other realistic airway model.

[0038] In some embodiments, the device is adapted to integrate with any particle-laden (aerosol) flow in unconfined or confined geometries such as a cascade impactor to receive the particles.

[0039] In some embodiments, the device further comprises a lid covering at least a part of the porous material, wherein the optical imaging module is dispositioned on the lid.

[0040] In some embodiments, the lid is detachable.

[0041] The skilled person would appreciate that the lid is advantageously detachable for porous material replacement and cleaning.

[0042] In some embodiments, the device further comprises a vacuum source configured to facilitate particles deposition on the porous material, wherein the vacuum source is connected to the lid.

[0043] In some embodiments, the optical imaging module comprises an optical coherence tomography (OCT) probe.

[0044] In some embodiments, the porous material is a membrane, a porous-based biomaterial for tissue or a filter paper.

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[0045] In some embodiments, the membrane has a pore diameter of between about 0.001 μm and about 1000 μm , preferably about 0.4 μm . For example, the pore diameter may be between about 0.001 μm and about 0.01 μm , between about 0.01 μm and about 0.1 μm , between about 0.1 μm and about 1 μm , between about 1 μm and about 10 μm , between about 10 μm and about 50 μm , between about 50 μm and about 100 μm , between about 100 μm and about 500 μm , or between about 500 μm and about 1000 μm , and about 0.001 μm , about 0.01 μm , 0.1 μm , 1 μm , 50 μm , 100 μm , 200 μm , 300 μm , 400 μm , 500 μm , 600 μm , 700 μm , 800 μm , 900 μm or 1000 μm .

[0046] In some embodiments, the device further comprises a data processing unit that provides displacement map from phase difference between consecutive temporal axial scans calculated from the optical imaging module to thereby provide the deposition profile.

[0047] In some embodiments, the device can consist of additional sub-modules or components, that enable live cells, and/or tissue imaging using the OCT to study mucociliary clearance effects. These imaging capabilities include quantifying/ monitoring ciliary health through their beat frequency and/or change in tissue elasticity/stiffness before and/or after drug, particles, or any form of other aerosols (e.g. Toxins, pollutants) is deposited. These measurements will be correlated with the dissolution measurements.

[0048] In some embodiments, the device comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 optical imaging modules. For example, the device may comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 optical imaging modules.

[0049] The skilled person would understand that any suitable particles that are able to scatter light at the same or substantially the same wavelength range as the incident light may be used. Particularly, any suitable drug particles may be used as long as it is not fully transparent or translucent. For example, the particles may be selected from the group consisting of mannitol or diclofenac.

[0050] The skilled person would appreciate that any suitable dissolution medium may be used. The dissolution medium needs to have a suitable optical transparency or semi-transparency, enabling light to reach the mirror and be reflected towards the objective. For example, the dissolution medium may be ethanol, water, phosphate buffer solutions (pbs), or biorelevant medias (e.g., simulated lung fluid(SLF)).

[0051] In some embodiments, the device is configured to obtain an initial baseline before deposition signifies axial measurement of an empty membrane.

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[0052] In some embodiments, the device is configured to obtain a baseline optical path length (OPL) of the reflector when the chamber contains no dissolution media.

[0053] According to a second aspect of the present invention there is provided a method of monitoring a dynamic profile of particles, comprising the steps of:

- a) depositing the particles on a porous material, the porous material being wetted with a dissolution medium;
 - b) obtaining a deposition profile of the particles on the porous material using a first optical imaging module to thereby obtain a diffusion rate of the particles through the porous material;
- wherein the dynamic profile of particles is function of the obtained diffusion rate.

[0054] In some embodiments, the deposition profile of the particles comprises dynamic deposition thickness of particles.

[0055] In some embodiments, the method comprises the steps of:

- a) depositing the particles on the porous material comprising two portions, a first portion of the porous material being wetted with the dissolution medium and a second portion of the porous material not being wetted with any dissolution medium;
 - b) obtaining the deposition profile of the particles on the first portion of the porous material using the first optical imaging module to thereby obtain the diffusion rate of the particles;
 - c) obtaining a deposition profile of the particles on the second portion of the porous material using a second optical imaging module to thereby obtain a deposition rate of the particles;
- wherein the dynamic profile of particles is function of the obtained deposition rate and diffusion rate.

[0056] In some embodiments, the method further comprises a step of obtaining the deposition rate of the particles from the second optical imaging module to thereby obtain the diffusion rate of the particles.

[0057] In some embodiments, the first optical imaging module and/or the second optical imaging module provide light beams for obtaining the diffusion an/or deposition rate of particles. In a particular embodiment, the light beams are substantially parallel to each other.

[0058] In some embodiments, the method further comprises a step of providing a compartment to contain the dissolution medium, wherein the dissolution medium is in contact

with the wetted porous material. In some embodiments, the compartment is a first compartment.

[0059] In some embodiments, the method further comprises a step of obtaining a dynamic optical path length through the dissolution medium using a third optical imaging module to thereby obtain a dissolution rate of the particles through the dissolution medium, and wherein the dynamic profile of the particles is a function of the obtained deposition rate, and/or diffusion rate and/or dissolution rate.

[0060] In some embodiments, the step of obtaining an optical path length comprises directing a light beam from the third optical imaging module through the dissolution medium to a mirror dispositioned on a wall of the compartment or the first compartment.

[0061] In some embodiments, the first optical imaging module and the second optical imaging module provide light beams for obtaining the diffusion and deposition rate of particles, and the third optical imaging module provides the light beam substantially perpendicular to the light beams provided by the first and the second optical imaging modules.

[0062] In some embodiments, the method further comprises a step of measuring the concentration of particles in the dissolution medium to thereby obtain a dissolution rate of particles using an electrochemical device operably connected with the compartment or the first compartment.

[0063] In some embodiments, the electrochemical device is any suitable device that involves electrical resistance measurement, similar to the process/device used for transepithelial electrical resistance measurement (TEER).

[0064] In some embodiments, the method further comprises a step of receiving the particles from an airway model.

[0065] In some embodiments, the method further comprises a step of receiving the particles from a particle-laden (aerosol) flow in unconfined or confined geometries such as a cascade impactor.

[0066] In some embodiments, the optical imaging modules are dispositioned on a lid covering at least a part of the porous material.

[0067] In some embodiments, the lid is detachable.

[0068] In some embodiments, the method further comprises a step of facilitating particle deposition on the porous material by a vacuum source connected to the lid.

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[0069] In some embodiments, the optical imaging module comprises an optical coherence tomography (OCT) probe.

[0070] In some embodiments, the porous material is a membrane, a porous-based biomaterial for tissue or a filter paper.

[0071] In some embodiments, the membrane has a pore diameter of between about 0.001 μm and about 1000 μm , preferably about 0.4 μm . For example, the pore diameter may be between about 0.001 μm and about 0.01 μm , between about 0.01 μm and about 0.1 μm , between about 0.1 μm and about 1 μm , between about 1 μm and about 10 μm , between about 10 μm and about 50 μm , between about 50 μm and about 100 μm , between about 100 μm and about 500 μm , or between about 500 μm and about 1000 μm , and about 0.001 μm , about 0.01 μm , 0.1 μm , 1 μm , 50 μm , 100 μm , 200 μm , 300 μm , 400 μm , 500 μm , 600 μm , 700 μm , 800 μm , 900 μm or 1000 μm .

[0072] In some embodiments, the method further comprises a step of obtaining a displacement map from phase difference between consecutive temporal axial scans calculated from the optical imaging module to thereby provide the deposition profile.

[0073] In some embodiments, the method further comprises a step of obtaining an initial baseline before deposition signifies axial measurement of an empty membrane.

[0074] In some embodiments, the method further comprises a step of obtaining a baseline optical path length (OPL) of the reflector when the chamber contains no dissolution media.

[0075] The skilled person will appreciate that embodiments of the first aspect may apply to the second aspect, where appropriate.

[0076] According to a third aspect of the present invention there is provided a method of monitoring a dynamic profile of particles, comprising using a device according to the first aspect of the present invention, wherein the dynamic profile of particles is a function of the obtained deposition rate, and/or diffusion rate and/or dissolution rate.

[0077] Other aspects of the present invention will become apparent to those ordinarily skilled in the art upon review of the following description of specific embodiments of the invention.

Definitions

[0078] In describing and claiming the present invention, the following terminology will be used in accordance with the definitions set out below. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments of the

invention only and is not intended to be limiting. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one having ordinary skill in the art to which the invention pertains.

[0079] Unless the context clearly requires otherwise, throughout the description and the claims, the words “comprise”, “comprising”, and the like are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense; that is to say, in the sense of “including, but not limited to”.

[0080] As used herein, the phrase “consisting of” excludes any element, step, or ingredient not specified in the claim. When the phrase “consists of” (or variations thereof) appears in a clause of the body of a claim, rather than immediately following the preamble, it limits only the element set forth in that clause; other elements are not excluded from the claim as a whole. As used herein, the phrase “consisting essentially of” limits the scope of a claim to the specified elements or method steps, plus those that do not materially affect the basis and novel characteristic(s) of the claimed subject matter.

[0081] With respect to the terms “comprising”, “consisting of”, and “consisting essentially of”, where one of these three terms is used herein, the presently disclosed and claimed subject matter may include the use of either of the other two terms. Thus, in some embodiments not otherwise explicitly recited, any instance of “comprising” may be replaced by “consisting of” or, alternatively, by “consisting essentially of”.

[0082] Other than in the operating examples, or where otherwise indicated, all numbers expressing quantities of ingredients or reaction conditions used herein are to be understood as modified in all instances by the term “about”. The examples are not intended to limit the scope of the invention. In what follows, or where otherwise indicated, “%” will mean “weight %”, “ratio” will mean “weight ratio” and “parts” will mean “weight parts”.

[0083] The term ‘substantially’ as used herein shall mean comprising more than 50% by weight, where relevant, unless otherwise indicated.

[0084] The recitation of a numerical range using endpoints includes all numbers subsumed within that range (e.g., 1 to 5 includes 1, 1.5, 2, 2.75, 3, 3.80, 4, 5, etc.).

[0085] Further, unless expressly stated to the contrary, “or” refers to an inclusive or and not to an exclusive or. For example, a condition A or B is satisfied by any one of the following: A is true (or present) and B is false (or not present), A is false (or not present) and B is true (or present), and both A and B are true (or present).

[0086] The terms “preferred” and “preferably” refer to embodiments of the invention that may afford certain benefits, under certain circumstances. However, other embodiments may also be preferred, under the same or other circumstances. Furthermore, the recitation of one or more preferred embodiments does not imply that other embodiments are not useful and is not intended to exclude other embodiments from the scope of the invention.

[0087] It must also be noted that, as used in the specification and the appended claims, the singular forms “a”, “an” and “the” include plural referents unless the context clearly dictates otherwise.

[0088] As used herein, with reference to numbers in a range of numerals, the terms “about,” “approximately” and “substantially” are understood to refer to the range of -10% to +10% of the referenced number, preferably -5% to +5% of the referenced number, more preferably -1 % to +1 % of the referenced number, most preferably -0.1 % to +0.1 % of the referenced number. Moreover, with reference to numerical ranges, these terms should be construed as providing support for a claim directed to any number or subset of numbers in that range. For example, a disclosure of from 1 to 10 should be construed as supporting a range of from 1 to 8, from 3 to 7, from 1 to 9, from 3.6 to 4.6, from 3.5 to 9.9, from 8 to 10, and so forth.

[0089] The prior art referred to herein is fully incorporated herein by reference.

[0090] Although exemplary embodiments of the disclosed technology are explained in detail herein, it is to be understood that other embodiments are contemplated. Accordingly, it is not intended that the disclosed technology be limited in its scope to the details of construction and arrangement of components set forth in the following description or illustrated in the drawings. The disclosed technology is capable of other embodiments and of being practiced or carried out in various ways.

Brief Description of the Drawings

[0091] Preferred embodiments of the invention will now be described, by way of example only, with reference to the accompanying drawings in which:

[0092] Figure 1 shows: (a) a perspective view of a device of the present invention; (b) a top view of the device.

[0093] Figure 2 shows: (a) a perspective view of a lid of the device; (b) a top view of the lid.

[0094] Figure 3 shows: (a) a perspective of a base unit of the device comprising a first and a second compartments; (b) a top view of the base unit.

[0095] Figure 4 shows a diagram illustrating the multi-channel OCT back end.

[0096] Figure 5 shows a diagram showing that the device connected with an airway model.

[0097] Figure 6 shows a data processing routine for the OCT probes to quantify the deposition, diffusion and dissolution characteristics.

[0098] Figure 7 shows visualization of mannitol dry powder deposition on a membrane-like film using OCT measurements: (a) 3D rendering of powder deposition within a region of interest measuring $10.2 \times 10.8 \text{ mm}^2$ laterally, with a depth of 2.5 mm; (b) Cross-sectional depth image extracted from (a) following the path along the red arrows. The thin film layer is shown by the yellow arrow.

[0099] Figure 8 shows characterization of diffusion patterns of diclofenac particles through a membrane ($0.4 \text{ }\mu\text{m}$ pore diameter) of a Transwell diffusion cell apparatus: (a) Evolution of the overall area of the powder deposition layer as assessed from OCT cross-sectional images over time. (b) A linear regression line on the scatter plot illustrating the correlation between transported diclofenac mass (mg) to the dissolution media and the cumulative reduction in the total drug deposition area (mm^2).

[00100] Figure 9 shows obtaining dissolution rate of particles by quantifying the refractive index modulation of dissolution medium using OCT: (a) OCT cross-sectional image capturing a solution droplet placed onto a flat aluminium plate. The refractive index (n_o) was determined using the ratio of optical thickness (OT) to the geometrical thickness (GT) of the droplet; (b) Representative refractive indices for various solutions: ethanol, water, and three mannitol concentrations (1%, 3.13%, and 5.25% w/w). Findings exhibit strong correlation with readings from the commercial refractive index detector (RID) apparatus.

[00101] Figure 10 shows an illustration of the measurement of the refractive index of the dissolution media using the third optical imaging probe. The geometric width, z_o , of the dissolution compartment is equivalent to the optical path length (OPL) in the absence of dissolution media, given that the refractive index of air is approximately 1. Upon introducing the dissolution media to the compartment, the OPL increases due to the higher group refractive index, n_g , of the solution compared to that of air. Consequently, the new OPL becomes $z_o + \Delta z$. Here, the depth position 'z' is determined from OCT images of third OCT probe. RM and RM' represent the optical positions of the reflective mirror in the absence and presence of the dissolution media within the compartment, respectively.

[00102] Figure 11 shows an example realisation of an embodiment of the device.

[00103] Figure 12 shows sensitivity evaluation of the dissolution probe (third optical imaging module) using various solutions.

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[00104] Figure 13 shows an illustration of how the thickness of powder deposition on the filter evolves over time.

[00105] Figure 14 illustrates results showing the change in optical path length (OPL) as powder particles deposited on filter paper and diffuse into and dissolve in the solution.

[00106] Figure 15 shows representative dissolution response profiles of different formulations in water.

Detailed Description of the Invention

[00107] The skilled addressee will understand that the invention comprises the embodiments and features disclosed herein as well as all combinations and/or permutations of the disclosed embodiments and features.

Particle Analyser

[00108] In some embodiments, the device of the present invention is a multifunctional device capable of simultaneously quantifying deposition, diffusion and dissolution properties of particles, for example solid aerosols. The invention combines a dose collection porous material, for example a filter or membrane, and a dissolution chamber with integrated optical imaging module, for example high resolution optical coherence tomography (OCT) probes for deposition and diffusion imaging as well as a dissolution quantifying unit based on combined electrochemistry and OCT techniques. The first function of the OCT probe is to monitor aerosol deposition microstructure and demonstrate visually, in real-time how they accumulate on surfaces, and how rapidly the particles transfer through a membrane. The second function of the OCT is to measure changes in optical characteristics of dissolution media with measurement accuracy complemented through the electrochemistry technique.

[00109] Figure 1(a) shows a device 100 for monitoring a dynamic profile of particles. It comprises a detachable lid 101 housing three optical imaging modules 103, 104 and 105, and a base unit 102 connected with a micro-transport electrochemical unit 106. A membrane 107 is positioned on top of the base unit to collect particles for deposition and diffusion analysis and can be readily replaced. The lid 101 is designed to be removable to facilitate replacement of the membrane. The bottom of the lid has an aperture, enabling attachment of a vacuum source for imposing a flow through the device whilst deposition, diffusion and dissolution rates are measured. Figure 1(b) shows a top view of the device as shown in Figure 1(a).

[00110] Figure 2(a) shows a lid 200 of the device as shown in Figure 1(a). The lid has three OCT probes 202, 203 and 201 are used to monitor particle deposition, diffusion and dissolution, respectively, during real-time measurements. The pair of probes 202 and 203 monitor the

behaviour of particles as they deposit onto and diffuse across the membrane, whereas the probe 201 quantifies the dynamic changes in the refractive index of the dissolution medium. Figure 2(b) shows a top view of the lid as shown in Figure 2(b).

[00111] Figure 3(a) shows a base unit 300 of the device as shown in Figure 1(a). This unit comprises two compartments: the left compartment 301 facilitates membrane contact with the dissolution medium, enabling diffusion measurements, while the right compartment 302 keeps the membrane dry, facilitating dynamic deposition measurements. In the first compartment, a mirror 303 is affixed to the partitioning wall, enabling the assessment of the solution's refractive index via the detection of Optical Path Length (OPL) changes by the OCT probe (201 or 103).

[00112] Figure 4 illustrates a multi-channel OCT system being illuminated by a superluminescent diode (SLD) emitting a broadband light (e.g., 50 nm bandwidth at full width half maximum (FWHM) and centre wavelength of 840 nm). The outgoing light is split into the three channels and subsequently to the sample and reference arms of each channel using a fused fiber-optic coupler. For each channel, the beam in the sample arm is focused on to the sample (i.e., particle deposition for the first and second optical modules, and the mirror for the third optical module) using a scan (objective) lens of appropriate focal length. The back-scattered light from the sample and the reference light reflected off a flat reference mirror is recombined in the coupler to form an interference fringe. The fringe signal (OCT signal), is spectrally resolved and detected using detector(s), which is normally a spectrometer. The spectral signal is acquired and transferred to a computer for post-processing.

[00113] Figure 5 depicts the schematic representation of a typical experimental configuration designed for simulating the delivery of respiratory drugs. It features an upper airway model connected to the device. To load the dry powder, a dry powder inhaler (DPI) is connected at the upper airway's inlet, and it utilizes enforced airflow from either a compressed air line or a vacuum pump. This airflow causes the particles to deposit on the membrane, and the deposition measurement is subsequently carried out by the first and second optical modules.

[00114] Figure 6 shows a data processing routine for the OCT probes to quantify the deposition, diffusion and dissolution characteristics. The initial baseline before deposition signifies the axial measurement of an empty membrane, whereas the baseline optical path length (OPL) of the reflector is obtained when the chamber contains no dissolution media.

Real time data processing and visualization

[00115] The following data processing routine represent one of the examples of using OCT probes to generate real-time visual representations of drug deposition, diffusion and dissolution dynamics as illustrated in Figure 6.

From raw data to displacement map (common steps for the three channels)

[00116] Preprocessing: The raw OCT data contains the interference spectrum resulting from the interaction between the reference beam and the light reflected from the sample, such as particle deposition. In spectral domain OCT, the detected interferogram pattern, I , is a function of wavenumber, k , and the scattering layer of the sample is characterized by its optical depth position, z , as

$$I(k) = I_{DC} + I_{SC} + S(k) \sum_{n=1}^N (\sqrt{R_n R_r} \cos(2k \cdot z_n)) \quad (A1)$$

where R_n and R_r are reflectivity of the n^{th} layer of the sample and the reference mirror, respectively, $S(k)$ is the optical power density of the light source and $k = 2\pi/\lambda$ is the wavenumber which is inversely related to wavelength λ of the light. Equation (A1) shows that the detected spectrum signal contains unwanted components, mainly the direct current (I_{DC}) and self-correlation (I_{SC}) signals, which can compromise the OCT signal (depicted by the third term in the equation). To mitigate the impact of these undesirable signals, it is common practice to apply DC subtraction and filtering techniques, such as bandpass filters.

[00117] Fast Fourier Transform (FFT): The filtered OCT interferogram signal needs to be converted from k -space to spatial domain, yielding the depth resolved reflectivity information of the sample. To generate the sample depth profile (cross-sectional profile), an inverse Fourier transformation is conventionally applied to equation (A1), yielding a complex signal, $I(z)$, given by

$$I(z) = FFT^{-1}[I(k)] = A(z) \cdot \exp(i\phi(z)) \quad (A2)$$

where $\phi(z)$ is the phase and $A(z)$ is the magnitude which represents the conventional structural reflectivity profile of the sample. Understandably, one can repeat multiple A-scans at several adjacent positions on the sample to produce a cross-sectional image (B-scan). The intensity map (a 2D image) is usually displayed using a logarithmic scale to enhance contrast.

$$A_{dB}(z) = 20 \cdot \log_{10}(|A(z)|) \quad (A3)$$

[00118] The intensity map provides a cross-sectional view of the deposition, unveiling not only its surface features but also the internal microstructure, including pores. Importantly, this structural image allows for the determination of deposition thickness, and thus, the dynamic changes in the deposition profile can be analyzed through a sequence of temporal frames. However, the resolution of dynamic thickness changes during deposition is constrained by the axial resolution of the OCT system, approximately 3 to 15 μm . To achieve a more finely resolved thickness alterations, the OCT signal phase profile, which corresponds to alterations

in the optical path of the beam due to deposition increase/decrease, can be utilized, as elaborated below.

[00119] Phase unwrapping: Further processing of the complex matrix's phase component enables the detection of minute changes in optical path length. In the present scenario, the depth location of the deposition surface shifts as particles accumulate dynamically at the deposition site or diffuse across the membrane. Similarly, the apparent axial position, specifically the optical path length (refer to Fig. 10), of the reflective mirror (located within the dissolution chamber's inner compartment) changes in response to variations in the refractive index of the dissolution media. In all three instances (i.e., the three OCT channels), the dynamic alterations in deposition thickness and/or the dissolution media's refractive index lead to changes in OPL for the light backscattered by the corresponding scatterers or reflective mirrors at position z over time t . Consequently, these changes induce variations in the phase of the OCT signals and can be related as

$$\Delta d(z, t) = \Delta \phi(z, t) \cdot \lambda / (4\pi) \quad (\text{A4})$$

where $\Delta d(z, t)$ is the axial optical displacement between scans and $\Delta \phi$ the induced phase change due to change in the axial position of scatterer. The phase change in equation (A4) is employed after unwrapping the temporal phases to generate a continuous phase profile, extending beyond the typical $-\pi$ to π radians range.

Channel specific procedures

Ch-1: Computing deposition profile

[00120] The deposition thickness can increase as more and more particles land on the membrane during the inhalation. Continuous acquisition during the deposition would enable to capture the dynamic changes in the deposition thickness. Using the temporal frames acquired during deposition, the minute changes in the thickness of the deposition can be quantified from the displacement profiles obtained from the previous step (eq. (A4)). The displacement map of the deposition surface can be used to produce the deposition profile. This profile represents the rate of increase in the thickness of the deposition over time. The instantaneous deposition thickness obtained by tracking the surface of the displacement/phase map of instantaneous OCT frames as the cumulative sum of the surface axial positions up to that point of interest as

$$T(t) = \sum_{\tau=0}^{\tau=t} \Delta d(z_s, \tau) \quad (\text{A5})$$

where the $T(t)$ is the deposition thickness at time t , and z_s is the axial position of the deposition interface at time t . Thus, the deposition thickness profile can be produced for the period of inhalation.

Ch-2: Determining diffusion profile

[00121] Similar to the deposition measurement discussed above, the estimation of the diffusion profile involves assessing changes in deposition thickness as particles diffuse across the membrane. However, the phenomenon at the diffusion site can be delineated into two phases: the initial phase involving simultaneous deposition and diffusion (occurring during inhalation simulation) and the subsequent phase involving solely diffusion.

[00122] During the first phase, particles are both depositing on and diffusing across the membrane. Since the OCT acquisition speed (frame rate) typically exceeds the diffusion rate, alterations in deposition thickness during this period manifest as both a decrease (attributed to diffusion) and an increase (resulting from deposition). To extract the contribution to diffusion, the cumulative sum is computed for the frame-to-frame change in the deposition surface that leads to an increase in its depth position using equation (A5). The decrease in the depth position, indicating particle deposition between frames within a specific time interval, is excluded.

[00123] In the second phase, where simultaneous deposition ceases, the temporal decrease in deposition thickness signifies the particle diffusion profile across the membrane. This reduction in deposition thickness over time can be obtained using a similar equation (A5), yielding to the diffusion profile over time.

Ch-3: Computing dissolution profile

[00124] The refractive index of a dissolution medium is directly influenced by its concentration. This index is determined by comparing the speed of light in the medium to its speed in a vacuum or air. To better understand this relationship, one can consider that as the number of particles or molecules in the media increases, the speed of light decreases. For instance, a particle-free water solution has a lower refractive index than a solution containing a few grams of lactose, causing light to move more slowly. We utilize this phenomenon to monitor changes in the concentration of the dissolution medium as powder particles dissolve.

[00125] The process involves measuring the optical path length (OPL) of a reflective mirror within the inner compartment of the dissolution chamber. Initially, the geometric width of the mirror is measured when the chamber is empty (denoted as z_0 in Fig. 1A), and subsequently, the changes in OPL are measured when the dissolution medium is present (Δz in Fig. 1A). As

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a result, the refractive index of the medium can be correlated with the OPL before and after the inclusion of the dissolution medium using Snell's law.

$$n_g = (z_o + \Delta z) / z_o \quad (A5)$$

[00126] While particles dissolve in the medium, the continuous changes in the OPL of the reflective mirror can be used to determine the temporal group refractive index, $n_g(t)$, using the instantaneous changes in OPL, $\Delta z(t)$, as.

$$n_g(t) = (z_o + \Delta z(t)) / z_o \quad (A6)$$

where t represents the measurement time elapsed since the initiation of the dissolution process.

[00127] Ultimately, the dissolution profile can be correlated with the dynamic variation in the media's refractive index, enabling the measurement of a dissolution rate. Additionally, it is possible to ascertain the instantaneous molar concentration of the media by employing a standard correlation between the refractive index and molar concentration.

Other embodiments

[00128] In some embodiments of the invention, the device comprises a data processing unit configured to analyse data obtained from OCT probes.

[00129] In some embodiments, the data processing unit implements the following steps to quantify particle deposition behaviour using an OCT probe (e.g., probe 105), which include:

- evaluating micro-modulation within the deposition profile (e.g., its thickness, area, volume) by analysing a sequence of high-temporal resolution OCT images;
- monitoring and tracing particle behaviour (e.g., particle velocity) at deposition sites from the OCT image, estimating the probability of particles settling on the deposition membrane or re-entering the flow after reaching the deposition site. This is achieved by cross-correlating temporal sequences of two-dimensional and/or three-dimensional image patches derived from optical coherence tomography images.

[00130] In some embodiments of the invention, the data processing unit implements the following steps to obtain a diffusion profile using particle deposition-diffusion dynamics acquired from an OCT probe (e.g., probe 104), which include:

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- determining the dynamics of deposition (i.e., changes in its thickness, area, volume) during the diffusion process;
- segmenting OCT images of deposition into wetted and non-wetted regions by identifying differences in image contrast between these areas upon contact with the media. Applying this process repeatedly to temporal OCT frames enables the quantification of the diffusion rate.

[00131] In some embodiments of the invention, the data processing unit obtains dissolution medium concentration as particles dissolve. This is accomplished by quantifying the modulation in the optical path length between the probe tip and the target mirror within the dissolution medium. This enables the quantification of the refractive index of the solution by comparing measured micro-modulation in the optical path length to an empty chamber (in the absence of dissolution medium). The method involves correlating changes in refractive index with the particle mass transported to the media, quantified by the electrochemical unit.

[00132] In some embodiments, the device enables a comprehensive real-time visualization of deposition, diffusion, and dissolution attributes, encompassing:

- deposition profile (its thickness, area, volume at ROI), and dissolution profile (refractive index changes and percentage of transported particle mass to the dissolution medium);
- particle dynamics at diffusion and deposition sites, accentuating differences between concurrent deposition-diffusion and exclusive deposition locales.

[00133] In some embodiments of the invention, the method of monitoring a dynamic profile of particles also include the steps as described above.

Lab-scale measurement results

[00134] Figures 7, 8 and 9 show representative particle deposition, diffusion and dissolution measurement results, respectively, in lab-scale set ups.

Further examples

[00135] Figure 11 shows an example realisation of an embodiment of the device, featuring a dissolution chamber with a rectangular protrusion that provides access to the dissolution media through an optical window. The optical window is created using a removable glass, affixed to the protrusion on both sides. During measurements, the dissolution sensor probe (the third optical imaging module) is attached to the protrusion, aligning the OCT beam path with the optical window. The beam travels through the media during its round trip between the collimator and the mirror. Hence, interferometric imaging (i.e., OCT) allows the measurement of the

change in the optical path length (OPL) between the collimator and the mirror as the properties of the dissolution media change due to particle dissolution. A key advantage of this configuration is that the mirror remains outside the solution, preventing its potential degradation (e.g., due to corrosion) over time. Additionally, the glass window is easily accessible for cleaning or replacement if necessary. For deposition measurement, a second OCT probe (not shown) directs the light beam onto the filter, which is mounted on top of the dissolution chamber and in contact with the solution, to monitor changes in the deposition profile as particles land on the filter and diffuse into dissolution media.

[00136] Figure 12 shows sensitivity evaluation of the dissolution probe using various solutions. Measurements were taken with different solutions in the dissolution compartment (the first compartment). (a) Comparison of the relative optical path length (OPL) difference between cold and warm tap water. The results show a longer OPL for cold water compared to warm water. As water heats up, its density and refractive index decrease, causing a decrease in the speed of light. (b) Analysis of a food colouring solution at various concentration levels. Concentration was adjusted by adding water. The OPL changes noticeably with variations in concentration, allowing clear distinction from pure water.

[00137] Figure 13 shows an illustration of how the thickness of powder deposition on the filter evolves over time. Panels (a), (b), and (c) display representative 2D spatial maps (depth projected view) of the deposition thickness from the measurement area, captured using the deposition OCT probe at 0, 30, and 60 minutes, respectively. Panel (d) shows the average deposition thickness in the region of interest at various time points.

[00138] Figure 14 illustrates results showing the change in optical path length (OPL) as powder particles deposited on filter paper and diffuse into and dissolve in the solution. Measurements were taken over time while the solution was stirred with a magnetic stirrer to facilitate mixing. The observed increase in OPL indicates a rising refractive index, suggesting the dissolution of more particles into the solution over time.

[00139] Figure 15 shows representative dissolution response profiles of different formulations in water. The profiles illustrate changes in optical path length (OPL) between the reference mirror and the fiber exit point (the collimator tip), which reflects alterations in the optical properties of the solution as the powder dissolves. The aim was to evaluate the device's ability to detect variations in the dissolution behavior of different powders. SV010 is a coarse lactose commonly used as a carrier in inhaled drug delivery. LH300 is a fine grade lactose powder. Lactose blend is a powder formulation containing 4.5% salbutamol sulfate as the active ingredient, 5% fine lactose, and the remainder being coarse lactose. ARIDOL is a commercial inhalable formulation containing mannitol as the active ingredient. All measurements were

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carried out by directly adding 40 mg of powder to 16 mL of dissolution medium, with continuous stirring using a magnetic stirrer throughout the measurement process.

Industrial Applicability

[00140] It will be appreciated that the above-described invention provides a device and a method for evaluating inhaled drug delivery system. However, the invention may also be used for wider industries that test and/or analyse particles, particularly solid particles.

[00141] The invention has the potential to cut product development time in half or more, potentially saving millions of USD in development time for any new dry powder inhaler device.

[00142] Other embodiments of the present invention as described herein are defined in the following paragraphs:

1. A device for monitoring a dynamic profile of particles, comprising:
 - a porous material for depositing the particles thereon, the porous material having two portions;
 - a first compartment configured to contain a dissolution medium, the dissolution medium being in contact with a first portion of the porous material, wherein a second portion of the porous material is not in contact with any dissolution medium; and
 - a plurality of optical imaging modules comprising:
 - a first optical imaging module configured to obtain a deposition profile of the particles on the first portion of the porous material to thereby obtain a diffusion rate of the particles; and
 - a second optical imaging module configured to obtain a deposition profile of the particles on the second portion of the porous material to thereby obtain a deposition rate of the particles,wherein the dynamic profile of particles is a function of the obtained deposition rate and diffusion rate.
2. The device according to paragraph 1, wherein the deposition profile of the particles comprises dynamic deposition thickness of the particles.
3. The device according to any one or more of the preceding paragraphs, wherein the first optical imaging module is further configured to obtain the deposition rate of the particles from the second optical imaging module to thereby obtain the diffusion rate of the particles.
4. The device according to any one or more of the preceding paragraphs, further comprising a second compartment, wherein the second portion of the porous material is in contact with the second compartment; and wherein the second compartment is

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essentially devoid of any dissolution medium such that the second portion of the porous material is not in contact with any dissolution medium.

5. The device according to any one or more of the preceding paragraphs, wherein the first optical imaging module and the second optical imaging module are configured to provide light beams for obtaining the diffusion and deposition rate of particles.
6. The device according to any one or more of the preceding paragraphs, wherein the plurality of optical imaging modules further comprises a third optical imaging module configured to obtain a dynamic optical path length through the dissolution medium to thereby obtain a dissolution rate of the particles through the dissolution medium, and wherein the dynamic profile of the particles is a function of the obtained deposition rate, diffusion rate and dissolution rate.
7. The device according to any one or more of the preceding paragraphs, wherein the optical path length is obtained by directing a light beam from the third optical imaging module through the dissolution medium to a mirror dispositioned on a wall of the first compartment.
8. The device according to any one or more of the preceding paragraphs, further comprising an electrochemical device operably connected with the first compartment, the electrochemical device configured to measure the concentration of particles in the dissolution medium to thereby obtain a dissolution rate of the particles.
9. The device according to any one or more of the preceding paragraphs, wherein the electrochemical device is a device that involves electrical resistance measurement.
10. The device according to any one or more of the preceding paragraphs, adapted to connect with an airway model to receive the particles.
11. The device according to any one or more of the preceding paragraphs, adapted to integrate with a particle-laden (aerosol) flow in unconfined or confined geometry to receive the particles.
12. The device according to any one or more of the preceding paragraphs, further comprising a lid covering at least a part of the porous material, wherein the plurality of optical imaging modules is dispositioned on the lid.
13. The device according to any one or more of the preceding paragraphs, wherein the lid is detachable.
14. The device according to any one or more of the preceding paragraphs, further comprising a vacuum source configured to facilitate particle deposition on the porous material, wherein the vacuum source is connected to the lid.
15. The device according to any one or more of the preceding paragraphs, wherein the optical imaging module comprises an optical coherence tomography (OCT) probe.

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16. The device according to any one or more of the preceding paragraphs, wherein the porous material is a membrane, a porous-based biomaterial for tissue or a filter paper.
17. The device according to any one or more of the preceding paragraphs, wherein the membrane has a pore diameter of between about 0.001 μm and about 1000 μm , preferably about 0.4 μm .
18. The device according to any one or more of the preceding paragraphs, further comprising a data processing unit that provides a displacement map from phase difference between consecutive temporal axial scans calculated from the plurality of optical imaging modules to thereby provide the deposition profile.
19. A method of monitoring a dynamic profile of particles, comprising the steps of:
 - a) depositing the particles on a porous material having two portions, a first portion of the porous material being in contact with a dissolution medium and a second portion of the porous material being not in contact with any dissolution medium;
 - b) obtaining a deposition profile of the particles on the first portion of the porous material using a first optical imaging module to thereby obtain a diffusion rate of the particles;
 - c) obtaining a deposition profile of the particles on the second portion of the porous material using a second optical imaging module to thereby obtain a deposition rate of the particles;wherein the dynamic profile of particles is function of the obtained deposition rate and diffusion rate.
20. The method according to paragraph 19, wherein the deposition profile of the particles comprises dynamic deposition thickness of particles.
21. The method according to any one or more of the preceding paragraphs, further comprising a step of obtaining the deposition rate of the particles from the second optical imaging module to thereby obtain the diffusion rate of the particles.
22. The method according to any one or more of the preceding paragraphs, wherein the first optical imaging module and the second optical imaging module provide light beams for obtaining the diffusion and deposition rate of particles.
23. The method according to any one or more of the preceding paragraphs, further comprising a step of obtaining a dynamic optical path length through the dissolution medium using a third optical imaging module to thereby obtain a dissolution rate of the particles through the dissolution medium, and wherein the dynamic profile of the particles is a function of the obtained deposition rate, diffusion rate and dissolution rate.
24. The method according to any one or more of the preceding paragraphs, wherein the step of obtaining an optical path length comprises directing a light beam from the third

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optical imaging module through the dissolution medium to a mirror dispositioned on a wall of the first compartment.

25. The method according to any one or more of the preceding paragraphs, further comprising a step of measuring the concentration of particles in the dissolution medium to thereby obtain a dissolution rate of particles using an electrochemical device operably connected with the first compartment.
26. The method according to any one or more of the preceding paragraphs, wherein the electrochemical device is a device that involves electrical resistance measurement.
27. The method according to any one or more of the preceding paragraphs, further comprising a step of receiving the particles from an airway model.
28. The method according to any one or more of the preceding paragraphs, further comprising a step of receiving the particles from a particle-laden (aerosol) flow in unconfined or confined geometry.
29. The method according to any one or more of the preceding paragraphs, wherein the optical imaging modules are dispositioned on a lid covering at least a part of the porous material.
30. The method according to any one or more of the preceding paragraphs, wherein the lid is detachable.
31. The method according to any one or more of the preceding paragraphs, further comprising a step of facilitating particle deposition on the porous material by a vacuum source connected to the lid.
32. The method according to any one or more of the preceding paragraphs, wherein the optical imaging module comprises an optical coherence tomography (OCT) probe.
33. The method according to any one or more of the preceding paragraphs, wherein the porous material is a membrane, a porous-based biomaterial for tissue or a filter paper.
34. The method according to any one or more of the preceding paragraphs, wherein the membrane has a pore diameter of between about 0.001 μm and about 1000 μm , preferably about 0.4 μm .
35. The method according to any one or more of the preceding paragraphs, further comprising a step of obtaining a displacement map from phase difference between consecutive temporal axial scans calculated from the plurality of optical imaging modules to thereby provide the deposition profile.
36. A method of monitoring a dynamic profile of particles, comprising using a device according to any one or more of the preceding paragraphs, wherein the dynamic profile of particles is a function of the obtained deposition rate, diffusion rate and/or dissolution rate.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. A device for monitoring a dynamic profile of particles, comprising:
a porous material for depositing the particles thereon, wherein the porous material
5 is wetted with a dissolution medium; and
a first optical imaging module configured to obtain a deposition profile of the particles
on the porous material to thereby obtain a diffusion rate of the particles through the
porous material;
wherein the dynamic profile of particles is a function of the obtained diffusion rate.
10
2. The device according to claim 1, wherein the deposition profile of the particles
comprises dynamic deposition thickness of the particles.
3. The device according to claim 1 or claim 2, wherein the porous material comprises
15 two portions, a first portion of the porous material being wetted with the dissolution
medium and a second portion of the porous material not being wetted with any
dissolution medium, the device further comprises a second optical imaging module
configured to obtain a deposition profile of the particles on the second portion of the
porous material to thereby obtain a deposition rate of the particles, and the dynamic
20 profile of particles is a function of the obtained deposition rate and diffusion rate.
4. The device according to claim 3, wherein the first optical imaging module is further
configured to obtain the deposition rate of the particles from the second optical
imaging module to thereby obtain the diffusion rate of the particles.
25
5. The device according any one of claims 1 to 4, wherein the first optical imaging
module and/or the second optical imaging module are configured to provide light
beams for obtaining the diffusion and/or deposition rate of particles.
6. The device according to any one of claims 1 to 5, further comprising a compartment
30 to contain the dissolution medium, wherein the dissolution medium is in contact with
the wetted porous material.
7. The device according to claim 6, further comprising a third optical imaging module
35 configured to obtain a dynamic optical path length through the dissolution medium
to thereby obtain a dissolution rate of the particles through the dissolution medium,

and wherein the dynamic profile of the particles is a function of the obtained deposition rate, and/or diffusion rate and/or dissolution rate, preferably the optical path length is obtained by directing a light beam from the third optical imaging module through the dissolution medium to a mirror disposed on a wall of the compartment.

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8. The device according to claim 6 or claim 7, further comprising an electrochemical device operably connected with the compartment, the electrochemical device configured to measure the concentration of particles in the dissolution medium to thereby obtain a dissolution rate of the particles, preferably the electrochemical device is a device that involves electrical resistance measurement.

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9. The device according to any one of claims 1 to 8, wherein the optical imaging module comprises an optical coherence tomography (OCT) probe.

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10. The device according to any one of claims 1 to 9, further comprising a data processing unit that provides a displacement map from phase difference between consecutive temporal axial scans calculated from the optical imaging module to thereby provide the deposition profile.

20

11. A method of monitoring a dynamic profile of particles, comprising the steps of:
a) depositing the particles on a porous material, the porous material being wetted with a dissolution medium;
b) obtaining a deposition profile of the particles on the porous material using a first optical imaging module to thereby obtain a diffusion rate of the particles through the porous material;
wherein the dynamic profile of particles is function of the obtained diffusion rate.

25

12. The method according to claim 11, wherein the deposition profile of the particles comprises dynamic deposition thickness of particles.

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13. The method according to claim 11 or claim 12, comprising the steps of:
a) depositing the particles on the porous material comprising two portions, a first portion of the porous material being wetted with the dissolution medium and a second portion of the porous material not being wetted with any dissolution medium;

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- b) obtaining the deposition profile of the particles on the first portion of the porous material using the first optical imaging module to thereby obtain the diffusion rate of the particles;
 - c) obtaining a deposition profile of the particles on the second portion of the porous material using a second optical imaging module to thereby obtain a deposition rate of the particles;
- wherein the dynamic profile of particles is function of the obtained deposition rate and diffusion rate.

- 10 14. The method according to claim 13, further comprising a step of obtaining the deposition rate of the particles from the second optical imaging module to thereby obtain the diffusion rate of the particles.
- 15 15. The method according to any one of claims 11 to 14, wherein the first optical imaging module and/or the second optical imaging module provide light beams for obtaining the diffusion and/or deposition rate of particles.
- 20 16. The method according to any one of claims 11 to 15, further comprising a step of providing a compartment to contain the dissolution medium, wherein the dissolution medium is in contact with the wetted porous material.
- 25 17. The method according to claim 16, further comprising a step of obtaining a dynamic optical path length through the dissolution medium using a third optical imaging module to thereby obtain a dissolution rate of the particles through the dissolution medium, and wherein the dynamic profile of the particles is a function of the obtained deposition rate and/or diffusion rate and/or dissolution rate, preferably the step of obtaining an optical path length comprises directing a light beam from the third optical imaging module through the dissolution medium to a mirror disposed on a wall of the compartment.
- 30 18. The method according to claim 16 or claim 17, further comprising a step of measuring the concentration of particles in the dissolution medium to thereby obtain a dissolution rate of particles using an electrochemical device operably connected with the compartment, preferably the electrochemical device is a device that involves electrical resistance measurement.
- 35

19. The method according to any one of claims 11 to 18, wherein the optical imaging module comprises an optical coherence tomography (OCT) probe.

5 20. The method according to any one of claims 11 to 19, further comprising a step of obtaining a displacement map from phase difference between consecutive temporal axial scans calculated from the optical imaging modules to thereby provide the deposition profile.

10

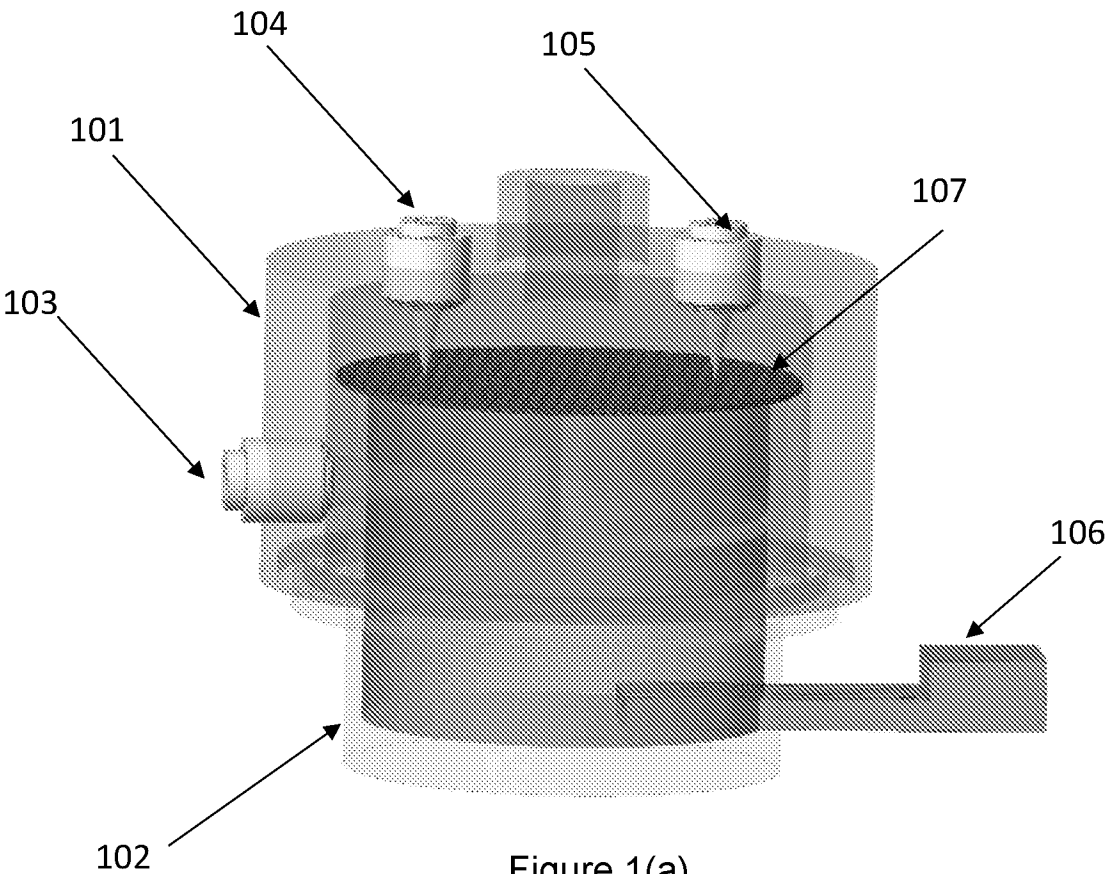


Figure 1(a)

100

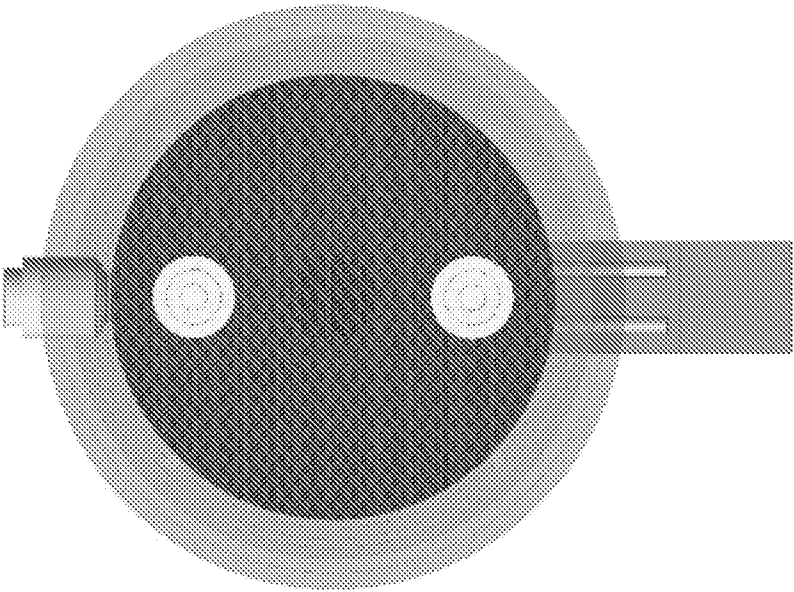


Figure 1(b)

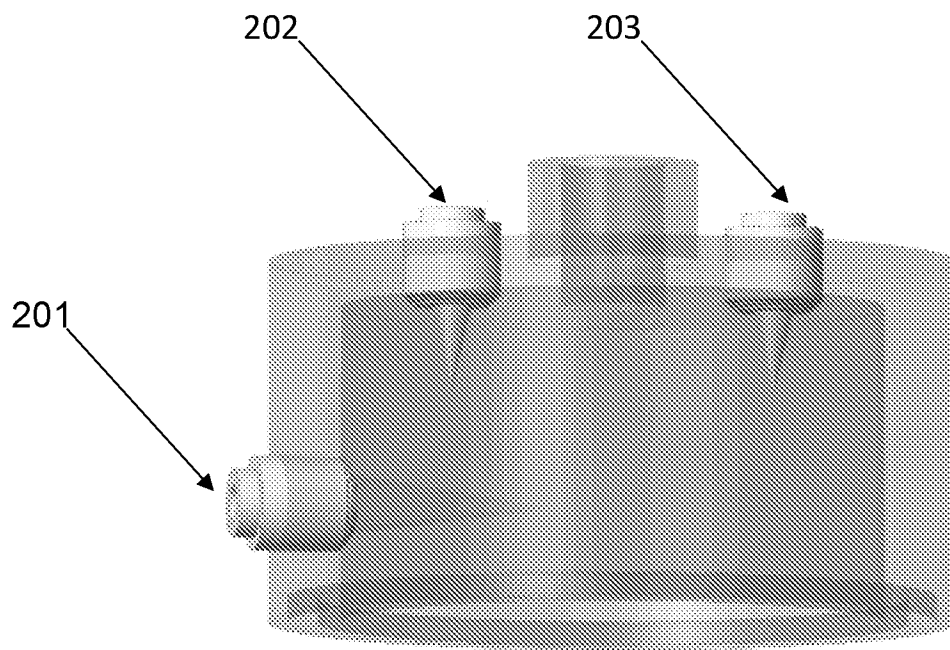


Figure 2(a)

200

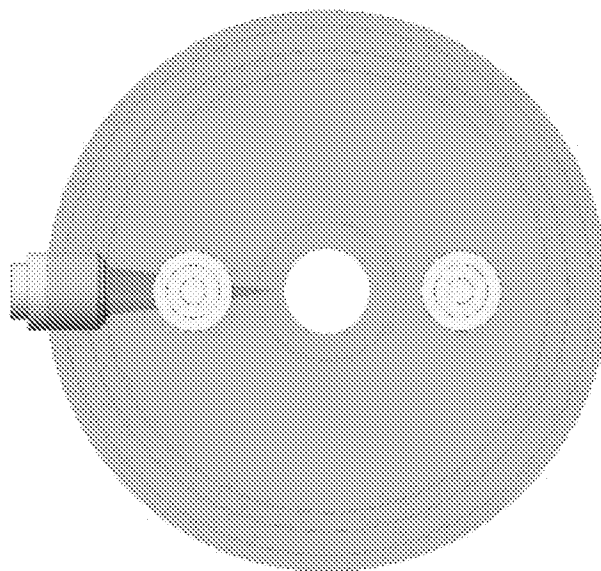


Figure 2(b)

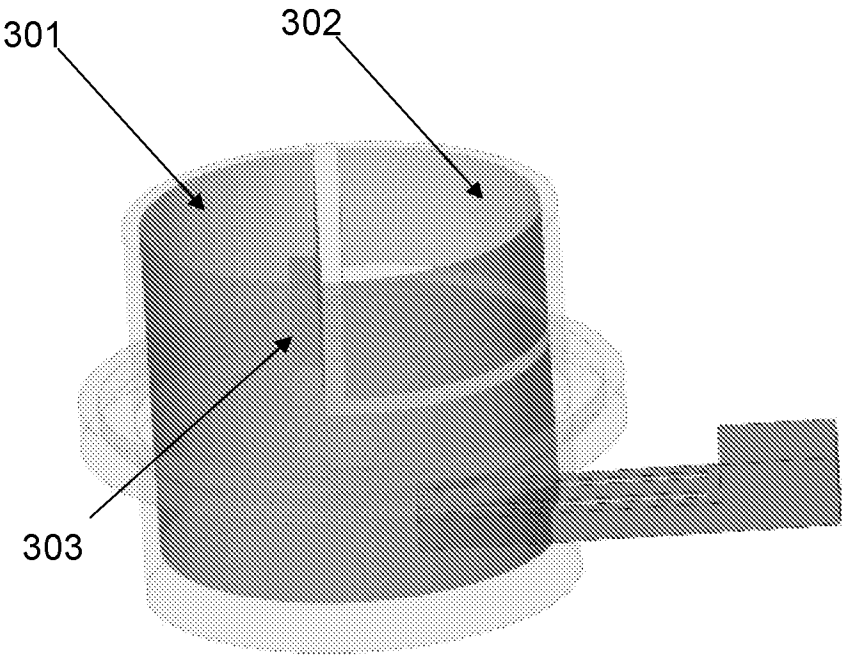


Figure 3(a)

300

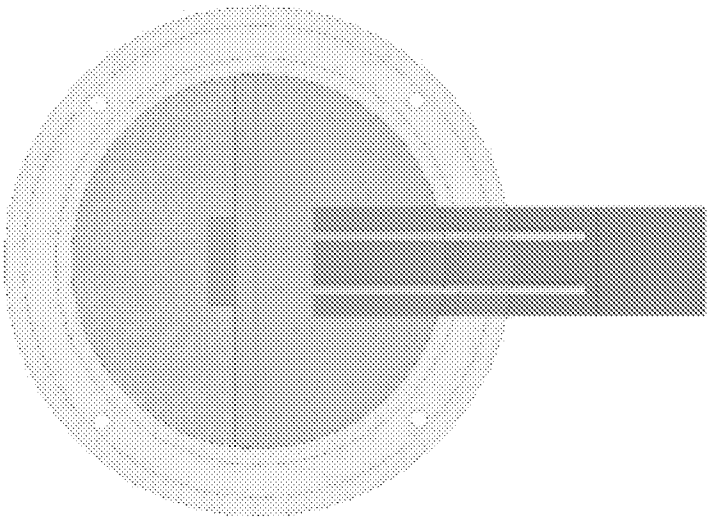


Figure 3(b)

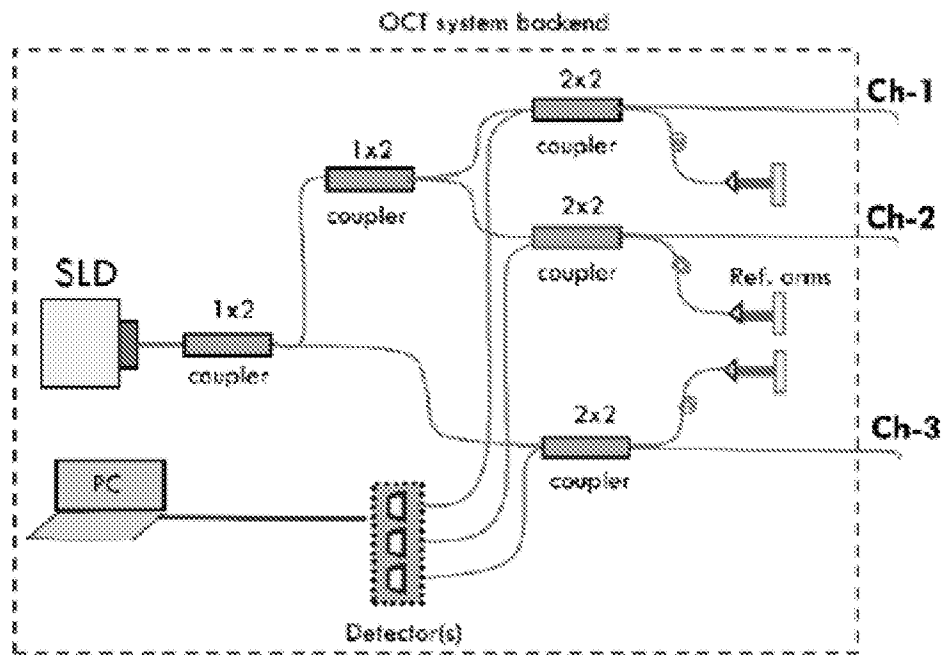


Figure 4

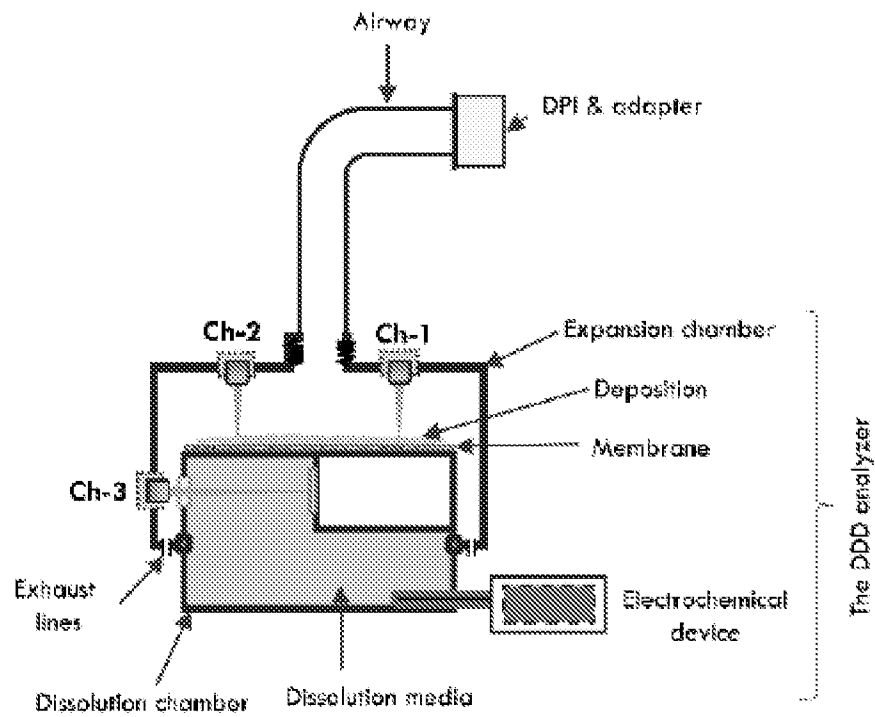


Figure 5

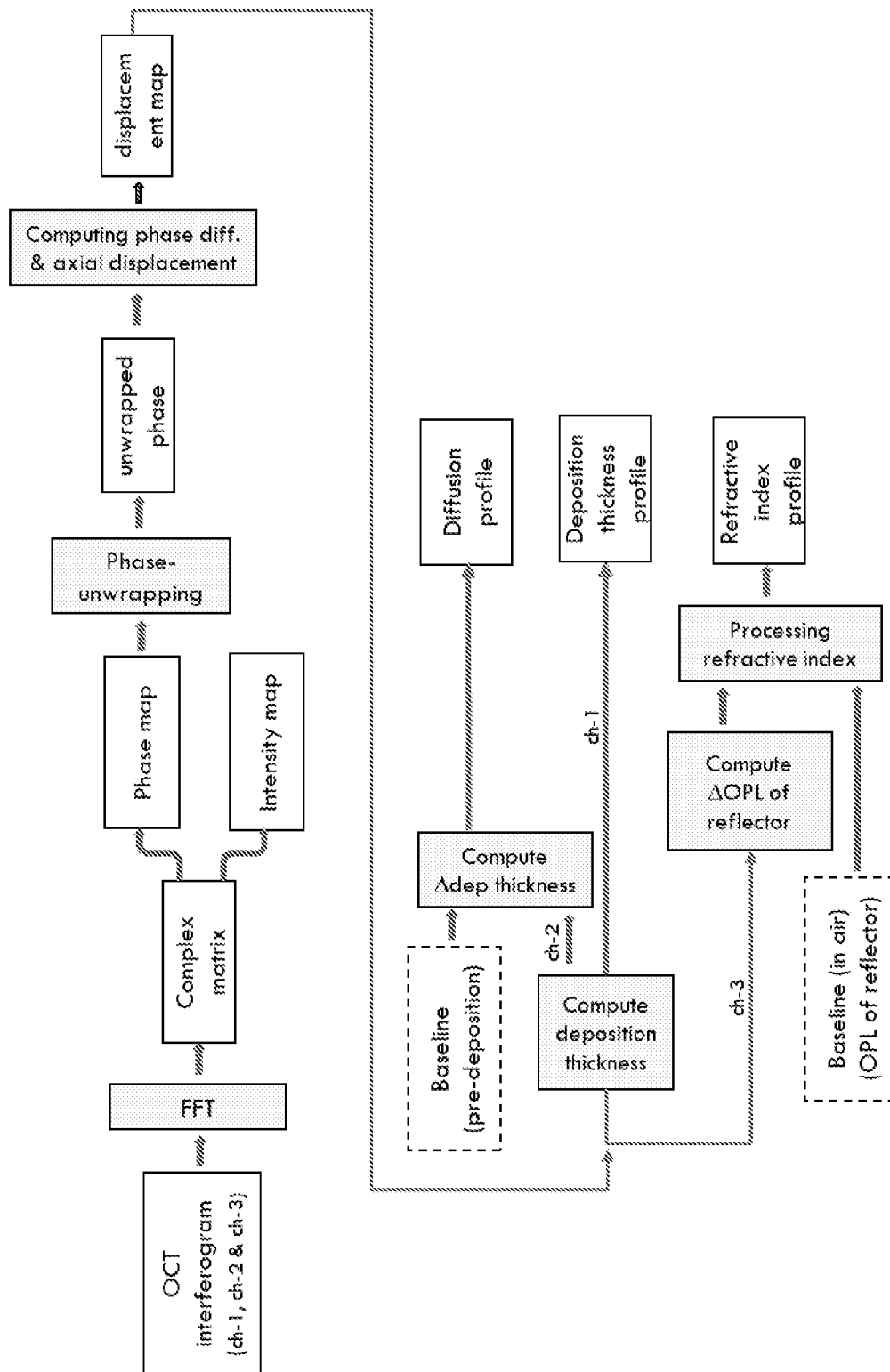


Figure 6

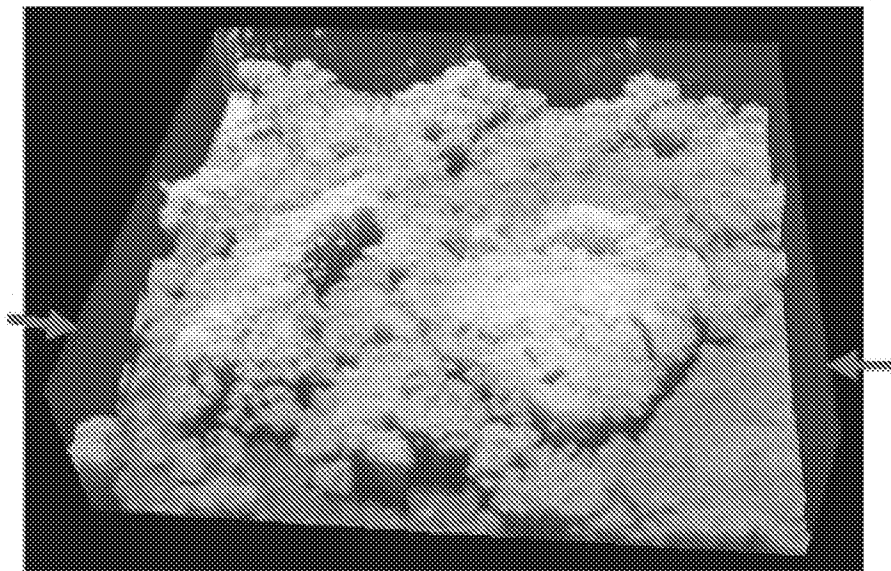


Figure 7(a)

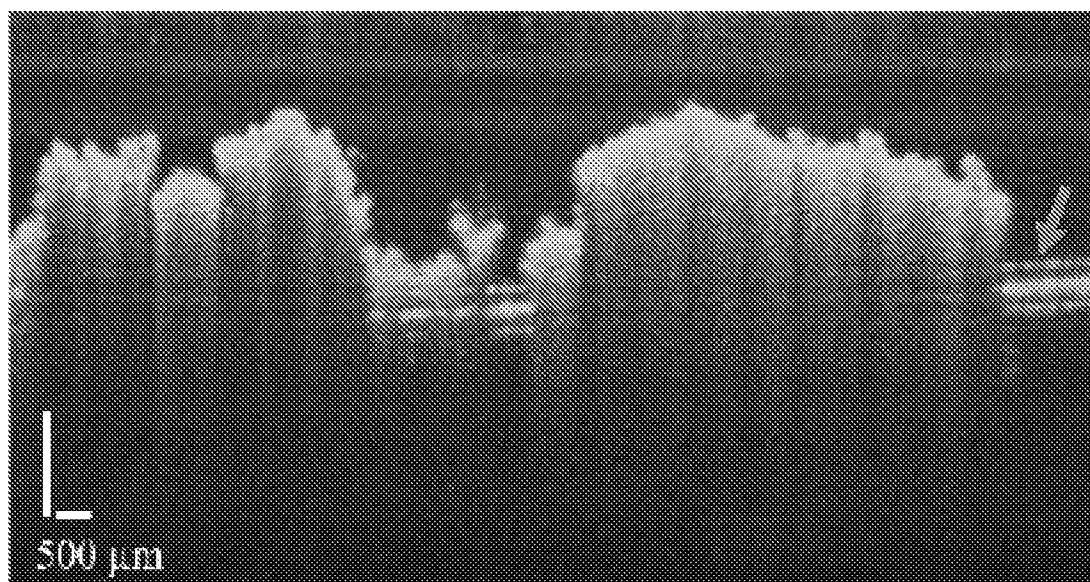


Figure 7(b)

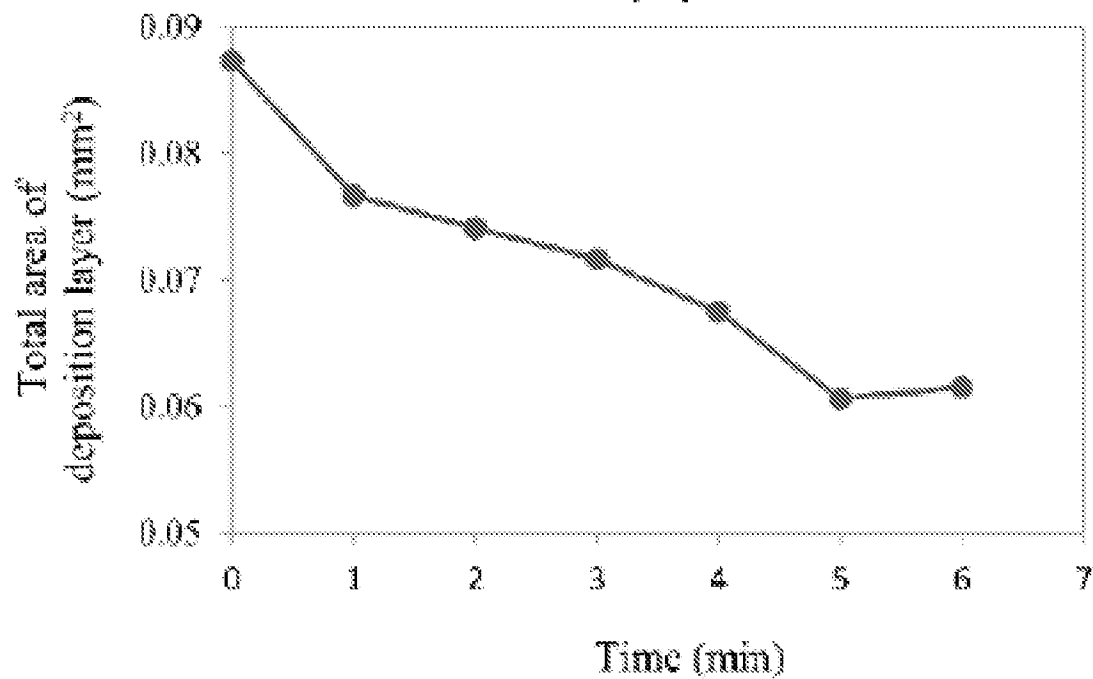


Figure 8(a)

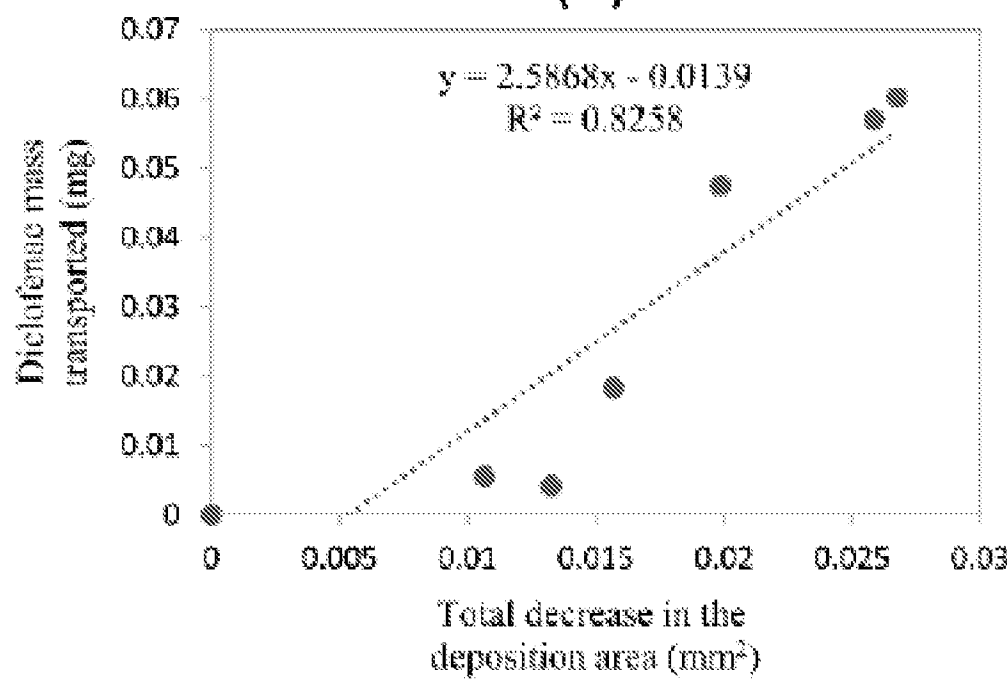


Figure 8(b)

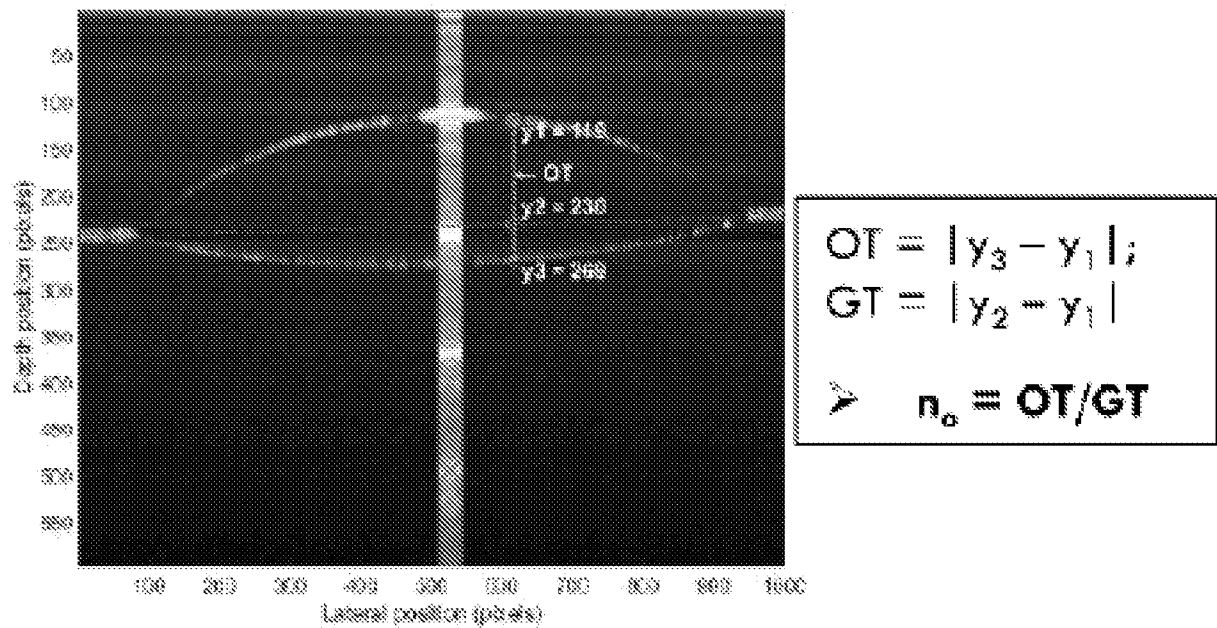


Figure 9(a)

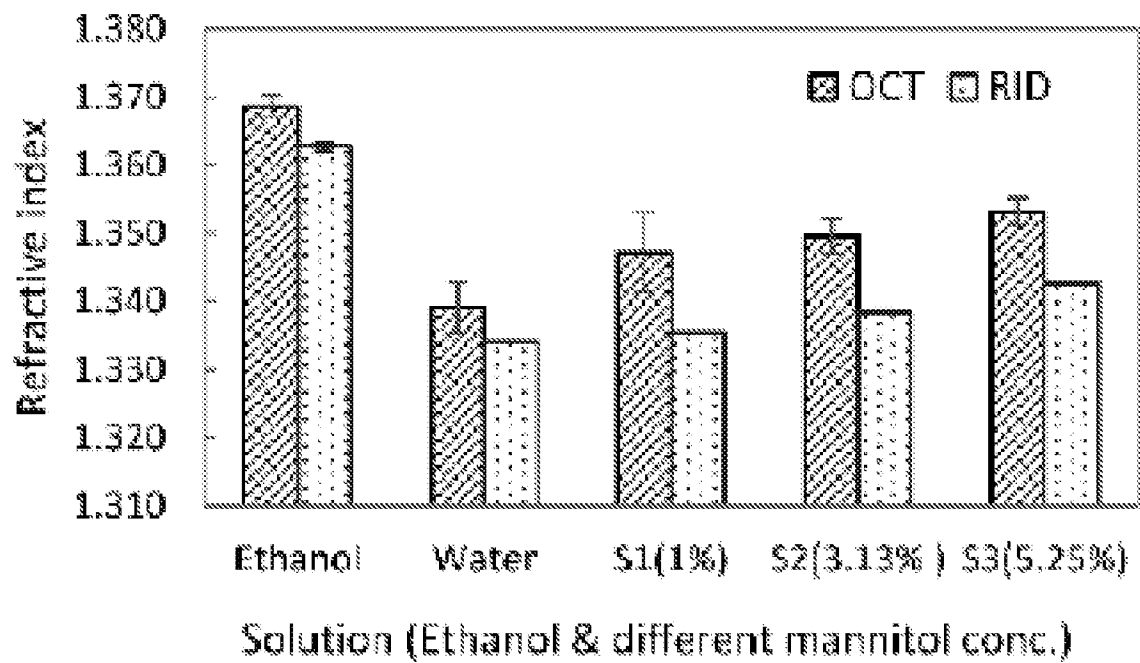


Figure 9(b)

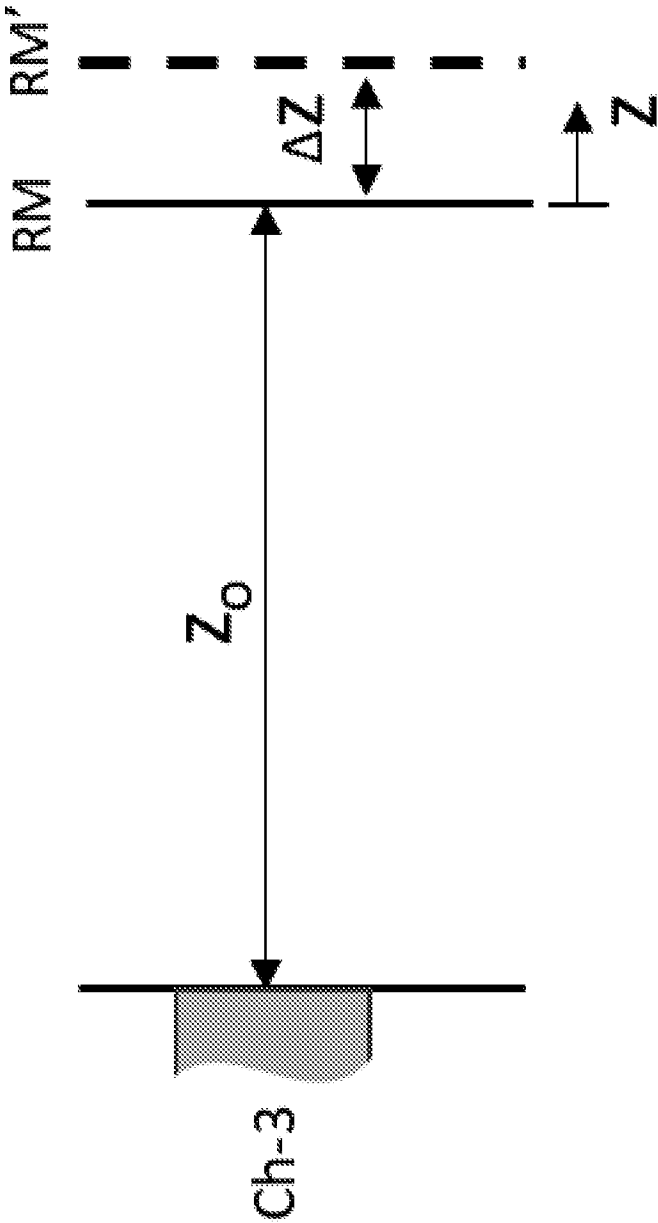


Figure 10

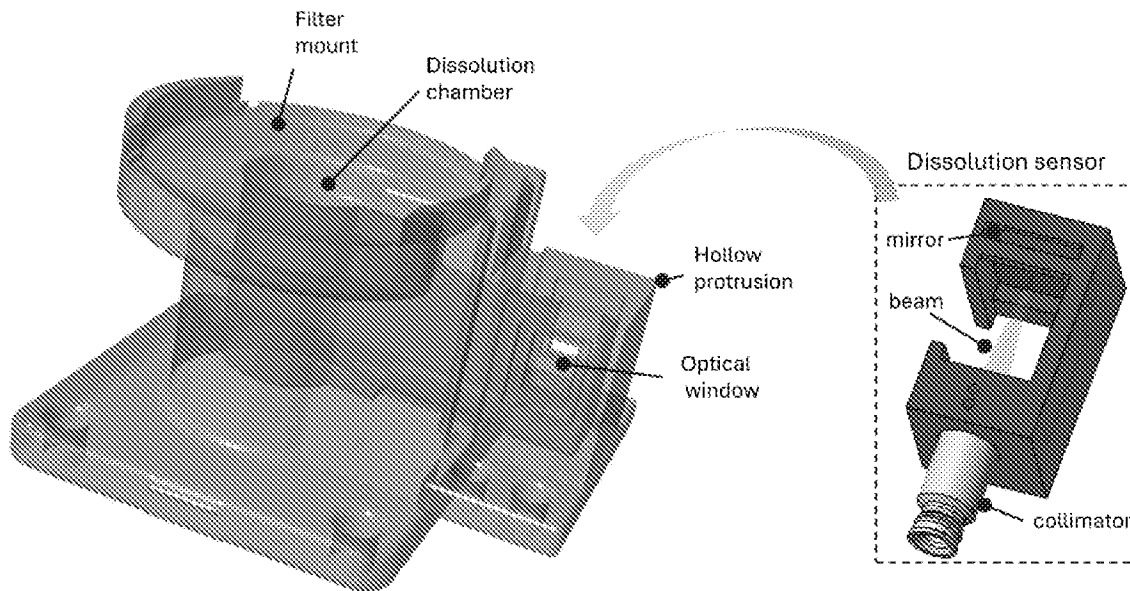


Figure 11

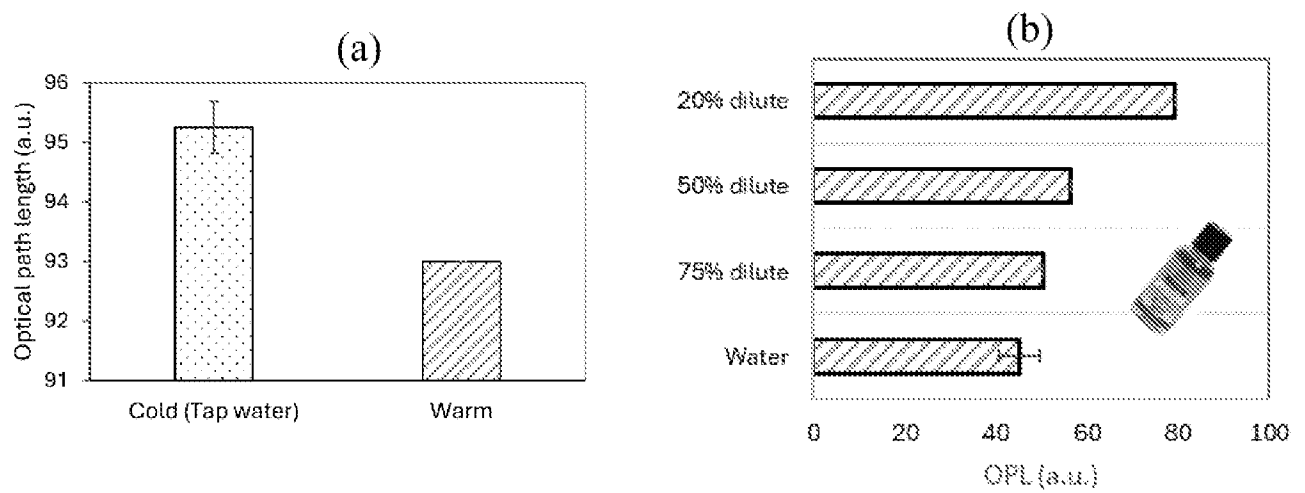


Figure 12

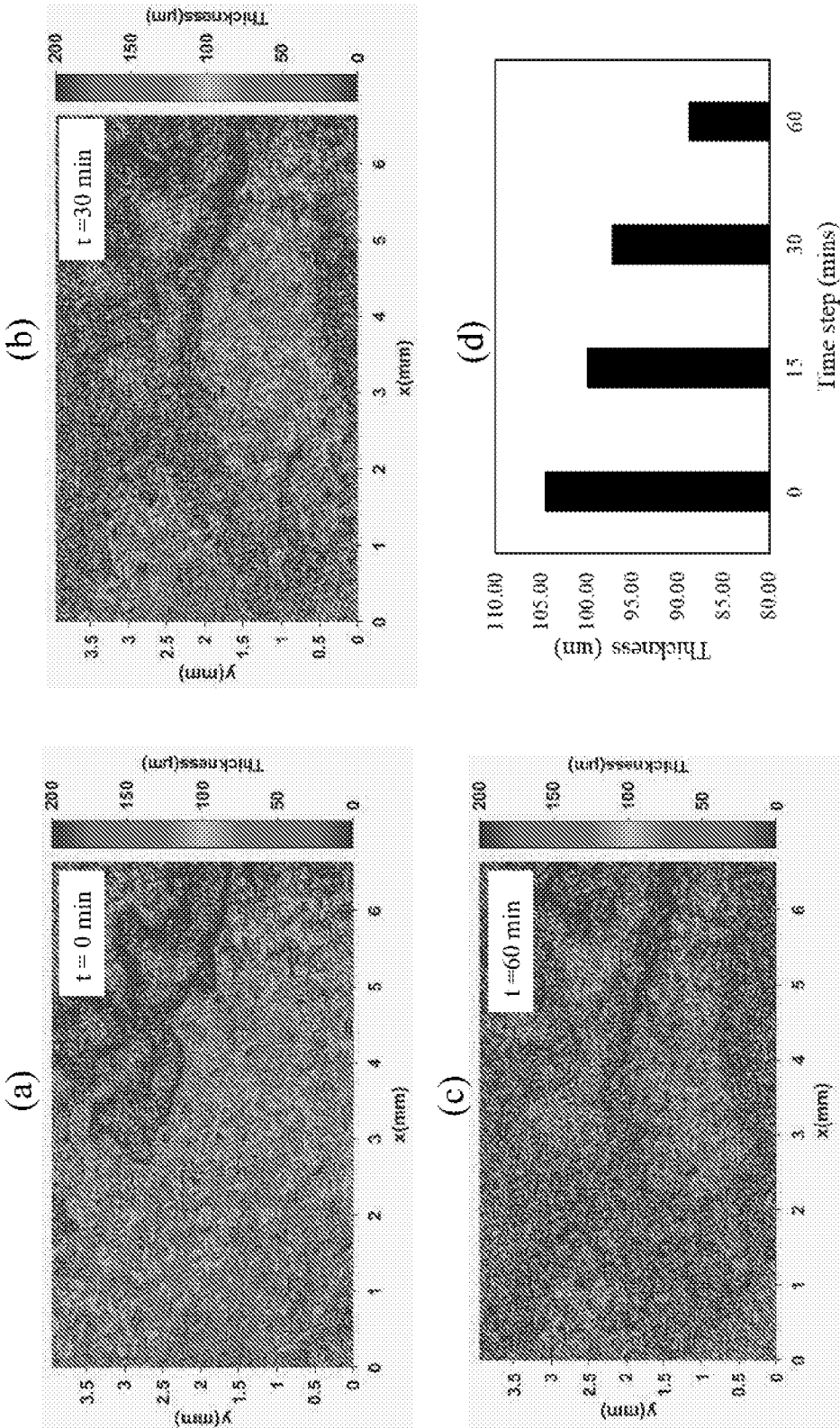


Figure 13

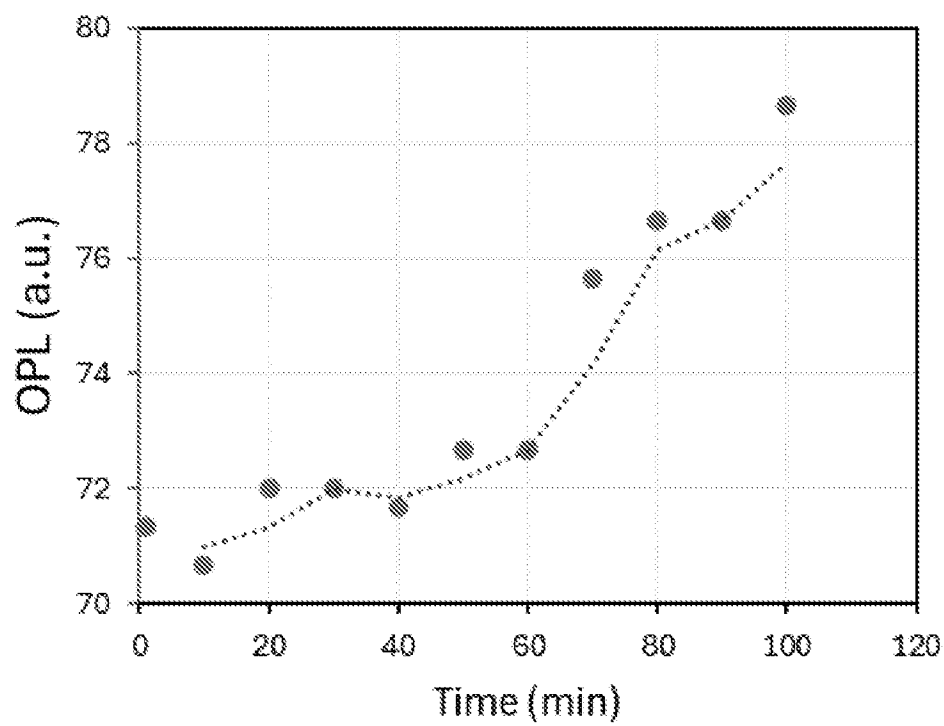


Figure 14

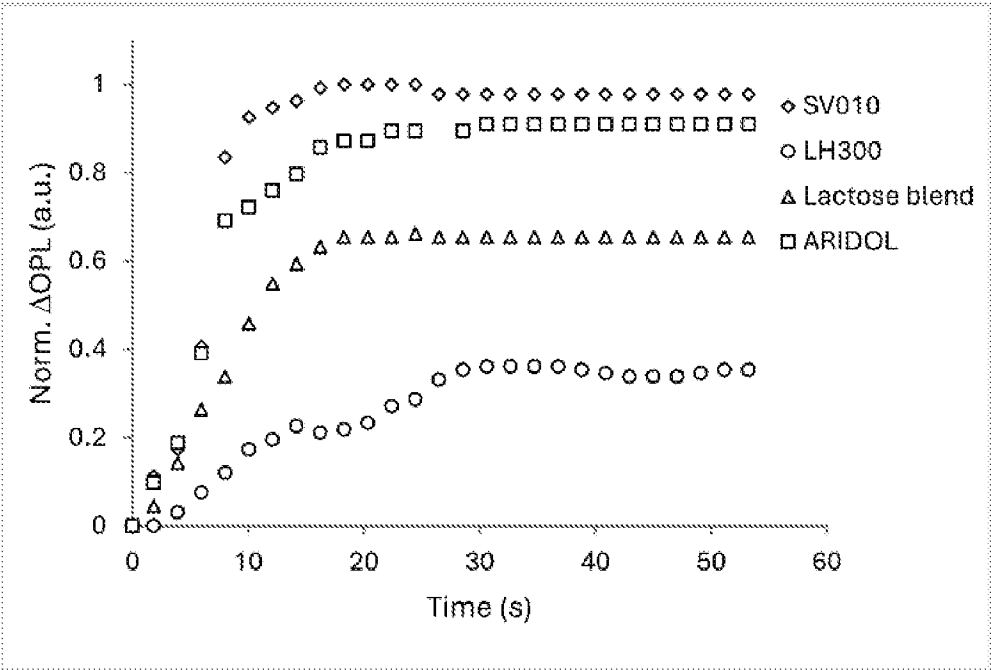


Figure 15

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU2024/051385

A. CLASSIFICATION OF SUBJECT MATTER

G01N 15/06 (2024.01) G01N 21/17 (2006.01) G01N 21/47 (2006.01)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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

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

Google Scholar/Patents: particle, deposition, thickness, multichannel, OCT, inhaled drug delivery system, multiple, imaging and similar terms

Espacenet: IPC/CPC – G01N15/0625, G01N2015/0038, G01N2015/0042, A61M15/00; particle, spray, diffusion, dissolution, porous, inhaler and similar terms

Patenw: IPC/CPC – G01N15/0625, G01N2015/0038, G01N2015/0042, A61M15/00; diffusion, deposition, dissolution, rate, particle, inhaler, airway, aerosol, drug delivery, thickness, profile, membrane, porous, filter, second, two, multiple, third, three, plurality, imaging, OCT, dynamic, in vivo, in vitro, in situ, IVIVC, real time and similar terms.

DOCDB and DWPI/IP Australia internal databases: inventor and applicant name search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

☒ Further documents are listed in the continuation of Box C☒ See patent family annex

* Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"D" document cited by the applicant in the international application	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier application or patent but published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

12 February 2025

Date of mailing of the international search report

12 February 2025

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INTERNATIONAL SEARCH REPORT		International application No.
C (Continuation).	DOCUMENTS CONSIDERED TO BE RELEVANT	PCT/AU2024/051385
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	MEKONNEN, TAYE, "A novel optical coherence tomography (OCT) design and application of OCT in inhaled drug delivery system", Diss. Macquarie University, November 2020 Chapter 6, Figure 6.1, 6.2	1-2, 5-12, 15-20 3, 4, 13, 14
X A	US 2022/0003737 A1 (THE SOLUBILITY COMPANY OY) 06 January 2022 para [0109]-[0118], [0165], [0141], Figure 2	1, 11 2-10, 12-20
A	WO 2019/090392 A1 (MACQUARIE UNIVERSITY, et al.) 16 May 2019	7, 17

INTERNATIONAL SEARCH REPORT		International application No.	
Information on patent family members		PCT/AU2024/051385	
This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.			
Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
US 2022/0003737 A1	06 January 2022	US 2022003737 A1	06 Jan 2022
		US 12146871 B2	19 Nov 2024
		CA 3021753 A1	02 Nov 2017
		CN 109154548 A	04 Jan 2019
		CN 109154548 B	22 Feb 2022
		EP 3449236 A1	06 Mar 2019
		EP 3449236 B1	13 Mar 2024
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		US 2019094197 A1	28 Mar 2019
		US 11131658 B2	28 Sep 2021
		WO 2017187023 A1	02 Nov 2017
WO 2019/090392 A1	16 May 2019	WO 2019090392 A1	16 May 2019
End of Annex			
Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001. Form PCT/ISA/210 (Family Annex)(July 2019)			