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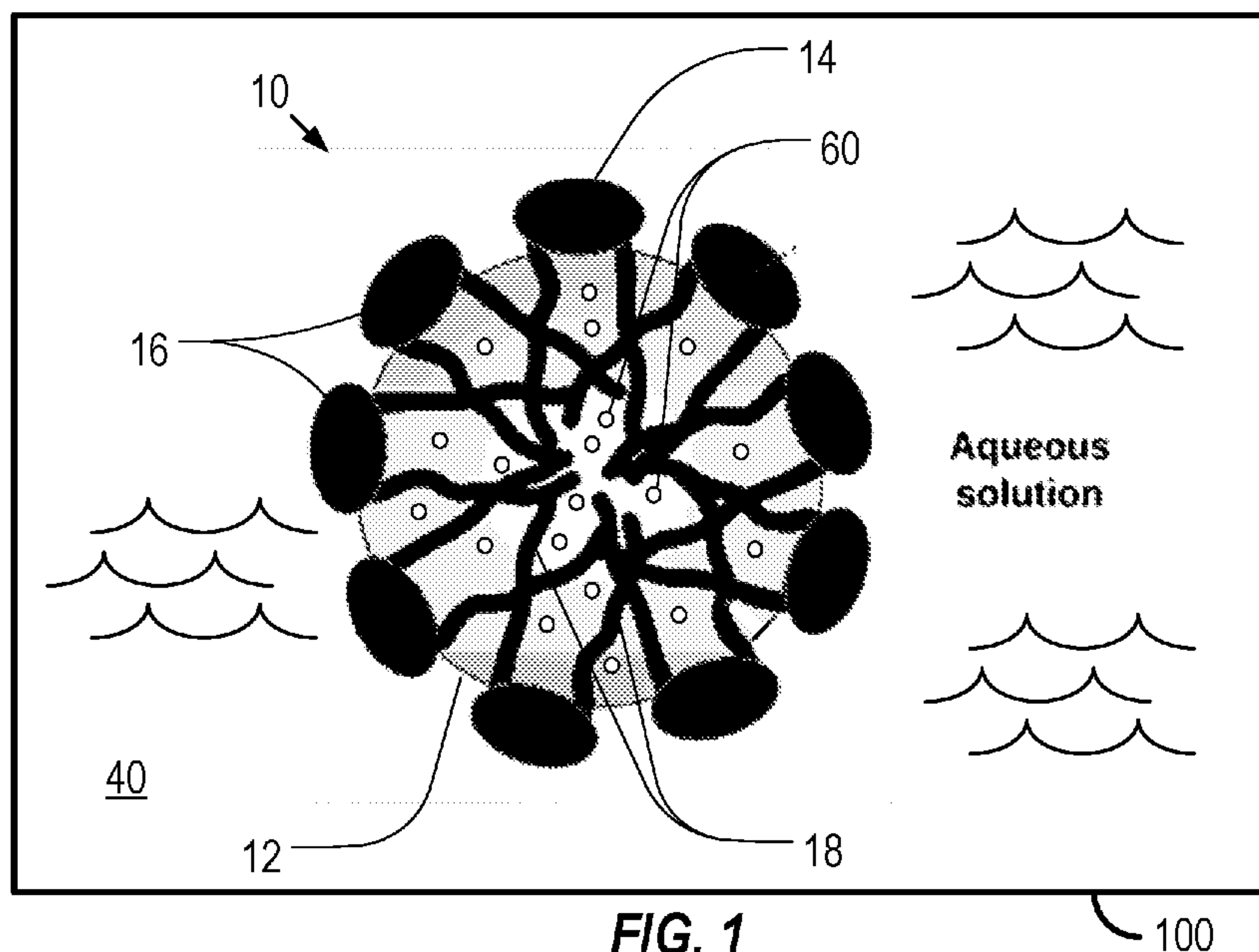


FIG. 1

(57) Abstract: A liquid-filled cartridge for use with an electronic device for delivery of a substance into a body through respiration includes a liquid container; and a liquid contained within the container for aerosolizing and inhaling by a person using the electronic device. The liquid includes a plurality of nanoparticles in a nanoemulsion, the nanoparticles including the encapsulation of the substance to be delivered into the body through respiration. The nanoemulsion preferably is produced using a microfluidizing machine.

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BACKGROUND OF THE INVENTION

[002] The invention generally relates to apparatus, systems, formulations, and methods pertaining to liquids that are aerosolized and inhaled by persons using electronic devices, whether intended for personal or recreational use, or for the administration of medicines.

[003] Inhalation delivery systems now play an increasing role in the targeted delivery of active ingredients to the human pulmonary system. This is true both for medical purposes, such as the targeted delivery of anti-cancer medications to the lungs, as well as for recreational/personal purposes, such as vaping, in which a liquid that includes the active ingredient is vaporized using heating so that the active ingredient can be inhaled into the human body.

[004] Unfortunately, as inhalation delivery systems using heating have increased in prominence, concerns about their short and long term safety have come into focus. This is particularly true for vaping where there exist ongoing concerns about the possible presence of harmful and potentially harmful constituents (HPHCs) in the inhaled vapor. Moreover, inhalation delivery systems are often unable to provide the desired effect to a user. This may be attributable to the pre-vaporized liquid becoming unstable over time or the active ingredient itself not being properly sized or dispersed for deposition in the alveolar lung.

[005] Accordingly, a need exists for an active ingredient delivery system that enhances the shelf-life of the pre-vaporized liquid component and enhances the efficacy of the desired treatment/effect, while avoiding the presence of undesired HPHCs in the inhaled vapor. This, and other needs, are believed to be addressed by one or more aspects and features of the invention.

SUMMARY OF THE INVENTION

[006] The invention includes many aspects and features. Moreover, while many aspects and features relate to, and are described in, the context of THC/CBD delivery systems, the invention is not limited to use only in pulmonary delivery of THC/CBD, as will become apparent from the following summaries and detailed descriptions of aspects, features, and one or more embodiments of the invention.

[007] In an aspect, a liquid-filled cartridge for use with an electronic device for delivery of a substance into a body through respiration comprises: (a) a liquid container; and (b) a liquid contained within the container for aerosolizing and inhaling by a person using the electronic device, the liquid comprising a plurality of nanoparticles in a nanoemulsion, each nanoparticle comprising an encapsulation of the substance to be delivered into the body through respiration.

[008] In a feature, the liquid is an oil-in-water nanoemulsion.

[009] In a feature, each nanoparticle is a micelle.

- [010] In a feature, each nanoparticle is a liposome.
- [011] In a feature, the substance is encapsulated by a polymer.
- [012] In a feature, the substance is encapsulated by a surfactant. The surfactant preferably comprises high purity polyoxyethylene sorbitan monooleate.
- [013] In a feature, the encapsulated substance comprises tetrahydrocannabinol.
- [014] In a feature, the encapsulated substance comprises cannabidiol.
- [015] In a feature, the encapsulated substance comprises tetrahydrocannabinol and cannabidiol.
- [016] In a feature, the encapsulated substance comprises a pharmaceutical compound.
- [017] In a feature, the encapsulated substance comprises nicotine.
- [018] In a feature, wherein the nanoparticles are suspended within an aqueous solution. The aqueous solution preferably comprises a saline; the aqueous solution preferably comprises sodium chloride; and, the nanoparticles preferably are suspended within an aqueous solution of 0.9% sodium chloride.
- [019] In a feature, a pH of the liquid is between about 5.5 and about 8.
- [020] In a feature, wherein a pH of the liquid is between about 6.5.
- [021] In a feature, a molecular ratio of the encapsulated substance to an encapsulating agent of the nanoparticle between about 0.1:1 to about 10:1.
- [022] In a feature, a polydispersity index measurement of the liquid is less than 0.3.
- [023] In a feature, the cartridge is a single-use, disposable cartridge.
- [024] In a feature, the cartridge is refillable.
- [025] In another aspect, a method of manufacturing cartridges for use with an electronic device for delivery of a substance into a body through respiration comprises filling a liquid container of the cartridge with a liquid for aerosolizing and inhaling by a person using the electronic device, the liquid comprising a plurality of nanoparticles in a nanoemulsion, each nanoparticle comprising an encapsulation of the substance to be delivered into the body through respiration.
- [026] In a feature, the method further comprises a preliminary step of producing the nanoemulsion by processing the substance to be delivered together with the encapsulating agent using a microfluidizing machine.
- [027] In a feature, the method further comprises operating the microfluidizing machine such that a temperature of the processing does not exceed 65°C while producing the nanoemulsion.
- [028] In a feature, the method further comprises the step of adjusting pH of the nanoemulsion so as to be between about 5.5 and 8.
- [029] In a feature, the method further comprises the step of chemically bonding the substance to be encapsulated with another molecule prior to processing the substance with the encapsulating agent using the microfluidizing machine. The polydispersity index measurement of the nanoemulsion after processing using the microfluidizing machine preferably is less than 0.3.
- [030] In another aspect, a method of manufacturing a liquid for aerosolizing and inhaling by a person using an electronic device for the delivery of a substance to the body of the person through

respiration, the method comprising producing a liquid comprising a plurality of nanoparticles in a nanoemulsion by processing the substance together with an encapsulating agent using a microfluidizing machine such that the plurality of nanoparticles of the liquid comprises the encapsulated substance.

[031] In a feature, the method further comprises operating the microfluidizing machine such that a temperature of the processing does not exceed 65°C while producing the liquid.

[032] In a feature, the method further comprises adjusting pH of the nanoemulsion so as to be between about 5.5 and 8.

[033] In a feature, the method further comprises the step of chemically bonding the substance to be encapsulated with another molecule prior to processing the substance with the encapsulating agent using the microfluidizing machine.

[034] In a feature, a polydispersity index measurement of the nanoemulsion after processing using the microfluidizing machine is less than 0.3.

[035] Another aspect of the invention relates to a liquid formulation for aerosolization. The liquid formulation includes an aqueous solution, one or more encapsulating agents, and an active ingredient or “value added molecule(s)”.

[036] In a feature of this aspect, the active ingredient is encapsulated by one or more encapsulating agents to form a nanoparticle. In another feature of this aspect, the nanocarrier comprises a liposome. In still another feature of this aspect, the nanocarrier comprises a micelle.

[037] In another feature of this aspect, the nanoparticles have an average diameter of less than 1,000 nanometers.

[038] In another feature of this aspect, the one or more encapsulating agents comprise a polymer. In another feature of this aspect, the one or more encapsulating agents comprise a surfactant. In still another feature of this aspect, the surfactant comprises a high purity polyoxyethylene sorbitan monooleate, such as “SUPER REFINED Polysorbate 80”.

[039] In another feature of this aspect, the aqueous solution comprises a saline solution. In another feature of this aspect, the saline solution comprises a 0.9% saline solution.

[040] In another feature of this aspect, the active ingredient comprises tetrahydrocannabinol. In another feature of this aspect, the active ingredient comprises cannabidiol. In another feature of this aspect, the active ingredient comprises tetrahydrocannabinol and cannabidiol. In another feature of this aspect, the active ingredient comprises nicotine. In still another feature of this aspect, the active ingredient comprises a pharmaceutical compound.

[041] In another feature of this aspect, a ratio of the one or more encapsulating agents to the active ingredient is between about 0.1:1 to about 10:1.

[042] In another feature of this aspect, a pH measurement of the liquid formulation is between about 5.5 and about 8. In another feature of this aspect, a pH measurement of the liquid formulation is about 6.5.

[043] In another feature of this aspect, a polydispersity index measurement of the liquid formulation is less than 0.3.

[044] In another feature of this aspect, the active ingredient is chemically bonded to another molecule.

[045] Another aspect of the invention relates to a method of preparing a liquid formulation for aerosolization. The method comprises the steps of mixing nanoparticles that include an active ingredient in a solution to form a liquid mixture and processing the liquid mixture with a microfluidizer.

[046] In a feature of this aspect, a temperature of the liquid mixture does not exceed 65°C during the processing step.

[047] In another feature of this aspect, the method further comprises the step of adjusting the pH of the liquid mixture.

[048] In another feature of this aspect, the method further comprises the step of chemically bonding the active ingredient with another molecule.

[049] In another feature of this aspect, nanoparticles of the microfluidized liquid mixture have an average diameter less than 1,000 nanometers.

[050] In another feature of this aspect, a polydispersity index measurement of the microfluidized liquid mixture is less than 0.3.

[051] In another feature of this aspect, the solution comprises an aqueous solution. In another feature of this aspect, the aqueous solution comprises a 0.9% saline solution.

[052] In another feature of this aspect, the nanoparticles comprise encapsulated nanoparticles. In another feature of this aspect, the active ingredient is contained within the encapsulated nanoparticles. In another feature of this aspect, the nanocarrier comprises a liposome. In still another feature of this aspect, the nanocarrier comprises a micelle.

[053] In another feature of this aspect, the active ingredient comprises tetrahydrocannabinol. In another feature of this aspect, the active ingredient comprises cannabidiol. In another feature of this aspect, the active ingredient comprises tetrahydrocannabinol and cannabidiol. In another feature of this aspect, the active ingredient comprises nicotine. In still another feature of this aspect, the active ingredient comprises a pharmaceutical compound.

[054] In addition to the aforementioned aspects and features of the invention, it should be noted that the invention further encompasses the various logical combinations and subcombinations of such aspects and features. Thus, for example, claims in this or a divisional or continuing patent application or applications may be separately directed to any aspect, feature, or embodiment disclosed herein, or combination thereof, without requiring any other aspect, feature, or embodiment.

BRIEF DESCRIPTION OF THE DRAWINGS

[055] One or more preferred embodiments of the invention now will be described in detail with reference to the accompanying drawings, wherein the same elements are referred to with the same reference numerals, and wherein,

[056] FIG. 1 is a schematic diagram of an active ingredient pulmonary delivery nanoparticle in the form of a micelle in accordance with one or more aspects of the invention;

[057] FIG. 2 is a schematic diagram of an active ingredient pulmonary delivery nanoparticle in the form of a liposome carrying an active ingredient within a bilayer in accordance with one or more aspects of the invention; and

[058] FIG. 3 is a schematic diagram of an active ingredient pulmonary delivery nanoparticle in the form of a liposome carrying an active ingredient in a hydrophilic core in accordance with one or more aspects of the invention.

DETAILED DESCRIPTION

[059] As a preliminary matter, it will readily be understood by one having ordinary skill in the relevant art (“Ordinary Artisan”) that the invention has broad utility and application. Furthermore, any embodiment discussed and identified as being “preferred” is considered to be part of a best mode contemplated for carrying out the invention. Other embodiments also may be discussed for additional illustrative purposes in providing a full and enabling disclosure of the invention. Furthermore, an embodiment of the invention may incorporate only one or a plurality of the aspects of the invention disclosed herein; only one or a plurality of the features disclosed herein; or combination thereof. As such, many embodiments are implicitly disclosed herein and fall within the scope of what is regarded as the invention.

[060] Accordingly, while the invention is described herein in detail in relation to one or more embodiments, it is to be understood that this disclosure is illustrative and exemplary of the invention and is made merely for the purposes of providing a full and enabling disclosure of the invention. The detailed disclosure herein of one or more embodiments is not intended, nor is to be construed, to limit the scope of patent protection afforded the invention in any claim of a patent issuing here from, which scope is to be defined by the claims and the equivalents thereof. It is not intended that the scope of patent protection afforded the invention be defined by reading into any claim a limitation found herein that does not explicitly appear in the claim itself.

[061] Thus, for example, any sequence(s) and/or temporal order of steps of various processes or methods that are described herein are illustrative and not restrictive. Accordingly, it should be understood that, although steps of various processes or methods may be shown and described as being in a sequence or temporal order, the steps of any such processes or methods are not limited to being carried out in any particular sequence or order, absent an indication otherwise. Indeed, the steps in such processes or methods generally may be carried out in various different sequences and orders while still falling within the scope of the invention. Accordingly, it is intended that the scope of patent protection afforded the invention be defined by the issued claim(s) rather than the description set forth herein.

[062] Additionally, it is important to note that each term used herein refers to that which the Ordinary Artisan would understand such term to mean based on the contextual use of such term herein. To the extent that the meaning of a term used herein—as understood by the Ordinary Artisan based on the contextual use of such term—differs in any way from any particular dictionary definition of such term, it is intended that the meaning of the term as understood by the Ordinary Artisan should prevail.

[063] With regard to any method claim including a condition precedent step, such method requires the condition precedent to be met and the step to be performed at least once but not necessarily every time during performance of the claimed method.

[064] Furthermore, it is important to note that, as used herein, “comprising” is open-ended insofar as that which follows such term is not exclusive. Additionally, “a” and “an” each generally denotes “at least one” but does not exclude a plurality unless the contextual use dictates otherwise. Thus, reference to “a picnic basket having an apple” is the same as “a picnic basket comprising an apple” and “a picnic basket including an apple”, each of which identically describes “a picnic basket having at least one apple” as well as “a picnic basket having apples”; the picnic basket further may contain one or more other items beside an apple. In contrast, reference to “a picnic basket having a single apple” describes “a picnic basket having only one apple”; the picnic basket further may contain one or more other items beside an apple. In contrast, “a picnic basket consisting of an apple” has only a single item contained therein, i.e., one apple; the picnic basket contains no other item.

[065] When used herein to join a list of items, “or” denotes “at least one of the items” but does not exclude a plurality of items of the list. Thus, reference to “a picnic basket having cheese or crackers” describes “a picnic basket having cheese without crackers”, “a picnic basket having crackers without cheese”, and “a picnic basket having both cheese and crackers”; the picnic basket further may contain one or more other items beside cheese and crackers.

[066] When used herein to join a list of items, “and” denotes “all of the items of the list”. Thus, reference to “a picnic basket having cheese and crackers” describes “a picnic basket having cheese, wherein the picnic basket further has crackers”, as well as describes “a picnic basket having crackers, wherein the picnic basket further has cheese”; the picnic basket further may contain one or more other items beside cheese and crackers.

[067] The phrase “at least one” followed by a list of items joined by “and” denotes an item of the list but does not require every item of the list. Thus, “at least one of an apple and an orange” encompasses the following mutually exclusive scenarios: there is an apple but no orange; there is an orange but no apple; and there is both an apple and an orange. In these scenarios if there is an apple, there may be more than one apple, and if there is an orange, there may be more than one orange. Moreover, the phrase “one or more” followed by a list of items joined by “and” is the equivalent of “at least one” followed by the list of items joined by “and”.

[068] Additionally, as used herein unless context dictates otherwise, the following terms have the following meanings.

[069] “Liquid” means a substance that flows freely but is of constant volume, generally having a consistency like that of water (lower viscosity) or oil (higher viscosity). Liquid is generic to and encompasses a solution, a suspension, and an emulsion.

[070] “Solution” means a homogeneous mixture of two or more components. The dissolving agent is the solvent. The substance that is dissolved is the solute. The components of a solution are atoms, ions,

or molecules, and the components are usually a nanometer or less in any dimension. An example of a solution is sugar mixed with water.

[071] “Suspension” means a mixture of components that can be evenly distributed by mechanical methods such as shaking or stirring, but that will eventually settle out over an extended period of time. The components in a suspension are generally larger than those in solutions. An example of a suspension is oil mixed with water.

[072] “Colloidal dispersion” means a heterogenous liquid mixture in which a component is dispersed in another component and does not tend to settle out over an extended period of time. The dispersed components generally is larger than components of a solution and smaller than components of a suspension.

[073] “Aerosol” means a colloidal dispersion of a solid or liquid in a gas.

[074] “Emulsion” means a colloidal dispersion of a liquid in a liquid. An example of an emulsion is milk.

[075] “Nanoemulsion” means an emulsion in which the dispersed component comprises nanoparticles.

[076] “Nanoparticle” means a molecule has—or aggregate of molecules have—having no dimension greater than about a micrometer (1,000 nanometers). In accordance with preferred embodiments of aspects and features of the invention, nanoparticles preferably have a dimension of between about 50 and about 200 nanometers.

[077] “Micelle” means a vesicle having a layer of molecules that encapsulate and transport a substance to cells of a body. The encapsulating molecules in a micelle may be surfactants or polymers, for example. A typical micelle in an aqueous solution forms an aggregate with the hydrophilic “head” regions in contact with the surrounding solvent, creating a hydrophobic tail region in the interior of the aggregate.

[078] “Liposome” means a vesicle having at least one bilayer of molecules that encapsulates and transports a substance to cells of a body.

[079] “Microfluidizing machine” means an apparatus that uses microreactor technology to make nanoemulsions through the interaction of liquid streams in defined microchannels. Such technology is described, for example, in U.S. patent application publications 2012/0236680 and 2019/0299171.

Microfluidizing machines principally utilize high shear forces and impact to emulsify a liquid-liquid system, dispersing one immiscible liquid into another within an interaction chamber. A “Y” chamber preferably is used and may be single-slotted or multi-slotted. Fundamentally, such microreactor technology comprises a large pump that forces a formulation through a very small orifice (i.e., microchannel) at pressures ranging from as low as 3.4 MPa (500 psi) to as high as 275 MPa(40,000 psi). Preferred microfluidizing machines correspond to the processors manufactured, sold, or distributed by Mircofluidics of Newton or Westwood, Massachusetts, under the registered trademark MICROFLUIDIZER, and any and all other apparatus that have the same or equivalent structure for performing the same or equivalent function with the same or equivalent result.

[080] Referring now to the drawings, one or more preferred embodiments in accordance with one or more aspects and features of the invention are next described. The following description of one or more preferred embodiments is merely exemplary in nature and is in no way intended to limit the invention, its implementations, or uses.

[081] An active ingredient delivery system for inhalation in accordance with the invention is contemplated to be capable of accommodating and delivering a range of different types of active ingredients to the body through the pulmonary system. Active ingredients capable of delivery using one or more delivery systems described herein include, but are not limited to, pharmaceutical compounds, tetrahydrocannabinol (THC), cannabidiol (CBD), and nicotine. The following description of embodiments sets forth one or more active ingredient delivery systems largely within the context of delivering THC and/or CBD, but it should be understood that active ingredient delivery systems described herein are also usable for delivery of nicotine, pharmaceuticals, micronutrients, and other types of active ingredients by inhalation and are not limited to delivery of THC/CBD.

[082] THC and CBD are two of several different cannabinoids found in plants of the *Cannabis* genus. Using extraction techniques, THC and CBD can be isolated from the plant matrix for medicinal and/or recreational use. THC and CBD interact with different receptors in the human brain and, thus, cause a different treatment or effect in the user. For purposes of the below discussion, THC and CBD may be referenced together as “THC/CBD.” It should be understood that, as used herein, “THC/CBD” refers to a cannabinoid-based active ingredient that includes both THC and CBD, THC without CBD, or CBD without THC.

[083] THC and CBD are hydrophobic molecules that do not readily mix with aqueous solutions like water. To facilitate delivery to the human body, THC/CBD molecules are encapsulated into nanoparticles comprising oil droplets of the THC/CBD active ingredient surrounded by one or more encapsulation agents, such as surfactants or emulsifiers, which shield the oil droplets from the surrounding aqueous environment. The shielded oil droplets can then mix into aqueous solutions. One example of such a mixture is a nanoemulsion, where the oil phase includes the hydrophobic THC/CBD molecules shielded by one or more surfactants from the surrounding aqueous phase.

[084] FIG. 1 is a schematic diagram of an active ingredient pulmonary delivery nanoparticle in the form of a micelle **10** in accordance with one or more aspects of the invention. In FIG. 1, the hydrophobic droplet **12** comprised of oil containing THC/CBD molecules is surrounded by a monolayer **14** of one or more encapsulation agents, which forms an aggregate. In at least some embodiments, the monolayer **14** is a lipid-based monolayer. Molecules forming the monolayer **14** include hydrophilic heads **16** that are in contact with the surrounding aqueous solution **40** and hydrophobic tails **18** that extend toward the micelle center. The hydrophilic heads **16** form the boundary of the monolayer **14** that facilitates isolation of the hydrophobic component, including the hydrophobic active ingredient **60**, to permit mixing of the micelle **10** into the aqueous solution **40**. As shown in FIG. 1, the micelle **10** is largely spherical in shape, although non-spherical shapes are also possible. As shown in FIG. 1, the micelle **10** and the aqueous solution **40** are contained within a cartridge **100**.

[085] FIG. 2 is a schematic diagram of an active ingredient pulmonary delivery nanoparticle in the form of a liposome **20** carrying an active ingredient **60** within a bilayer in accordance with one or more aspects of the invention. In FIG. 2, the oil component resides in a hydrophobic area **22** of the liposome **20** between a bilayer of one or more encapsulation agents. In at least some embodiments, the bilayer is a lipid-based bilayer. Molecules that form the outer layer **24** of the bilayer include hydrophilic heads **28** that are in contact with the surrounding aqueous solution **50** and hydrophobic tails **30** that extend into the hydrophobic area **22** between the layers **22,24**. Lipid molecules that form the inner layer **26** of the bilayer include hydrophilic heads **32** that are in contact with the aqueous solution **52** at the center of the liposome **20** and hydrophobic tails **34** that extend into the hydrophobic area **22** of the bilayer. The hydrophilic heads **28,32** form the boundaries of the bilayer that facilitate isolation of the hydrophobic area, which includes the hydrophobic active ingredient **60**. With the hydrophobic area **22** isolated, the liposome **20** can be mixed into the surrounding aqueous solution **50**. As indicated in FIG. 2, the liposome **20** is largely spherical in shape, although non-spherical shapes are also possible. As shown in FIG. 2, the liposome **20** and the surrounding aqueous solution **50** are contained within a cartridge **100**.

[086] Liquid mixtures that include active ingredient delivery nanoparticles in accordance with FIGS. 1 or 2 include an active ingredient, an encapsulation agent, and an aqueous solution. As described herein, one contemplated active ingredient includes THC/CBD molecules, although a wide range of other active ingredients are contemplated to be deliverable to the human pulmonary system in accordance with the invention, including, but not limited to, pharmaceutical compounds, micronutrients, and nicotine. Encapsulation agents to encapsulate hydrophobic active ingredient molecules are compounds with a hydrophobic region and a hydrophilic region. It is contemplated that encapsulation agents include, but are not limited to, lipids, polymers, and surfactants. Encapsulation agents can be used singly or in combination with each other. The aqueous solution is a medium that can be selected and formulated to achieve an osmotic balance with respect to human physiology. In at least some embodiments, the aqueous solution is a 0.9% saline solution, which is understood to provide a preferred osmotic balance with human physiology of the lungs. Furthermore, a 0.9% saline solution as the aqueous medium facilitates a safer user experience, particularly when the liquid mixture is aerosolized.

[087] With respect to polymers as encapsulation agents, it is contemplated that polymers include, but are not limited to, poly(lactic-*co*-glycolic) acid (PLGA), polylactic acid (PLA), polyglycolic acid (PGA), polycaprolactone (PCL), and polyhydroxybutyrate (PHB).

[088] With respect to surfactants as encapsulation agents, it is contemplated that surfactants include, but are not limited to: high purity polyoxyethylene sorbitan monooleate (also known by its trade name, SUPER REFINED® Polysorbate 80); polyoxyethylene sorbitan monooleate; (also known by its trade name, TWEEN® Polysorbate 80); polyoxyethylene sorbitan monostearate (also known by its trade name TWEEN® Polysorbate 60); polyoxyethylene sorbitan monopalmitate (also known by its trade name TWEEN® Polysorbate 40); polyoxyethylene sorbitan monolaurate (also known by its trade name TWEEN® Polysorbate 20); lecithin; dipalmitoylphosphatidylcholine (DPPC); 1,2-distearoyl-*sn*-glycero-3-phosphocholine (DSPC); sorbitan monostearate (also known by its trade name SPAN 60); and sorbitan

monopalmitate (also known by its trade name SPAN 40). When using one or more surfactants as an encapsulating agent, a ratio of surfactant combinations is determined by hydrophilic-lipophilic balance (HLB) values inherent to each surfactant. The combination of surfactants yields a weighted average HLB value that can be used to match the target application in order to enhance or optimize mixing of nanoparticles containing the active ingredient into the aqueous solution. For example, an HLB value measuring from approximately 8 to approximately 16 is satisfactory for oil-in-water emulsions.

[089] In at least some embodiments, the encapsulating agent includes a high purity or high-grade surfactant, which is understood to enhance the shelf-life of the resulting mixture as well as to improve the efficacy and safety of the resulting mixture. One such high purity surfactant that can be used in the formulation is high purity polyoxyethylene sorbitan monooleate, which is also known by its trade name, SUPER REFINED® Polysorbate 80. SUPER REFINED® Polysorbate 80 is manufactured and sold by Croda International Plc of the United Kingdom.

[090] A ratio of the surfactant relative to the active ingredient affects the size of the resulting nanoparticles (e.g., micelles and/or liposomes that contain the active ingredient). In various embodiments, it is contemplated that the surfactant-to-active-ingredient ratio can range from approximately 0.1:1 to approximately 10:1. Size of the resulting nanoparticles that contain the active ingredient affects a variety of characteristics of the final product, including pulmonary deposition of the active ingredient, absorption of the active ingredient, and the product shelf-life.

[091] In at least some embodiments, a process for producing a liquid mixture that includes active-ingredient nanocarriers in accordance with FIGS. 1-3 is accomplished using a microfluidics approach. Microfluidics involves utilizing a network of channels having very small dimensions to process the liquid mixture in order to achieve homogeneous mixture with consistently-sized nanoparticles. In one such embodiment, a microfluidizer is utilized to achieve the desired nanoparticle dispersal and uniform mixture with consistently-sized nanoparticles. During a processing step using a microfluidizer, it is contemplated that a temperature of the liquid mixture does not exceed a temperature threshold of 65°C. By not exceeding a predetermined temperature threshold, the risk of generating harmful HPHCs in the mixture via heat is reduced, thereby enhancing consumer safety. Additionally, processing the liquid mixture using a microfluidizer facilitates processing without the use of chemical solvents, which further reduces the risk of generating harmful HPHCs in the final liquid mixture. Still further, use of a microfluidics approach helps to maintain sterility in the materials used to produce the final liquid mixture, which also enhances consumer safety.

[092] Using a microfluidics approach, the processed liquid includes nanoparticles of a uniformly small size and a low polydispersity index (PDI) value. In at least some embodiments, it is contemplated that THC/CBD nanoparticles in the final liquid mixture have an average diameter less than 1,000 nanometers or, alternatively, have a dimension that is no larger than 1,000 nanometers. It is believed that nanoparticles of this scale provide enhanced pulmonary deposition of the active ingredient into the alveolar lung region, which facilitates increased pulmonary absorption. Furthermore, nanoparticles of this scale enhance the stability of the final liquid mixture, which increases its shelf-life. Additionally, in at

least some embodiments, it is contemplated that the final liquid mixture has a PDI value measuring less than 0.3. The PDI value provides a measurement of the broadness of size distribution. A low PDI value is indicative of a high level of particle size uniformity in a mixture. In accordance with contemplated embodiments of the invention, the PDI value is 0.3 or less, which is believed to indicate a liquid mixture with increased stability and enhanced shelf-life. A PDI measurement scale assigns a value of 0.0 to a population of particles where the particles have a perfectly uniform size and a value of 1.0 to a highly polydisperse population of particles with multiple size populations.

[093] In at least some embodiments, it is contemplated that the pH of the final liquid mixture can be adjusted to accommodate a specific objective. For example, in some embodiments, a pH value of the final liquid mixture that is greater than approximately 3 and less than approximately 10 can improve the inhalation experience for the user by reducing a cough reaction. In preferred embodiments, a pH value of the final liquid mixture that is greater than approximately 5.5 and less than approximately 8, more preferably, is about 6.5, so as to match the pH of the human respiratory tract, improve consumer safety, enhance pulmonary absorption of the active ingredient, and enhance or optimize shelf-life of the liquid.

[094] The final liquid mixture includes many THC/CBD-encapsulated nanoparticles that are uniformly suspended in an aqueous solution for downstream aerosolization by an aerosolizing device for inhalation. Such devices may include, for example, vaporizers and nebulizers.

[095] In at least some embodiments, the encapsulated molecules are chemically bonded to other molecules in a conjugated system. Establishing a conjugated system with chemical bonds between the active ingredient molecules and other molecules facilitates more efficient encapsulation of the active ingredients via the techniques described herein. In some contemplated embodiments, then THC/CBD molecules are chemically bonded with molecules of stearic acid and/or oleic acid. Establishing a conjugated system, as described herein, is understood to enhance or optimize encapsulation of THC/CBD molecules as well as other drugs or pharmaceutical compounds.

[096] It is contemplated that formulations and methods as described herein can be applied to hydrophobic drugs or compounds other than THC/CBD. It is further contemplated that formulations and methods as described herein can be applied to hydrophilic drugs or compounds with modifications. One such modification includes encapsulating the hydrophilic drug or compound into a hydrophilic core of a liposomal nanoparticle. Another such modification includes conjugation of the hydrophilic drug or compound to a hydrophobic molecule (such as by chemical bonding) in order to achieve an overall hydrophobic compound capable of being encapsulated in the manner as set forth in FIGS. 1 and 2.

[097] Regarding encapsulation of a hydrophilic drug or compound into a hydrophilic core of a liposomal nanoparticle, reference is made to FIG. 3, which is a schematic diagram of an active ingredient pulmonary delivery nanoparticle in the form of a liposome **120** carrying a hydrophilic active ingredient **160** in a hydrophilic core **158** in accordance with one or more aspects of the invention. In FIG. 3, the hydrophobic component resides in a hydrophobic area **122** of the liposome **120** between a bilayer of one or more encapsulation agents. In at least some embodiments, the bilayer is a lipid-based bilayer. Molecules that form the outer layer **124** of the bilayer include hydrophilic heads **128** that are in contact

with the surrounding aqueous solution **150** and hydrophobic tails **130** that extend into the hydrophobic area **122** of the bilayer. Lipid molecules that form the inner layer **126** of the bilayer include hydrophilic heads **132** that are in contact with the aqueous solution **152** at the core **158** of the liposome **120** and hydrophobic tails **134** that extend into the hydrophobic area **122** of the bilayer. The hydrophilic heads **128,132** form the barriers of the bilayer that facilitate isolation of the hydrophobic area **122**. The hydrophilic active ingredient **160** is contained within the hydrophilic core **158**. With the hydrophobic area **122** isolated, the liposome **120** can be mixed into the surrounding aqueous solution **150**. As indicated in FIG. 3, the liposome **120** is largely spherical in shape, although non-spherical shapes are also possible. Also, the liposome **120** and the surrounding aqueous solution **150** are contained within a cartridge **100**.

[098] In at least some embodiments, it is further contemplated that the aqueous solution of the product can be buffered to mitigate pH over time. In this respect, it is contemplated that a saline solution can be converted to a phosphate buffer saline solution. Buffering the solution with the addition of a buffering agent can enhance consistency of the product, increase the shelf-life, and enhance the consumer experience when the product is aerosolized during use.

[099] In at least some embodiments, it is further contemplated that additives can be included in the aqueous solution of the product. Contemplated additives include, but are not limited to antioxidants (such as ascorbic acid, sodium ascorbate, or others) and preservatives (such as antimicrobials). In some respects, additives can provide a safer consumer experience when the product is aerosolized during use. In other respects, additives can enhance the shelf-life of the product.

[0100] Additives can also be used to enhance or complement the user experience. For example, additives can be included to enhance or complement the smell/taste during inhalation of the aerosolized product. Additives to enhance or complement the smell/taste during inhalation include, but are not limited to, menthol and mint. Furthermore, additives can be included to enhance or complement the inhalation sensation during inhalation of the aerosolized product. An additive that enhances or complements the inhalation sensation might mimic a throat hit sensation commonly associated with nicotine inhalation or the sensation might trigger a feeling of smoothness for the consumer.

[0101] In at least some embodiments, it is further contemplated that a carrier or diluent solution is used in connection with the active ingredient to increase stability of the resulting product. Additionally, a carrier or diluent solution can enhance manufacturing process efficiency with respect to the ability to encapsulate the active ingredient when forming the nanoparticles. One contemplated carrier or diluent solution includes a medium-chain triglyceride (MCT) oil.

[0102] Based on the foregoing description, it will be readily understood by those persons skilled in the art that the invention has broad utility and application. Many embodiments and adaptations of the invention other than those specifically described herein, as well as many variations, modifications, and equivalent arrangements, will be apparent from or reasonably suggested by the invention and the foregoing descriptions thereof, without departing from the substance or scope of the invention. Accordingly, while the invention has been described herein in detail in relation to one or more preferred embodiments, it is to be understood that this disclosure is only illustrative and exemplary of the invention

and is made merely for the purpose of providing a full and enabling disclosure of the invention. The foregoing disclosure is not intended to be construed to limit the invention or otherwise exclude any such other embodiments, adaptations, variations, modifications or equivalent arrangements, the invention being limited only by the claims appended hereto and the equivalents thereof.

What is claimed is:

1. A liquid-filled cartridge for use with an electronic device for delivery of a substance into a body through respiration, comprising:
 - (a) a liquid container; and
 - (b) a liquid for aerosolizing and inhaling by a person using the electronic device, the liquid being contained within the liquid container and comprising a nanoemulsion, each of a plurality of nanoparticles of the nanoemulsion comprising an encapsulation of the substance to be delivered into the body through respiration.
2. The liquid-filled cartridge of claim 1, wherein the liquid is an oil-in-water nanoemulsion.
3. The liquid-filled cartridge of claim 1, wherein each nanoparticle is a micelle.
4. The liquid-filled cartridge of claim 1, wherein each nanoparticle is a liposome.
5. The liquid-filled cartridge of claim 1, wherein the substance is encapsulated by a polymer.
6. The liquid-filled cartridge of claim 1, wherein the substance is encapsulated by a surfactant.
7. The liquid-filled cartridge of claim 6, wherein the surfactant comprises high purity polyoxyethylene sorbitan monooleate.
8. The liquid-filled cartridge of claim 1, wherein the encapsulated substance comprises tetrahydrocannabinol.
9. The liquid-filled cartridge of claim 1, wherein the encapsulated substance comprises cannabidiol.
10. The liquid-filled cartridge of claim 1, wherein the encapsulated substance comprises tetrahydrocannabinol and cannabidiol.
11. The liquid-filled cartridge of claim 1, wherein the encapsulated substance comprises a pharmaceutical compound.
12. The liquid-filled cartridge of claim 1, wherein the encapsulated substance comprises nicotine.
13. The liquid-filled cartridge of claim 1, wherein the nanoparticles are dispersed within an aqueous solution.
14. The liquid-filled cartridge of claim 13, wherein the aqueous solution comprises a saline.
15. The liquid-filled cartridge of claim 14, wherein the aqueous solution comprises sodium chloride.
16. The liquid-filled cartridge of claim 15, wherein the nanoparticles are dispersed within an aqueous solution of 0.9% sodium chloride.
17. The liquid-filled cartridge of claim 1, wherein a pH of the liquid is between about 5.5 and about 8.
18. The liquid-filled cartridge of claim 1, wherein a pH of the liquid is between about 6.5.
19. The liquid-filled cartridge of claim 1, wherein a molecular ratio of the encapsulated substance to an encapsulating agent of the nanoparticle is between about 0.1:1 to about 10:1.
20. The liquid-filled cartridge of claim 1, wherein a polydispersity index measurement of the nanoemulsion is less than 0.3.
21. A method of manufacturing cartridges for use with an electronic device for delivery of a substance into a body through respiration, comprising filling a liquid container of the cartridge with a liquid for aerosolizing and inhaling by a person using the electronic device, the liquid

- comprising a plurality of nanoparticles in a nanoemulsion, each nanoparticle comprising an encapsulation of the substance to be delivered into the body through respiration.
22. The method of claim 21, further comprising a preliminary step of producing the nanoemulsion by processing the substance to be delivered together with the encapsulating agent using a microfluidizing machine.
 23. The method of claim 22, further comprising operating the microfluidizing machine such that a temperature of the processing does not exceed 65°C while producing the nanoemulsion.
 24. The method of claim 38, further comprising the step of adjusting pH of the nanoemulsion so as to be between about 5.5 and 8.
 25. The method of claim 22, further comprising the step of chemically bonding the substance to be encapsulated with another molecule prior to processing the substance with the encapsulating agent using the microfluidizing machine.
 26. The method of claim 22, wherein a polydispersity index measurement of the nanoemulsion after processing using the microfluidizing machine is less than 0.3.
 27. A method of manufacturing a liquid for aerosolizing and inhaling by a person using an electronic device for the delivery of a substance to the body of the person through respiration, the method comprising producing a liquid mixture comprising a plurality of nanoparticles in a nanoemulsion by processing the substance together with an encapsulating agent using a microfluidizing machine such that the plurality of nanoparticles of the nanoemulsion comprises the encapsulated substance.
 28. The method of claim 27, further comprising operating the microfluidizing machine such that a temperature of the processing does not exceed 65°C while producing the nanoemulsion.
 29. The method of claim 27, further comprising the step of adjusting pH of the nanoemulsion so as to be between about 5.5 and 8.
 30. The method of claim 27, further comprising the step of chemically bonding the substance to be encapsulated with another molecule prior to processing the substance with the encapsulating agent using the microfluidizing machine.
 31. The method of claim 27, wherein a polydispersity index measurement of the nanoemulsion after processing using the microfluidizing machine is less than 0.3.

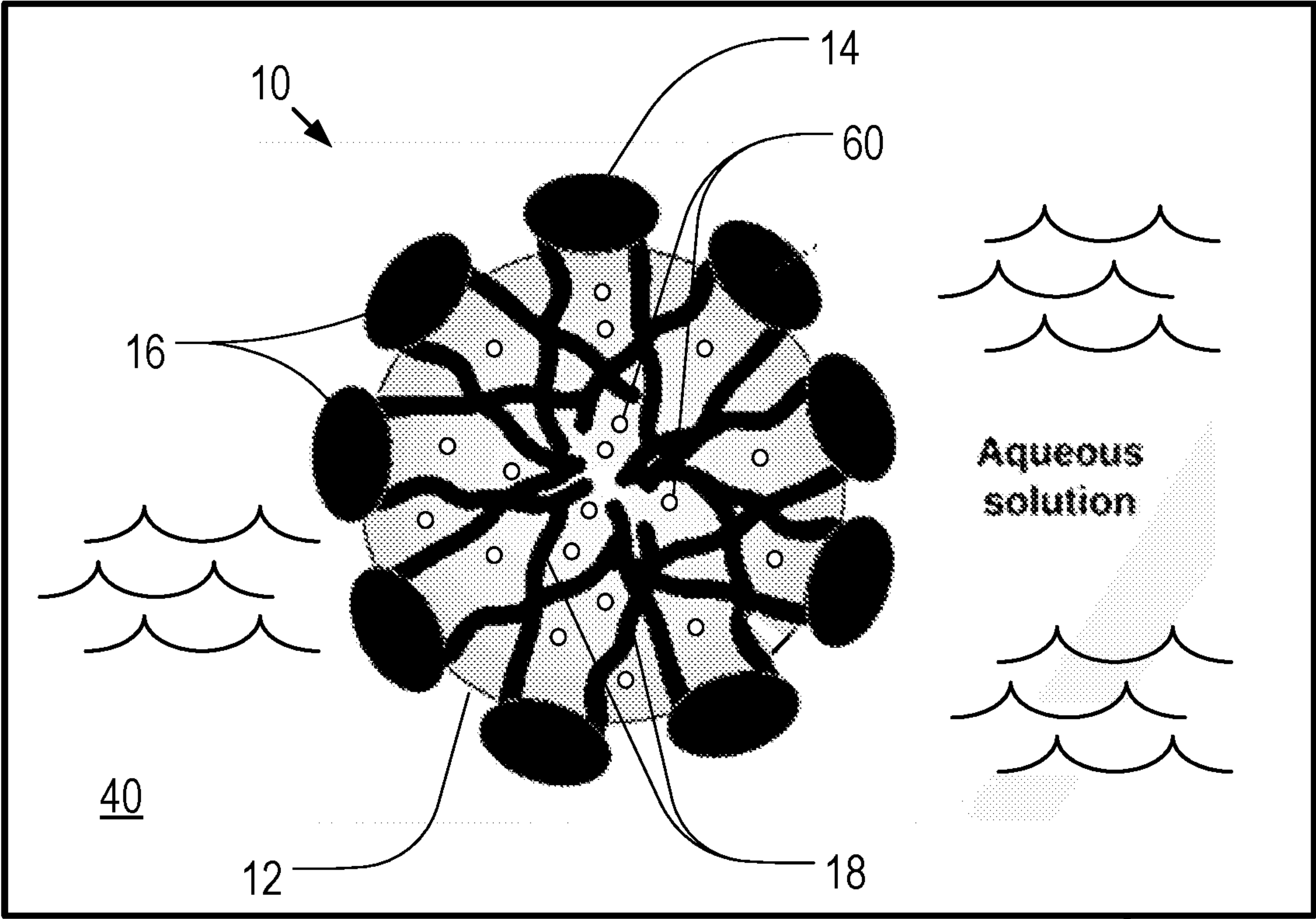


FIG. 1

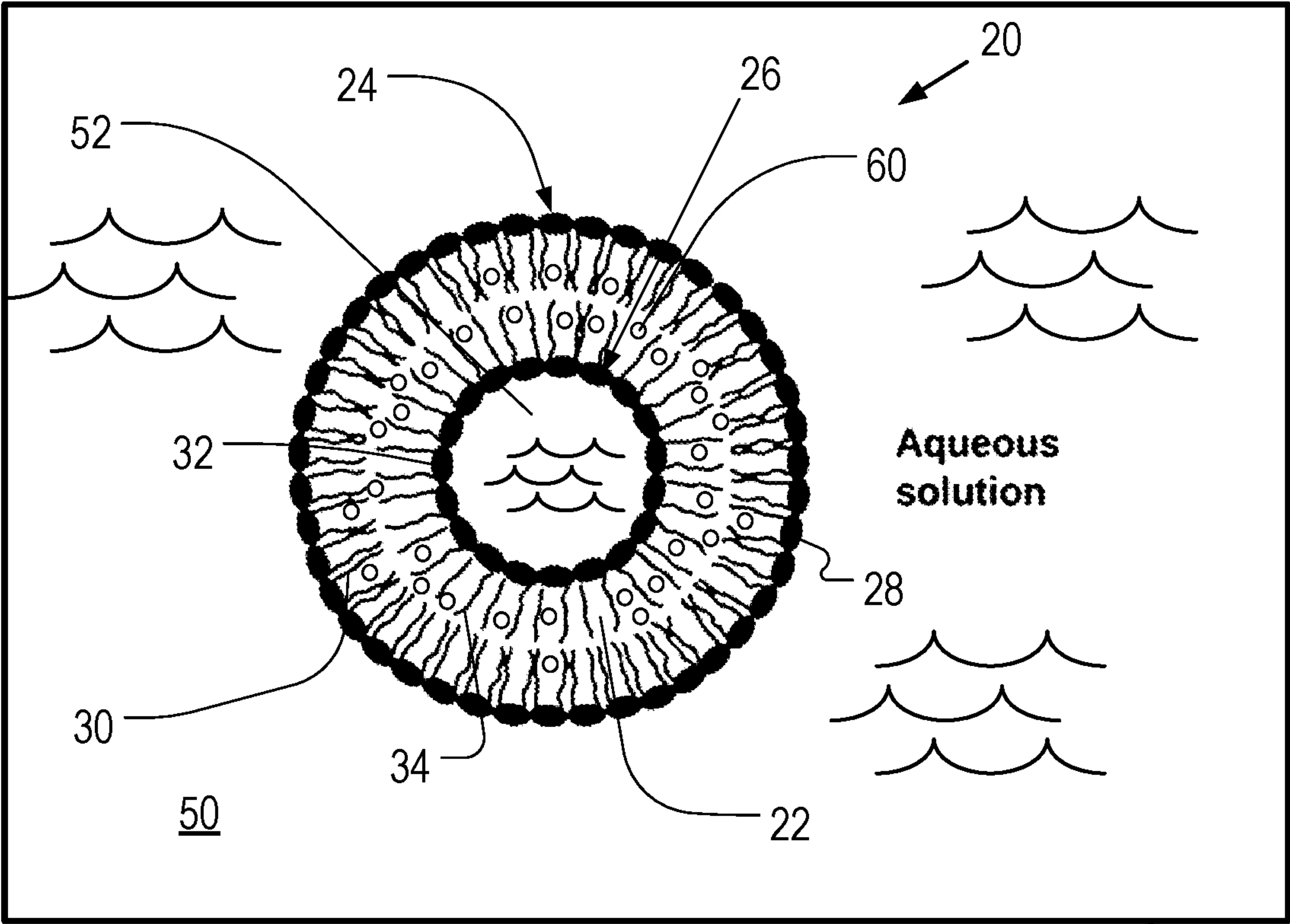
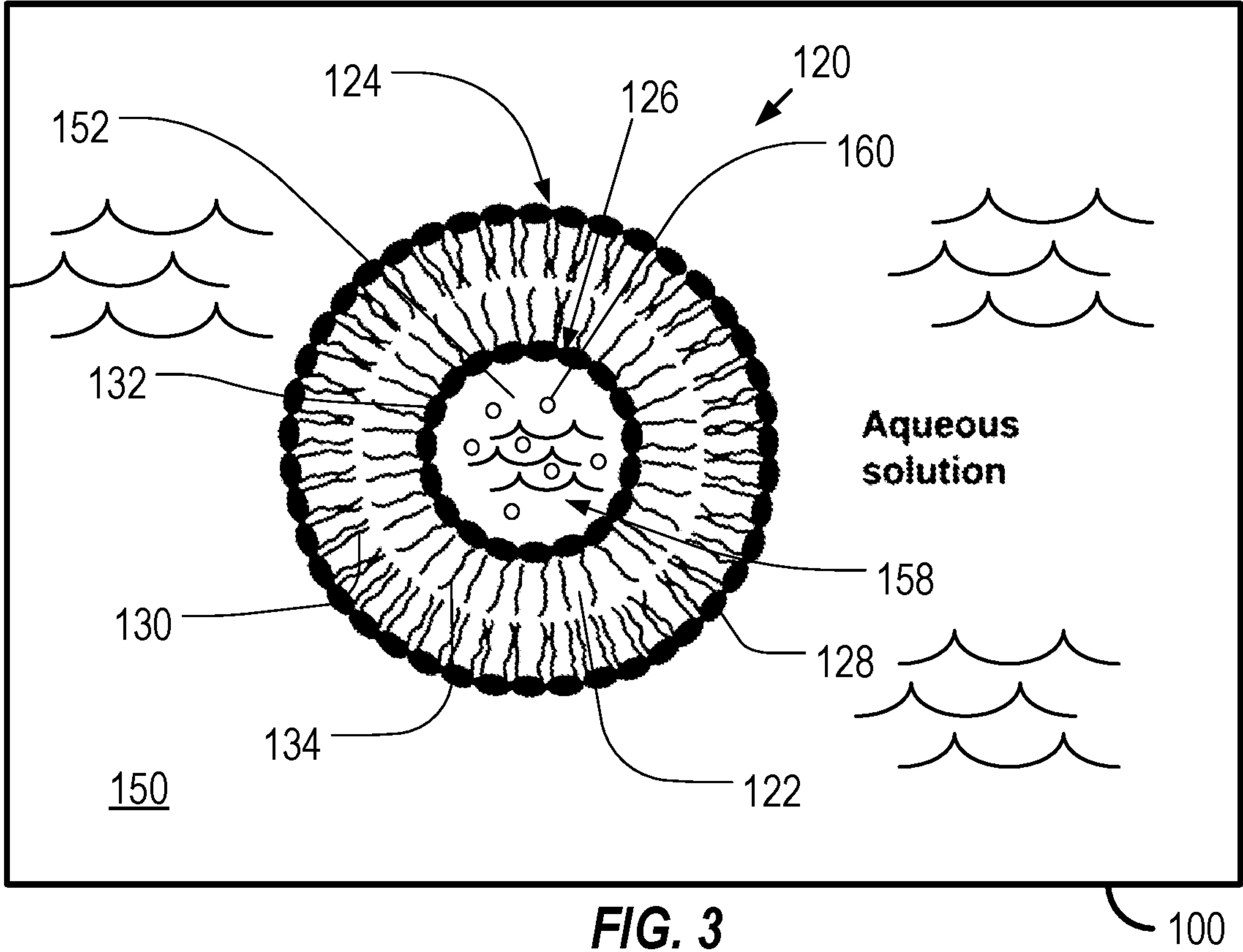


FIG. 2



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US20/56541

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A24F 40/10; A61K 9/12; A61M 15/00 (2020.01)

CPC - A61K 9/0073; A61K 9/0075; A61K 9/0078; A61K 9/1075; A61K 9/127; A61M 15/001; A61M 15/009

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)

See Search History document

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

See Search History document

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

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2017/0143627 A1 (SYNERGIA BIO SCIENCES PRIVATE LIMITED) 25 May 2017; paragraphs [0166], [0180]	1, 2, 11, 13, 17, 18, 20 --- 26, 29, 31
X --- Y	US 2018/0296493 A1 (NANOSPHERE HEALTH SCIENCES, LLC) 18 October 2018; paragraphs [0180], [0184], [0235], [0249]-[0250]; claims 14, 15	1, 6, 8-10, 13-15, 19 --- 7, 16
X	US 2019/0282502 A1 (FLURRY POWDERS, LLC) 19 September 2019; paragraphs [0021], [0026], [0055], [0076]	1, 12
X	US 2011/0117026 A1 (TSENG, Y ET AL.) 19 May 2011; paragraphs [0245], [0374]	1-5
X	WO 2017/183011 A1 (DEGEETER, D ET AL.) 26 October 2017; paragraphs [0006], [0042]-[0043], [0059]-[0061]	21
X --- Y	US 2010/0166673 A1 (SURBER, MW ET AL.) 01 July 2010; paragraphs [0040], [0151]-[0153], [0157], [0246]	21, 22, 24 --- 23, 25, 26
X --- Y	US 6,544,542 B1 (SONOKE, S ET AL.) 08 April 2003; column 1, lines 52-59; column 4, lines 17-32	27 --- 28-31
Y	US 2013/0058999 A1 (FOEGER, FA) 07 March 2013; paragraphs [0050], [0065]	7

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

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

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

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

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

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Date of the actual completion of the international search

08 December 2020 (08.12.2020)

Date of mailing of the international search report

12 JAN 2021

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US20/56541

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2016/0051582 A1 (LI, Q ET AL.) 25 February 2016; paragraph [0030]	16
Y	US 5,510,118 A (BOSCH, HW ET AL.) 23 April 1996; column 7, lines 63-67; column 8, lines 1-3	23, 28
Y	US 2003/0068277 A1 (VANBEVER, R ET AL.) 10 April 2003; paragraphs [0025], [0033], [0049]	25, 30
P,X	US 2020/0060349 A1 (RESPIRA TECHNOLOGIES, INC.) 27 February 2020; see entire document	1-31