

(51) International Patent Classification:
G01G 9/00 (2006.01)(21) International Application Number:
PCT/CN2015/094697(22) International Filing Date:
16 November 2015 (16.11.2015)

(25) Filing Language: English

(26) Publication Language: English

(71) Applicants: **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH). **MICROFLUIDIC INNOVATIONS, LLC**. [US/US]; 1205 West State Street, West Lafayette, Indiana 47906 (US).

(72) Inventors; and

(71) Applicants (for US only): **SANCHEZ-FELIX, Manuel** [US/US]; Novartis Institutes for BioMedical Research, Inc., 250 Massachusetts Avenue, Cambridge, Massachusetts 02139 (US). **KOU, Xiang** [CN/CN]; Novartis Pharmaceuticals (China), Building 8, 898 Halei Road, Pudong District, Shanghai 201203 (CN). **HOBAUGH, Mark**[US/US]; Microfluidic Innovations, LLC, 1205 West State Street, West Lafayette, Indiana 47906 (US). **WERELEY, Steven** [US/US]; Microfluidic Innovations, LLC, 1205 West State Street, West Lafayette, Indiana 47906 (US). **AMIN, Ahmed** [EG/US]; Microfluidic Innovations, LLC, 1205 West State Street, West Lafayette, Indiana 47906 (US).(74) Agent: **SHANGHAI PATENT & TRADEMARK LAW OFFICE, LLC**; 435 Guiping Road, Shanghai 200233 (CN).

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

[Continued on next page]

(54) Title: ACOUSTIC MATERIAL WEIGHING AND MANIPULATION

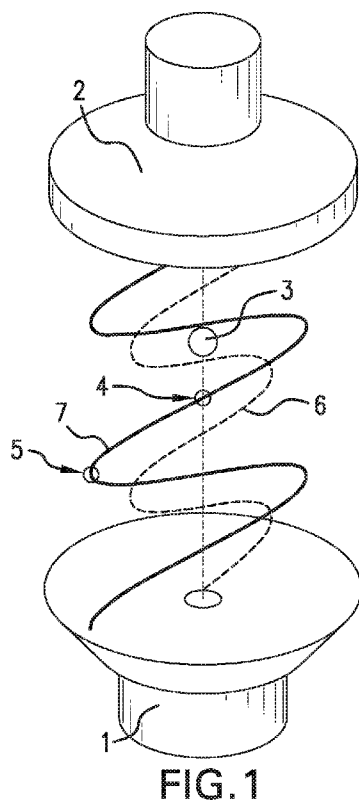


FIG. 1

(57) Abstract: A method of determining the weight of a material (3) which is in the form of a solid particle or a liquid droplet, comprising introducing said material (3) into an acoustic levitation field, so that it is positioned and kept in position by an acoustic node (4) of a standing wave in the acoustic levitation field, determining the position of the material (3) and using the position information to determine the weight of the material (3); to a method of dispensing a material (3) in the form of a solid particle or a liquid droplet or mixture, comprising introducing said material (3) into an acoustic levitation field, so that it is positioned and kept in position by an acoustic node (4) of a standing wave in the acoustic levitation field, determining information on any one or more features selected from the position, the shape, the weight and the orientation of the material (3) and using the obtained feature to dispense the material (3) into a final destination; and to apparatus for use in the methods mentioned.



(84) **Designated States** (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE,

SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

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

ACOUSTIC MATERIAL WEIGHING AND MANIPULATION

Summary of the Invention

[001] The invention relates to a method or process determining the weight, or other characteristics, especially of a material which is in the form of a solid particle or a liquid droplet, and to devices equipped for that purpose, as well as to related embodiments of the invention as disclosed in detail in the following.

Background of the Invention

[002] Standing acoustic waves can be relatively powerful, for example, they can cause dust to collect in a pattern corresponding to the wave's nodes. They can also be used for acoustic levitation, that is, for placing objects or materials in a hovering position without contact to any mechanical device or element. Increasing the power of the acoustic wave will increase the pressure in the standing nodes – eventually becoming high enough to balance the pull of gravity on objects placed in these nodes. Thus intensive sound is central to acoustic levitation -- transducers in many levitators produce sounds in excess of 150 decibels (dB).

[003] It is important to tune the correct frequency to match the distances between the transducer or transducers or the reflecting elements and/or vice versa in order to create the desired standing wave with stable nodes and antinodes. Most systems use ultrasonic waves, which are too high-pitched for people to hear. In addition to the frequency and volume of the wave, researchers also must pay attention to a number of other factors:

[004] The object or material being levitated should measure for example between one third and half of the wavelength of the sound. The sound wave must produce enough pressure to counteract the pull of gravity on the object or material in order to allow it to hover. The intensity of the sound must not overwhelm the surface tension of liquid droplets being levitated. If the sound field is too intense, the drop will flatten into a donut and then burst.

[005] US 6,109,098 describes methods and devices for determining the size of particles by sound attenuation and sound speed in liquid matrix.

[006] US 2012/0197005 A1 provides a method for producing a mixture of amorphous compounds, e.g. from crystalline materials, in an acoustic levitation field without liquid (in the gas phase), comprising supplying a solution containing the compounds; and allowing at least a portion of the solvent of the solution to evaporate while preventing the solute of the solution from contacting a nucleation point.

[007] Companies often have substantial libraries of compounds or substances in libraries that require dispensing prior to testing or preparation. For example pharmaceutical companies will have libraries that may contain up to a million compounds. The most desirable way to store these compounds is as a solid because it reduces the risk of stability issues or precipitation from solutions due to freeze/thawing. Weighing samples manually is often required if the compounds are solids and there are often errors or challenges in dispensing small quantities of highly variable materials with different morphologies (i.e. crystal shapes or amorphous materials or oils, etc). Furthermore only very small quantities may be required to be dispensed (<1 mg) and this is challenging to do accurately or without considerable loss of material or considerable time.

[008] Some compounds are highly potent or toxic and require special containment environment when weighing or preparing samples or products to prevent contamination of operators.

[009] Currently pharmacy (hospital and retail) provide patients with formulations of active pharmaceutical ingredients (API). This requires substantial storage area for the products and for pharmaceutical companies to spend considerable time and effort to develop formulations containing the API and excipients in a form that can be handled by patients in packaging. These formulations are generally designed to enable mass manufacturing of the product by ensuring that a consistent dose of the API is in the product taken by the patient (for example $\pm$ 10 % of the label claim) and that the patient or care provider can handle the product. Excipients are added to make the formulation appropriate for processing (for example, API flows in the equipment to dispense a

consistent dose in each capsule or tablet or other formulation option) or amenable to handling or compression e.g. into a tablet.

[0010] There are often issues with homogeneity of the product or stability of the product with excipients or issues with packaging. Furthermore, customarily 2 years of shelf life have to be generated on each product so that the product is stable during shipment, storage at the pharmacy and during period with the patient. In addition many patients are on multiple treatments and combination of API's. This makes it difficult for patients to be compliant.

[0011] Currently pharmaceutical companies will develop a product for the average patient and one or two or three dosage forms to manage size or gender or age differences.

[0012] Genetic and biomarker technology is generating a need for products that enable a specific dose and regime for a specific individual which is not easily met by the convention formulation approach presently.

[0013] This is currently performed manually and is the most labor intensive stage of most laboratory operations. It is also the largest source of errors resulting in subsequent experiments. The issue is that materials are different and cause issues such as electrostatic repulsion or attraction, sticking together or to surfaces, or are oily or gluing or are inconsistent in texture. Furthermore it is difficult to measure accurately amounts of 5 or less mg, especially < 1 mg, and consequently much material is wasted due to higher than required amounts being used to ensure an accurate weighing. To achieve desired low concentrations it is often required that the compound is dissolved in a solvent and diluted to the desired concentration. This may also lead considerable errors and require the repetition of experiments.

[0014] Novel drug delivery systems for local delivery that require a matrix or formulation can be challenging to prepare and ensure a consistent dose. This is because the mixing with a matrix is challenging and needs to be processed extensively.

[0015] Most processes used to crystallize a product generate material that is inconsistent with respect to size and morphology. This often means that milling or further processing is required leading to loss of material or time required to process material further. Chemical impurity or solid state polymorphs occurs during manufacturing.

[0016] Crystallization of solid from liquid and the subsequent characterization is routinely carried out in a separate manner. The disadvantages include: longer process procedures; storage; and sampling errors.

[0017] Also in other fields (e.g. agriculture related chemistry, chemistry and fine chemistry, also fields implying radioactive materials (where the use of contactless methods is especially useful, allowing to characterize and dispense material minimizing loss and radioactive contamination) or other materials used in trace amounts (e.g. antibodies, active proteins, nucleic acids), exact weighing and distribution of materials is desirable.

[0018] In view of these issues and limitations of drug or other material handling and dispensing, it is desirable to provide a method and devices allowing to determine exact amounts of materials and to allow to dispense them for example in containers or devices e.g. for the preparation of dosage forms without having to touch them by any mechanical means during weighing and dispensing.

General Description of the Invention

[0019] It has now been found that acoustic levitation provides a means to weigh materials, such as solid particles or liquid droplets, and to dispense them into appropriate containers or devices, making it possible to weigh and deliver exactly controlled amounts of such materials. Also other characterization is possible, as well as the dispensing of the material into desired destinations, e.g. (for example tableting, capsule, syringe or ampoule filling) devices or containers.

[0020] Ultrasound levitation thus allows to separate particles e.g. of an active pharmaceutical compound from a bulk reservoir either as individual particles or a group of particles, move (dispense or transfer) these particles to the capsule or other

formulation unit and deposit them there in a controlled manner, providing an accurate weight within known a known range or specification. This also allows the processing of crystals with morphology which have poor flow properties and that could normally not or only difficultly be used for drugs in a capsule or other dosage forms or formulations. The technology will also measure the weight of individual particles or a group of particles and is also appropriate to determine the number of particles of compound or carrier containing the compound.

[0021] In a first aspect, the invention describes a method of determining the weight of a material which is in the form of a solid particle or a liquid droplet, comprising introducing said material into an acoustic levitation field, so that it is positioned and kept in position by an acoustic node of a standing wave in the acoustic levitation field, determining the position of the material and using the position information to determine the weight of the material.

[0022] In a second aspect, the invention relates to a method of dispensing a material in the form of a solid particle or a liquid droplet or mixture, comprising introducing said material into an acoustic levitation field, so that it is positioned and kept in position by an acoustic node of a standing wave in the acoustic levitation field, determining information on any one or more features selected from the position, the shape, the weight and the orientation of the material and using the obtained feature to dispense the material into a final destination.

[0023] In a third aspect, the invention describes an apparatus (device) appropriate or equipped for carrying out said method, comprising an acoustic transducer, an acoustic reflector, and a unit for determining the position of a material which is in the form of a solid particle or a liquid droplet. This apparatus is preferably (e.g. computer) programmed or can be (e.g. computer) programmed to allow to determine the position of the material to be weighed and to use the position information to determine the weight of said material.

Detailed Description of the Invention

[0024] The method according to the first aspect of the invention, in a first invention sub-aspect, especially is used for determining the weight where the material particle or droplet has a weight in the range from 0.1 ng to 5 g, e.g. from 0.1 ng to 100 mg, in particular from 1 ng to 5 or 1 mg.

[0025] In one sub-aspect of the first aspect of the invention, the method is used where the solid material is a result of liquid material comprising a solution or dispersion, including a suspension of a solid material in a solvent or solvent mixture or an emulsion of a liquid material in a solvent or solvent mixture that is not miscible with the solvent.

[0026] In a further sub-aspect of the first aspect of the invention, the method according to the previous paragraph further comprises evaporating the solvent and forming the solid material in dry form. The dry form may, depending on the speed of evaporation, which may be supported by supplying energy, e.g. heat or microwave irradiation, may be amorphous, glassy, partially crystalline or completely crystalline (a mixture of solid states).

[0027] In yet a further sub-aspect of the first aspect of the invention, the method in the preceding paragraphs is used where the material is solid and can be pulverous, crystalline, amorphous, a granule, a particle agglomerate, a mixture of solid states, a micelle material, a liposome material, a viral material, e.g. for vaccination purposes, cell component (e.g. membrane vesicles or mitochondria) or a cell material (meaning wherever mentioned a material including one or more cells, such as bacterial or fungal cells, e.g. for vaccination purposes, or e.g. cells from the immune system, such as lymphocytes or phagocytes).

[0028] In another sub-aspect of the first aspect of the invention, the invention relates to the method according to any one of the preceding aspects (embodiments) wherein the material comprises a drug, a drug and excipient combination, an excipient, an intermediate for the synthesis of a drug, a cell component, a cellular material, a cell, or a plurality of cells. Alternatively, the material may be one useful in agriculture related chemistry, fine chemistry or other chemistry, a radioactive material or any other material used in small or trace amounts (e.g. antibodies, active proteins, nucleic acids), where exact weighing and distribution of materials is desirable.

[0029] In a further particular sub-aspect of the first aspect of the invention, the invention relates to the method according to any one of the preceding aspects, where the position is determined by an optical system, especially including a camera, or a laser detection system, e.g. a laser interferometer; a system for impedance measurement ; or by an acoustic system.

[0030] Yet another particular sub-aspect of the first aspect of the invention relates to the method according to any one of the preceding aspects, comprising further determining the shape of the material, especially where liquid droplet materials are used and more especially where solid materials are involved, e.g. in order to allow to determine the particle or crystal shape and/or size in order to allow to conclude on processability e.g. during the manufacture of a pharmaceutical or agrochemistry or cosmetic or chemistry or other formulation.

[0031] Another sub-aspect of the first aspect of the invention refers to the method according to any one of the preceding aspects of the first aspect of the invention, comprising further determining the orientation of the particle or droplet.

[0032] Another specific sub-aspect of the first aspect of the invention relates to the method according to the preceding paragraph wherein the orientation depends on the effect of the levitation field, acoustic node, or the material in the levitation field, or a combination of two or more of these parameters.

[0033] Another sub-aspect of the first aspect of the invention also relates to the method according to any one of the preceding invention aspects, further comprising determining whether the material is in solid form or in liquid form or a combination or mixture thereof (e.g. a suspension or an emulsion or a micelular form), as well as whether the material is crystalline or amorphous. Aggregates or combinations of the foregoing can also be determined. Another of the sub-aspects of the first aspect of the present invention relates to the method according to any one of the preceding aspects of the first aspect, wherein multiple particles or droplets are introduced into multiple nodes of (one and) the same standing wave simultaneously or sequentially and the determining of the weight of each takes place in parallel.

[0034] An important sub-aspect of the first aspect of the invention relates to the method according to any one of the preceding aspects wherein the material is a drug, an excipient, a drug formulation, or intermediate, or placebo or inactive material.

[0035] In a sub-aspect of the second aspect of the invention, the method there may comprise determining the weight by a method according to any one of the preceding aspects of the invention.

[0036] The method according to the second aspect of the invention, especially according to the preceding paragraph, wherein one or more material particles or droplets are dispensed into one or more further or final destinations is a further sub-aspect of the invention.

[0037] Another sub-aspect of the second aspect of the invention relates to the method according to any one of the second invention aspect and sub-aspects thereof wherein the further or final destination is selected based on information comprising one or more of the features selected from the position, the shape, the weight and/or the orientation of the material, especially one or more of a combination of these features including at least the weight.

[0038] The method according to the preceding paragraph wherein selecting the further or final destination based upon the weight, polymorphism, size and/or shape of the material is a further sub-aspect of the invention.

[0039] The method according to any one of the (sub-)aspects of the second aspect of the invention, comprising dispensing more than one material particle or droplet to the same further or final destination and thus accumulating the material at that destination, especially comprising accumulating up to 10 g of material at the same destination, forms another sub-aspect.

[0040] A further sub-aspect of the second invention relates to the method according to any one of the (sub-)aspects thereof mentioned so far, comprising using as the material a drug or drug formulation or placebo.

[0041] Another sub-aspect of the second aspect of the invention relates to the method according to any one of its (sub-)aspects mentioned so far, wherein more than one material is used, that is two different material. In particular in the case where the material is a drug, the sub-aspect comprises two or more drugs, and/or in the case of a drug formulation two or more excipients with one or more drugs .

[0042] Still another sub-aspect of the second aspect of the invention relates to the method according to any one of its (sub-)aspects mentioned so far, wherein the dispensing of the material is comprising shifting the position of said material so that it enters a device or container as further or final destination, especially comprising using a solid particle as material and shifting the position of the material so that it enters the device which is selected from a tableting and a capsule filling machine, more especially comprising shifting the position of the material into a container which is selected from a capsule, an ampoule, a syringe, a bottle, an infusion container, a sachet, a vial, a spray container or a blister pack, or food product (e.g. nutraceutical) container, each especially for pharmaceutical purposes, respectively.

[0043] A further sub-aspect of the second aspect of the invention relates to the method according to any one of its (sub-)aspects mentioned so far, comprising shifting the material to the destination by using multiple sound transducers, applying electrical fields, using gas (e.g. air) streams or blasts, moving the transducers of the levitating wave and/or superimposing a slow acoustic wave oriented in an angle different, for example greater than 0° relative to an axis of the levitating wave. For example, in embodiments where the levitating wave is arranged about a vertical axis, a transporting wave may be arrayed at any angle from the vertical axis. Additionally or alternatively shifting the material to the destination may be achieved by weakening or removing the acoustic levitation field, allowing the material to fall into a destination positioned below the material. Combinations of any of the foregoing may be employed.

[0044] The method according to any one of the aspects and sub-aspects of the second aspect of the invention, comprising, by shifting the material, supplying specific amounts or dosages into the device or container is another sub-aspect of the second invention aspect.

[0045] A further sub-aspect of the second aspect of the invention relates to the method according to any one of its (sub-)aspects mentioned so far, comprising affecting the material using mechanical means to transport it into the device or container.

[0046] The method according to any one of the sub-aspects of the second aspect of the invention, comprising using mechanical means to move the receiving device and container under the material and subsequently disabling the acoustic field to capture the particle in the device, forms an invention sub-aspect.

[0047] Yet another sub-embodiment (sub-aspect) of the second aspect of the invention relates to a method according to any one of the aspects or sub-aspects of the second invention mentioned so far, comprising determining the vertical position of the material in order to determine the weight of the material. This is especially important as it allows for precise delivery of amounts of material to containers or ampoules, which may be determined with standard deviations of 1 % or less and are thus much more precisely determined and distributed than in other weigh determination methods.

[0048] Another sub-aspect of the second aspect of the invention relates to the method according to any one of its preceding (Sub-)aspects, wherein the position of the material is determined by an optical system or a sound system; especially wherein the position and if part of the respective claim any other feature mentioned is determined with a high-speed microscopic system.

[0049] A further sub-aspect of the second aspect of the invention relates to the method according to any one of its preceding (sub-)aspects, comprising providing units of the material(s) with an electric charge of identical polarity in order to inhibit its or their aggregation or to allow to move (dispense) them by means of electric field(s); or with an electric charge of different polarity in order to promote its or their aggregation or to allow to move (dispense) them by means of electric field(s).

[0050] The method according to any one of the preceding (sub-)aspects of the second invention may comprise controlling one or more parameters selected from the groups

consisting of the temperature, charge, humidity, pressure, and operating conditions of the device housing the material (and/or levitation field).

[0051] The method according to any one of the preceding (sub-)aspects of the second aspect of the invention may comprise determining the weight by calibration with particles or droplets of known weight, e.g. by way of a calibration curve (which may be implemented in programmed form).

[0052] The present invention also, in a third aspect, relates to a device or apparatus appropriate, especially adapted or equipped, e.g. programmed and comprising the means, for executing a method according to any of the invention aspects and sub-aspects defined so far.

[0053] In one embodiment of the third aspect of the invention, the invention thus relates to an apparatus (device) comprising an acoustic transducer, an acoustic reflector, and a unit for determining the position of a material which is in the form of a solid particle or a liquid droplet.

[0054] This apparatus, as said unit for determining the position of the material, preferably is an optical system, especially comprising a microscope and a high-speed imaging device.

[0055] In preferred invention embodiment, the apparatus according to any one of the preceding two paragraphs comprises an input element for the material. Such input element may, for example, be a container with the material (which may already be in particle or droplet form, e.g. in the form of a fluid bed (maintained by gas and/or ultrasound) or spouted bed), a microfluidic element allowing to feed droplets of material, a micro cup, a funnel or the like.

[0056] The apparatus, according to any one of the invention embodiments defined herein before, further preferably comprises a unit or element for shifting the position of the material in an acoustic node.

[0057] The apparatus according to any one of the preceding embodiments may, in a further invention embodiment, comprise a unit to collect material positioned, characterized and/or weighed in an acoustic node. This unit may be a device or a container.

[0058] The definitions given in the following allow to replace one or more or all general terms of each invention aspect or sub-aspect in which they appear by the more specific definitions, thus defining specific and preferred invention embodiments.

[0059] Where a “material” is mentioned, this especially refers to a (relatively small) material portion.

[0060] “Particle” in particular means a (under the temperature conditions during application of a method or device according to the invention) solid material that may be a monolithic particle or an aggregate of solid material sub-particles, e.g. a granulate or agglomerate.

[0061] “Droplet” in particular means a material with a (under the temperature conditions during application of a method or device according to the invention) liquid continuous matrix which is the sole phase present, or they may comprise solid material (including micelles or liposomes) as non-continuous phase, e.g. as a suspension, or immiscible liquid material, e.g. sub-droplets, e.g. in a water-in-oil or oil-in-water emulsion. Droplets may be disrupted into sub-droplets or they may be united to form larger droplets in the acoustic field or when dispensed into a container or device.

[0062] A “micelle” material is especially one comprising supermolecular colloid particles, often including a packet of chain molecules in parallel arrangement, e.g. formed from surface active (amphiphilic) substances.

[0063] A “liposome material” is especially a material comprising spherical vesicles having at least one lipid bilayer.

[0064] A “viral material” may e.g. be formed from proteins and/or nucleic acids which at least partially correspond to proteins and/or nucleic acids in virus, or genetically modified

variants thereof, or complete virus (which may be inactivated e.g. for vaccination purposes).

[0065] A “cell component” may e.g. comprise membrane vesicles from organelle or the outer membrane of cells, or complete organelles, such as mitochondria.

[0066] As a “cell material”, preferably a material comprising one or more cells, such as bacterial or fungal cells, e.g. for vaccination purposes, or e.g. cells from the immune system, such as lymphocytes or phagocytes, e.g. cells allowing to provide monoclonal antibodies, can be meant.

[0067] An “optical system” (or optical unit) may comprise a camera, a laser detection system or a high speed (especially microscopic) system.

[0068] A “camera” is an optical instrument allowing to record images (single images or sequences of images, e.g. in the form of videos or movies) which may be stored, transmitted to another location, or both. A digital camera is one preferred embodiment. The camera may work with the light of the visible spectrum or with other portions of the electromagnetic spectrum, e.g. UV light.

[0069] A “laser detection system” is any laser system that allows to determine distances or positions of materials, or any other properties thereof, such as its surface properties, refractive index, density or the like. Examples are laser measuring devices or laser interferometers. Such systems e.g. allow for the testing of the kind of surface of a solid or liquid material according to the invention embodiments and make it possible to achieve high precision examination of surface topography. Exact imaging is possible e.g. by optical coherence tomography, phase contrast and differential interference contrast microscopy, angle-resolved low-coherence interferometry or phase-contrast X-ray imaging. Laser detection systems can also be used to determine indices of refraction and thermal properties.

[0070] A high-speed (especially microscopic) system, including or as part of a camera, may be an especially useful device to determine the position of the material.

[0071] In some embodiments of the invention, weight of a particle is determined by determining the vertical position (e.g., location of the particle relative to a lower sound transducer surface or any other reference height or datum), and comparing the determined location to a calibration plot in order to determine the weight of the particle.

[0072] It is also possible to change the strength of the acoustic field in order to change the position of the material to a specific height and to determine the weight by setting it in relation to the strength of the acoustic field, or to use a combination of any of the methods mentioned herein for determining the weight of a material .

[0073] Where a material is “dispensed” into one or more final destinations in accordance with one or more of the methods of the invention, this allows for the delivery of a very precise weight amount to the destination, and/or for the delivery of an otherwise characterized material, as mentioned above and below.

[0074] A device or container as final destination may comprise a device that allows for the distribution into a unit form of a pharmaceutical preparation, e.g. a container as mentioned in the following, and may e.g. be an ampoule filling, capsule filling or tablet forming device; a container may e.g. be selected from a capsule, an ampoule, a syringe, a bottle, an infusion container, a sachet, a vial and a blister pack.

[0075] A device or container as further destination may comprise a device or container that is useful or necessary for some further processing, distribution or handling of the material as an intermediate prior to achieving the final unit form of a pharmaceutical preparation, and may e.g. comprise a filling, transporting, or conditioning device; a container may e.g. be selected from a well, capsule, ampoule, syringe, bottle, infusion container, sachet, vial and blister.

[0076] The shifting the material to the destination by using multiple sound transducers may make use of superimposition of acoustic waves or a tuning of the waves so that together, at least during the dispensing of a material in liquid droplet or solid particle form, sound waves are influenced and added so as to provide a force that drives the material to or above the desired position. This effect may also be obtained by moving the transducers of the levitating wave to a position where the material is to be dispensed to.

Alternatively or in addition, superimposing a slow acoustic wave oriented in an angle different from 0° relative to an axis of the levitating wave may allow for such shift in the position of the material.

[0077] Especially if the material is charged (which may, for example, be achieved when it is supplied into the acoustic levitation field employed according to the invention) the particles may also be moved by applying electrical fields, e.g. using two or more electrodes of appropriate charge.

[0078] Also by using gas (e.g. air) streams or blasts, a material particle or droplet may experience a force allowing it to be dispensed at or moved to a desired destination.

[0079] The dispensing method may (in addition or in combination with any one or more of the other methods appropriate, e.g. as just mentioned) comprise shifting the material to the destination by weakening or removing the acoustic levitation field, allowing the material to fall into a desired destination positioned below the material.

[0080] Alternatively or in addition, mechanical means may be used to move the material hovering in the levitation field to a desired destination. These mechanical means may include directly inserting the destination device or container in the field which may lead to a disruption that allows the hovering material to be supplied to the destination. Alternatively, the mechanical means may be robot arms (e.g. equipped with forceps), plungers, e.g. in rod shape, threads, wires, filaments, sheet-like materials or the like.

[0081] The mechanical means may also be a ratchet or conveyor belt, bar or roller that allows to position containers or devices, e.g. vials or ampoules or open capsules or the like, below a position allowing to deliver the material to them, e.g. to a position below the lower confinement of the room in which acoustic levitation is effected, for example through a hole in said lower confinement.

[0082] Preferably, the dispensing takes place without need for the material to come into contact with a surface other than that in or at the destination, thus allowing to decrease risks of contamination or material loss on such surfaces.

[0083] The material treated or manipulated according to the invention may be supplied with an electric charge of identical polarity in order to inhibit its or their aggregation; or with an electric charge of different polarity in order to promote its or their aggregation. This allows to (e.g. also by moving the material portions towards or away from each other) to form larger particle aggregates or larger droplets. In the case of droplets, it is possible to explode them (e.g. by administration of sufficiently strong sound waves) into smaller droplets and thus to yield smaller material droplets.

[0084] The term “dispense” or “dispensing” of a material especially relates to its transfer and deposition at a desired destination. Thus the material can be delivered in a precise amount or with precise knowledge to a desired destination, even without contacting it with any surfaces other than those at the destination.

[0085] The term “food product” comprises, for example, a “nutraceutical” (sometimes also called “Functional Food”, “Functional Food product”, “Foodsceutical”, “Medicinal Food” or “Designer Food”) and, according to the present invention embodiments, is defined as food product (including beverages) suitable for human consumption – the expression comprises any fresh or processed food having a health-promoting and/or disease-preventing property beyond the basic nutritional function of supplying nutrients, including food made from functional food ingredients or fortified with health-promoting additives, especially with an effects in the prophylaxis or treatment of one or more of the disorders mentioned herein, in which a material obtained (especially dispensed) according to the invention is added as an ingredient (especially as additive) as health benefit agent, especially in an effective amount, as well as any partially or totally artificially composed food.

[0086] The nutraceuticals can alternatively be prepared in various forms, such as granules, tablets, pills, suppositories, capsules, suspensions, salves, lotions, suspensions, parenteral products (e.g. intra venous infusions or injects or subcutaneous injects) or the like.

[0087] The term “pharmaceutical formulation” (medicament) comprises any type of formulation known in the art. Said formulation may comprise one or more drugs (“active ingredients”) with or without (pharmaceutically acceptable) excipient(s).

[0088] Drugs may be selected from antibodies, vaccines, enzymes or small molecule organic drugs or other therapeutically active molecules.

[0089] The active ingredient(s) may, for example, be selected from the (non-limiting) group consisting of 5-alpha-reductase inhibitors, 5-aminosalicylates, 5HT3 receptor antagonists, AACE inhibitors with calcium channel blocking agents, ACE inhibitors with thiazides, adamantane antivirals, adrenal cortical steroids, adrenal corticosteroid inhibitors, adrenergic bronchodilators, agents for hypertensive emergencies, agents for pulmonary hypertension, aldosterone receptor antagonists, alkylating agents, allergenics, alpha-glucosidase inhibitors, alternative medicines, amebicides, aminoglycosides, aminopenicillins, aminosaliculates, AMPA receptor antagonists, amylin analogs, analgesic combinations, analgesics, androgens and anabolic steroids, angiotensin converting enzyme inhibitors, angiotensin II inhibitors with calcium channel blockers, angiotensin II inhibitors alone or with thiazides, angiotensin receptor blockers, angiotensin receptor blockers and neprilysin inhibitors, anorectal preparations, anorexiant, antacids, anthelmintics, anti-angiogenic ophthalmic agents, anti-CTLA-4 monoclonal antibodies, anti-infectives, antiadrenergic agents (central), e.g. with thiazides, antiadrenergic agents (peripheral), e.g. with thiazides, antiadrenergic agents, centrally acting antiadrenergic agents, peripherally acting antiandrogens, antianginal agents, antiarrhythmic agents, antiasthmatic combinations, antibiotics/antineoplastics, anticholinergics, antiemetics, anticholinergic antiparkinson agents, anticholinergic bronchodilators, anticholinergic chronotropic agents, anticholinergics/antispasmodics, anticoagulants, anticonvulsants, antidepressants, antidiabetic agents, antidiabetic combinations, antidiarrheals, antidiuretic hormones, antidotes, antiemetic/antivertigo agents, antifungals, antigonadotropic agents, antigout agents, antihistamines, antihyperlipidemic agents, antihyperlipidemic combinations, antihypertensive combinations, antihyperuricemic agents, antimalarial agents, antimalarial combinations, antimalarial quinolones, antimetabolites, antimigraine agents, antineoplastic detoxifying agents, antineoplastic interferons, antineoplastics, antiparkinson agents, antiplatelet agents, antipseudomonal penicillins, antipsoriatics, antipsychotics, antirheumatics, antiseptics and germicides, antithyroid agents, antitoxins and antivenins, antituberculosis agents, antituberculosis combinations, antitussives, antiviral agents, antiviral boosters, antiviral combinations, antiviral interferons, anxiolytics, sedatives, hypnotics, aromatase

inhibitors, atypical antipsychotics, azole antifungals, bacterial vaccines, barbiturate anticonvulsants, barbiturates, BCR-ABL tyrosine kinase inhibitors, benzodiazepine anticonvulsants, benzodiazepines, beta blockers with calcium channel blockers, beta blockers with thiazides, beta-adrenergic blocking agents, beta-lactamase inhibitors, bile acid sequestrants, biologicals, bisphosphonates, bone morphogenetic proteins, bone resorption inhibitors, bronchodilator combinations, bronchodilators, calcineurin inhibitors, calcitonin, calcium channel blocking agents, carbamate anticonvulsants, carbapenems, carbonic anhydrase inhibitor, anticonvulsants, carbonic anhydrase inhibitors, cardiac stressing agents, cardioselective beta blockers, cardiovascular agents, catecholamines, CD20 monoclonal antibodies, CD30 monoclonal antibodies, CD33 monoclonal antibodies, CD52 monoclonal antibodies, central nervous system agents, cephalosporins, cerumenolytics, CFTR combinations, CFTR potentiators, chelating agents, chemokine receptor antagonists, chloride channel activators, cholesterol absorption inhibitors, cholinergic agonists, cholinergic muscle stimulants, cholinesterase inhibitors, CNS stimulants, coagulation modifiers, colony stimulating factors, contraceptives, corticotropin, coumarins and indandiones, COX-2 inhibitors, decongestants, dermatological agents, diagnostic radiopharmaceuticals, diarylquinolines, dibenzazepine anticonvulsants, digestive enzymes, dipeptidyl peptidase 4 inhibitors, diuretics, dopaminergic antiparkinsonism agents, drugs used in alcohol dependence, echinocandins, EGFR inhibitors, estrogen receptor antagonists, estrogens, expectorants, factor Xa inhibitors, fatty acid derivative anticonvulsants, fibric acid derivatives, first generation cephalosporins, fourth generation cephalosporins, functional bowel disorder agents, gallstone solubilizing agents, gamma-aminobutyric acid analogs, gamma-aminobutyric acid reuptake inhibitors, gastrointestinal agents, general anesthetics, genitourinary tract agents, GI stimulants, glucocorticoids, glucose elevating agents, glycopeptide antibiotics, glycoprotein platelet inhibitors, glycolcyclines, gonadotropin releasing hormones, gonadotropin-releasing hormone antagonists, gonadotropins, group I antiarrhythmics, group II antiarrhythmics, group III antiarrhythmics, group IV antiarrhythmics, group V antiarrhythmics, growth hormone receptor blockers, growth hormones, guanylate cyclase-C agonists, H. pylori eradication agents, H2 antagonists, hedgehog pathway inhibitors, hematopoietic stem cell mobilizer, heparin antagonists, heparins, HER2 inhibitors, herbal products, histone deacetylase inhibitors, hormones, hormones/antineoplastics, hydantoin anticonvulsants, hydrazide derivatives, illicit (street) drugs, immune globulins, immunologic agents, immunostimulants, immunosuppressive agents, impotence agents, in vivo diagnostic bio-

logicals, incretin mimetics, inhaled anti-infectives, inhaled corticosteroids, inotropic agents, insulin-like growth factor, integrase strand transfer inhibitor, interferons, interleukin inhibitors, interleukins, intravenous nutritional products, iodinated contrast media, ionic iodinated contrast media, iron products, ketolides, laxatives, leprostatics, eukotriene modifiers, lincomycin derivatives, local injectable anesthetics, loop diuretics, lung surfactants, lymphatic staining agents, lysosomal enzymes, macrolide derivatives, macrolides, magnetic resonance imaging contrast media, mast cell stabilizers, meglitinides, metabolic agents, methylxanthines, mineralocorticoids, minerals and electrolytes, miscellaneous agents, miscellaneous analgesics, miscellaneous antibiotics, miscellaneous anticonvulsants, miscellaneous antidepressants, miscellaneous antidiabetic agents, miscellaneous antiemetics, miscellaneous antifungals, miscellaneous antihyperlipidemic agents, miscellaneous antihypertensive combinations, miscellaneous antimalarials, miscellaneous antineoplastics, miscellaneous antiparkinson agents, miscellaneous antipsychotic agents, miscellaneous antituberculosis agents, miscellaneous antivirals, miscellaneous anxiolytics, sedatives and hypnotics, miscellaneous bone resorption inhibitors, miscellaneous cardiovascular agents, miscellaneous central nervous system agents, miscellaneous coagulation modifiers, miscellaneous diagnostic dyes, miscellaneous diuretics, miscellaneous genitourinary tract agents, miscellaneous GI agents, miscellaneous hormones, miscellaneous metabolic agents, miscellaneous ophthalmic agents, miscellaneous otic agents, miscellaneous respiratory agents, miscellaneous sex hormones, miscellaneous topical agents, miscellaneous uncategorized agents, miscellaneous vaginal agents, mitotic inhibitors, monoamine oxidase inhibitors, mouth and throat products, mTOR inhibitors, mucolytics, multikinase inhibitors, muscle relaxants, mydriatics, narcotic analgesic combinations, narcotic analgesics, nasal anti-infectives, nasal antihistamines and decongestants, nasal lubricants and irrigations, nasal preparations, nasal steroids, natural penicillins, neprilysin inhibitors, neuraminidase inhibitors, neuromuscular blocking agents, neuronal potassium channel openers, next generation cephalosporins, nicotinic acid derivatives, NK1 receptor antagonists, NNRTIs, non-cardioselective beta blockers, non-iodinated contrast media, non-ionic iodinated contrast media, non-sulfonylureas, nonsteroidal anti-inflammatory agents, NS5A inhibitors, nucleoside reverse transcriptase inhibitors (NRTIs), nutraceutical products, nutritional products, ophthalmic anesthetics, ophthalmic anti-infectives, ophthalmic anti-inflammatory agents, ophthalmic antihistamines and decongestants, ophthalmic diagnostic agents, ophthalmic glaucoma agents, ophthalmic lubricants and irrigations, ophthalmic preparations, oph-

thalmic steroids, ophthalmic steroids with anti-infectives, ophthalmic surgical agents, oral nutritional supplements, other immunostimulants, other immunosuppressants, otic anesthetics, otic anti-infectives, otic preparations, otic steroids, otic steroids with anti-infectives, oxazolidinone anticonvulsants, oxazolidinone antibiotics, parathyroid hormone and analogs, PCSK9 inhibitors, penicillinase resistant penicillins, penicillins, peripheral opioid receptor antagonists, peripheral vasodilators, peripherally acting antiobesity agents, phenothiazine antiemetics, phenothiazine antipsychotics, phenylpiperazine antidepressants, phosphate binders, plasma expanders, platelet aggregation inhibitors, platelet-stimulating agents, polyenes, potassium sparing diuretics with thiazides, potassium-sparing diuretics, probiotics, progesterone receptor modulators, progestins, prolactin inhibitors, prostaglandin D2 antagonists, protease inhibitors, protease-activated receptor-1 antagonists, proteasome inhibitors, proton pump inhibitors, psoralens, psychotherapeutic agents, psychotherapeutic combinations, purine nucleosides, pyrrolidine anticonvulsants, quinolones, radiocontrast agents, radiologic adjuncts, radiologic agents, radiologic conjugating agents, radiopharmaceuticals, recombinant human erythropoietins, renin inhibitors, respiratory agents, respiratory inhalant products, rifamycin derivatives, salicylates, sclerosing agents, second generation cephalosporins, selective estrogen receptor modulators, selective immunosuppressants, selective phosphodiesterase-4 inhibitors, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, serotonergic neuroenteric modulators, sex hormone combinations, sex hormones, SGLT-2 inhibitors, skeletal muscle relaxant combinations, skeletal muscle relaxants, smoking cessation agents, somatostatin and somatostatin analogs, spermicides, statins, sterile irrigating solutions, streptomyces derivatives, succinimide anticonvulsants, sulfonamides, sulfonyleureas, synthetic ovulation stimulants, tetracyclic antidepressants, tetracyclines, therapeutic radiopharmaceuticals, therapeutic vaccines, thiazide diuretics, thiazolidine diones, thioxanthenes, third generation cephalosporins, thrombin inhibitors, thrombolytics, thyroid drugs, TNF alpha inhibitors, tocolytic agents, topical acne agents, topical agent, topical anesthetics, topical anti-infectives, topical anti-rosacea agents, topical antibiotics, topical antifungals, topical antihistamines, topical antineoplastics, topical antipsoriatics, topical antivirals, topical astringents, topical debridging agents, topical depigmenting agents, topical emollients, topical keratolytics, topical non-steroidal anti-inflammatories, topical photochemotherapeutics, topical rubefacient, topical steroids, topical steroids with anti-infectives, triazine anticonvulsants, tricyclic antidepressants, trifunctional monoclonal antibodies, ultrasound contrast media, upper

respiratory combinations, urea anticonvulsants, urea cycle disorder agents, urinary anti-infectives, urinary antispasmodics, urinary pH modifiers, uterotonic agents, vaccine combinations, vaginal anti-infectives, vaginal preparations, vasodilators, vasopressin antagonists, vasopressors, VEGF/VEGFR inhibitors, viral vaccines, viscosupplementation agents, vitamin and mineral combinations, and vitamins. These diseases are from the Drug Class Database of the FDA and are non-limiting.

[0090] The present invention relates also to pharmaceutical formulations (pharmaceutical compositions) that comprise an active ingredient as or included in a material obtained (e.g. dispensed) according to the invention and that can be used especially in the treatment of the diseases mentioned herein.

[0091] The material of the present invention may be used, for example, for the preparation of pharmaceutical compositions that comprise a pharmaceutically effective amount of a material.

[0092] The active ingredient in said material may be present in free form or in the form of a pharmaceutically acceptable salt, solvate, hydrate or polymorph, or in admixture with a significant amount of one or more inorganic or organic, solid or liquid, pharmaceutically acceptable excipients (carriers).

[0093] Compositions for enteral administration, such as nasal, buccal, rectal or, especially, oral administration, and for parenteral administration, such as intravenous, intramuscular or subcutaneous administration, to warm-blooded animals, especially humans, are especially preferred. The compositions comprise the active ingredient alone or, preferably, together with a pharmaceutically acceptable excipient (carrier). The dosage of the active ingredient depends upon the disease to be treated and upon the species, its age, weight, and individual condition, the individual pharmacokinetic data, and the mode of administration.

[0094] The pharmaceutical compositions comprise from approximately 0.0001% to approximately 100% (% referring to weight percent) active ingredient, single-dose administration forms comprising in the preferred embodiment from approximately 0.001% to approximately 100% active ingredient and forms that are not of single-dose

type comprising in the preferred embodiment from approximately 5% to approximately 20% active ingredient. Unit dose forms are, for example, coated and uncoated tablets, ampoules, vials, suppositories, sachets, sprinkles, spray containers or capsules. Further dosage forms are, for example, ointments, creams, pastes, foams, tinctures, sprays, etc. Examples are capsules or tablets or ampoules containing from about 0.0001 mg to about 1.0 g, e.g. from 0.001 to 5 mg material dispensed according to the invention embodiments.

[0095] The pharmaceutical compositions of the present invention are, taking reference to the inventive dispensing, otherwise prepared in a manner known per se, for example by means of conventional mixing, granulating, coating, dissolving or lyophilizing processes or by mixing using a method or device according to the invention.

[0096] Preference is given to the use of solutions of the material with the active ingredient, and also suspensions or dispersions, especially isotonic aqueous solutions, dispersions or suspensions which, for example in the case of lyophilized compositions comprising the active ingredient alone or together with a carrier can be made up before use. The pharmaceutical compositions may be sterilized and/or may comprise excipients, for example preservatives, stabilizers, wetting agents and/or emulsifiers, solubilizers, salts for regulating osmotic pressure and/or buffers and are prepared in a manner known per se, for example by means of conventional dissolving and lyophilizing processes. The said solutions or suspensions may comprise viscosity-increasing agents or solubilizers, such as sodium carboxymethylcellulose, carboxymethylcellulose, dextran, polyvinylpyrrolidone or gelatin.

[0097] Suspensions in oil comprise as the oil component the vegetable, synthetic or semi-synthetic oils customary for injection purposes. There may be mentioned as such especially liquid fatty acid esters that contain as the acid component a long-chained fatty acid having from 8 to 22, especially from 12 to 22, carbon atoms, for example lauric acid, tridecylic acid, myristic acid, pentadecylic acid, palmitic acid, margaric acid, stearic acid, arachidic acid, behenic acid or corresponding unsaturated acids, for example oleic acid, elaidic acid, erucic acid, brasidic acid or linoleic acid, if desired with the addition of anti-oxidants, for example vitamin E, β -carotene or 3,5-di-tert-butyl-4-hydroxytoluene. The alcohol component of those fatty acid esters has a maximum of 6 carbon atoms and is a

mono- or poly-hydroxy, for example a mono-, di- or tri-hydroxy, alcohol, for example methanol, ethanol, propanol, butanol or pentanol or the isomers thereof, but especially glycol and glycerol. The following examples of fatty acid esters are therefore to be mentioned: ethyl oleate, isopropyl myristate, isopropyl palmitate, "Labrafil M 2375" (polyoxyethylene glycerol trioleate, Gattefossé, Paris), "Miglyol 812" (triglyceride of saturated fatty acids with a chain length of C₈ to C₁₂, Hüls AG, Germany), but especially vegetable oils, such as cottonseed oil, almond oil, olive oil, castor oil, sesame oil, soybean oil and more especially groundnut oil.

[0098] Injection compositions are prepared in customary manner under sterile conditions; the same applies also to introducing the compositions into ampoules or vials and sealing the containers.

[0099] Pharmaceutical compositions for oral administration which are also especially preferred can be obtained by combining the material with the active ingredient with solid carriers, if desired granulating a resulting mixture, and processing the mixture, if desired or necessary, after the addition of appropriate excipients, into tablets, dragée cores or capsules. It is also possible for them to be incorporated into plastics carriers that allow the active ingredients to diffuse or be released in measured amounts.

[00100] Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and binders, such as starch pastes using for example corn, wheat, rice or potato starch, gelatin, tragacanth, methylcellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone, and/or, if desired, disintegrators, such as the above-mentioned starches, and/or carboxymethyl starch, crosslinked polyvinylpyrrolidone, agar, alginic acid or a salt thereof, such as sodium alginate. Excipients are especially flow conditioners and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol. Dragée cores are provided with suitable, optionally enteric, coatings, there being used, *inter alia*, concentrated sugar solutions which may comprise gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, or coating solutions in suitable organic solvents, or, for the preparation of enteric coatings, solutions of suitable cellulose

preparations, such as ethylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Capsules are dry-filled capsules made of gelatin or HPMC and soft sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The dry-filled capsules may comprise the active ingredient in the form of granules, for example with fillers, such as lactose, binders, such as starches, and/or glidants, such as talc or magnesium stearate, and if desired with stabilizers. In soft capsules the active ingredient is preferably dissolved or suspended in suitable oily excipients, such as fatty oils, paraffin oil or liquid polyethylene glycols, it being possible also for stabilizers and/or antibacterial agents to be added. Dyes or pigments may be added to the tablets or dragée coatings or the capsule casings, for example for identification purposes or to indicate different doses of active ingredient.

[00101] Tablet cores can be provided with suitable, optionally enteric, coatings through the use of, inter alia, concentrated sugar solutions which may comprise gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, or coating solutions in suitable organic solvents or solvent mixtures, or, for the preparation of enteric coatings, solutions of suitable cellulose preparations.

[00102] Pharmaceutical compositions for oral administration also and especially include hard capsules consisting of gelatin, and also soft, sealed capsules consisting of gelatin and a plasticizer. The hard capsules may contain the active ingredient in the form of granules, for example in admixture with fillers, binders, and/or glidants, and optionally stabilizers. In soft capsules, the active ingredient is preferably dissolved or suspended in suitable liquid excipients, to which stabilizers and detergents may also be added.

[00103] Pharmaceutical compositions suitable for rectal administration are, for example, suppositories that consist of a combination of the active ingredient and a suppository base.

[00104] For parenteral administration, aqueous solutions of an active ingredient in water-soluble form, for example of a water-soluble salt, or aqueous injection suspensions that contain viscosity-increasing substances, for example sodium carboxymethylcellulose, sorbitol and/or dextran, and, if desired, stabilizers, are especially suitable. The active ingredient, optionally together with excipients, can also be in the form of a lyophilizate

and can be made into a solution before parenteral administration by the addition of suitable solvents.

[00105] Solutions such as are used, for example, for parenteral administration can also be employed as infusion solutions.

[00106] As used herein, the term “excipient” especially refers to any pharmaceutically or nutraceutically acceptable carrier material as already mentioned and also and includes any and all solvents, dispersion media, coatings, surfactants, antioxidants, preservatives (*e.g.*, antibacterial agents, antifungal agents), isotonic agents, absorption delaying agents, salts, preservatives, drugs, drug stabilizers, binders, excipients, disintegration agents, lubricants, sweetening agents, flavoring agents, dyes, and the like and combinations thereof, as would be known to those skilled in the art. Except insofar as any conventional carrier is incompatible with the active ingredient, its use in the therapeutic or pharmaceutical compositions is contemplated.

[00107] The term “a therapeutically effective amount” especially refers to an amount of the material obtainable according to the present invention (especially the active ingredient forming it or comprised in it) that will elicit the biological or medical response of a subject suffering from a disease or disease symptoms, including ameliorating the status of a subject suffering from said disease, alleviating the disease or one or more of its symptoms, or preventing the disease, or the like. As used herein, the term “subject” refers to an animal. Typically the animal is a mammal. A subject also refers to for example, primates (*e.g.*, humans, male or female), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice, fish, birds and the like. In certain embodiments, the subject is a primate. In yet other embodiments, the subject is in particular a human.

[00108] The dosage of a material obtained (*e.g.* dispensed) or characterized according to the invention embodiments in pharmaceutical preparations and food products may vary according to the patient's needs, status and condition. For example, a daily dosage (which may be split up into two or more, *e.g.* up to three dosage units) may be in the range from 0.0001 mg to 5000 mg, such as from 0.001 to 5 mg, *e.g.* from 0.001 to 1 mg.

[00109] Placebo formulations may comprise solely the excipient material(s) and may be useful in the placebo treatment or in clinical trials.

[00110] Diseases (including disorders) may, for example, be selected from the group consisting of infectious and parasitic diseases, especially lower respiratory tract infections, diarrhea, AIDS, tuberculosis, and malaria; neuropsychiatric conditions, e.g. depression; injuries, especially motor vehicle accidents, cardiovascular diseases, principally heart attacks and stroke, premature birth and other perinatal deaths, gastrointestinal disorders, and cancer. Any disease or disorder encompassed by these general terms or any other disease or disorder may be comprised.

[00111] Where "intermediate" is referred to, this relates to any compound which is used as starting material or intermediate in the synthesis of a final drug molecule. Examples are organic low molecular weight compounds, enzymes, antibodies or specifically binding parts thereof, nucleic acids or nucleic acid derivatives, such as siRNA, or the like, especially selected from the active ingredients mentioned above.

[00112] In accordance with the foregoing, the present invention also comprises the following embodiments which can be claimed:

- (1) A material obtained (especially dispensed) according to the invention for use in the diagnostic or especially therapeutic (including prophylactic) treatment of an animal, preferably a mammal, especially a human; especially of any one or more of the particular disorders set forth hereinbefore and hereinafter.
- (2) A pharmaceutical or nutraceutical composition comprising a material obtained (especially dispensed) according to a method of the invention as active ingredient together with a pharmaceutically acceptable diluent or carrier, especially for use in the therapeutic and/or prophylactic treatment of a disease or disorder, e.g. mentioned herein.
- (3) A method for the treatment of a disorder, especially any one or more disorders, e.g. set forth herein, in a subject in need of such treatment, comprising administering a pharmaceutically effective amount of a material obtained (especially dispensed) according to a method of the invention, especially to an individual in need thereof.

(4) The use of a material obtained (especially dispensed) according to a method of the invention, for the manufacture of a medicament or food supplement for the treatment or prevention of a disease or disorder e.g. as mentioned herein;

(5) A method as defined above comprising co-administration, e.g. concomitantly or in sequence, a therapeutically effective amount of a material obtained (especially dispensed) according to a method of the invention, and a different pharmaceutically active compound and/or a pharmaceutically acceptable salt thereof, said different pharmaceutically active compound and/or salt thereof being especially for use in the treatment of any one or more of the disorders set forth hereinbefore or hereinafter.

(6) A combination product comprising a therapeutically effective amount of a material obtained (especially dispensed) according to a method of the invention, and a different pharmaceutically active compound and/or a pharmaceutically acceptable salt thereof, said second pharmaceutically active compound being especially for use or of use in the treatment of any one or more of the particular disorders set forth hereinbefore.

[00113] The Figures show exemplary invention embodiments as follows:

[00114] Fig. 1 shows a schematic representation of an embodiment of acoustic levitation of a particle.

[00115] Fig. 2 is a graph showing the distribution of sound pressure level (in dB) and the vertical position in an embodiment of an acoustic levitation field relative to the distance from a node **4** in mm.

[00116] Fig. 3 is a calibration curve for an embodiment of the invention for a determination of weight of a particle and its vertical position in an acoustic levitation field relative to the position with maximum sound pressure (the "datum").

[00117] Fig. 4 schematically represents an apparatus according to an embodiment of the invention that allows for the touch-free transport (dispensing) of a material to a desired destination, here capsule halves.

[00118] Fig. 5 schematically illustrates, in an embodiment of the invention, how material levitation is detected and converted to weight measurement.

[00119] Examples: The following examples illustrate the invention without limiting its scope.

[00120] In Fig. 1, the principle of acoustic levitation, according to various embodiments of the invention, is represented. A transducer **1** and a reflector **2** are set up in a distance that allows an acoustic standing wave to be formed between them. A material **3** (here in a non-limiting way a particle) is held in a hovering position (in levitation) above a node **4** (capture node, positive sound pressure area) of the acoustic standing wave, remote from the antinode **5** (rejection node, negative sound pressure area). Also the corresponding sound velocity wave **6** and the sound pressure wave **7** are represented schematically. The material **3** is kept in the upper area of the node **4** as there, the lower the position, the higher the pressure to keep it in its hovering position is. If the particle is (e.g. by shift of the position of the node or by decreasing the energy of the sound wave) reaching the lower half of the node **4**, it may drop through this lower part (with declining pressure) and the antinode **5** and then be held by the next node **4** in a hovering position or drop e.g. through a hole in the transducer to a desired destination. This allows for one way to deliver a material without touching (and thus e.g. contaminating or otherwise influencing the surface of it) it to a desired destination.

[00121] Fig. 2 shows an example for the measured sound level for an actually established standing acoustic wave (the sound pressure level profile in the particle levitator for one set of operating conditions actually used). Node **4** and antinode **5** of the actual sound pressure wave **7** and their height relative to the datum (a maximum sound pressure position, i.e. a node) are shown. The sound pressure level can, for example, be determined with a sound pressure calibration sensor **15**) as shown in Fig. 4.

[00122] In Fig. 3, the result of levitation height and corresponding weight determination of particles are shown. The particles levitate at different heights depending on their size and hence weight. The particles levitated at the height at which acoustic pressure forces are balanced by weight. Measurements of the sound pressure level in the particle levitator in Fig. 2. In an ideal case we would expect the sound pressure level to be perfectly sinusoidal. As real world effects are observed such as the presence of harmonics and other non-linearities which puts higher demands on a theoretical

relationship to predict the sound pressure level. Therefore, in the present case a calibration curve (represented in Fig. 3) was established by actually determining the position relative to a datum (a predetermined location – in this case the surface of the transducer) for a range of particles with known weights and generating a calibration plot.

[00123] However, alternatively also theoretical predictions of the weight/height (position) or the material particles can be used (e.g. based on determination of the sound pressure level at specific heights), or combinations or calibration and theoretical prediction.

[00124] Note that instead of particles also droplets can be used both for calibration as well as for the determination of the weight of material portions (particles or droplets).

[00125] In order to perform a calibration, in the example represented in Fig. 3 several different particle diameters were levitated within the acoustic particle levitator at the same time. The nominal particle diameters used were 20 microns (μm), 50 μm and 100 μm . The sizes of all three particle species are known to within 1% because they are calibration standard particles and hence can be treated as particles of known weight and density. (These particles are NIST-standard particles and exact diameters and density – and hence weight - are provided by the manufacturer). These particle diameters were chosen to span the particle size range that the experimentators were interested in and do not represent the maximum or minimum particle diameters that can be levitated.

[00126] By imaging with an optical system **14** (see e.g. the representations in Figs. 4 and 5, the levitation heights tabulated in Table 1 were determined:

Table 1. Particle levitation height versus weight

Particle diam (μm)	Position (mm)		Mass (kg)		Mass trend (kg)		Absolute error %		Mass (mg)	
100	(1)	0.290244	(2)	5.49E-10	(3)	5.78E-10	(4)	5	(5)	5.492E-04
50	(6)	0.6033835	(7)	6.87E-11	(8)	6.24E-11	(9)	10	(10)	6.865E-05
20	(11)	0.9706452	(12)	4.39E-12	(13)	4.59E-12	(14)	4	(15)	4.694E-06

[00127] These experimental values are represented in Fig. 3 in a logarithmic scale, where also the resulting exponential function is represented. Particle levitation height is shown on the horizontal axis in mm (origin is arbitrary), and weight is shown on the vertical axis.

[00128] The power law used to attain the plot in Fig. 3 results in a fit parameter that is very nearly 1.0 indicating an excellent fit. This is a 2 parameter to 3 data points function which means that there is one more degree of freedom in the model. Consequently it would be possible for the curve fit to not pass perfectly through all three points. For a parabolic fit, the fit parameter would be exactly 1.0 because there would be 3 degrees of freedom in the data and 3 degrees of freedom in the model. Table 1 shows the known weight of the particles in column 2 and the weight determined from the regression in column 3. Column 4 shows the absolute value of the percentage error between the known weight and the weight determined by the regression. The average error for this measurement is 5.3%.

[00129] By supplying two particles of different sizes (in this case, ibuprofen), it could be shown that the larger (heavier) particle has a lower position in the same node than the smaller (less heavy) particle (not shown).

Fig. 4 shows an example for an apparatus according to the invention that allows to both measure the material portion, e.g. particle, weight and to dispense the material to a device or container, here to capsule halves **22** on an output device **21**, here in the exemplary form of a conveyor or collection device. The standing wave is produced by sound transducers **1**, (here illustrated as an upper and lower transducer, but alternatively one of which may also be a sound reflector **2**).

[00130] The material (e.g. a particle or droplet of a drug material, such as an ibuprofen particle) is provided from a material supply **8** (here represented as an arrow) to the acoustic trap sites **11** via an input dispensing tube or channel **10**. The acoustic trap sites **11** correspond to nodes **4** in Fig. 1 and Fig. 2. In many embodiments, by varying the strength of the acoustic levitation field, the particles may be delivered to specific trap sites **11**. Arrow **12** represents the direction of particle flow in the Fig.

[00131] An optional optical system (not shown) may be positioned near particle introduction and allows to control the particle entry if desired. An additional or alternative optional optical system (not shown) may be positioned below a particle outdrop tube 19

[00132] The optical system **14** (e.g. a camera) allows to determine the position of a material portion (e.g. particle) at node **4** and thus provides the information required to determine its weight (e.g. from a calibration curve as shown in Fig. 3 which can be programmed into a computer **25** as shown in Fig. 5, for example). A sound pressure level calibrations sensor **15** may be provided e. g, in order to allow for calibration based on sound pressure and/or to control the sound pressure if for example by lowering the sound intensity (energy) or by switching it off the particle(s) are to be dispensed to a desired destination, such as the capsule halves **22** shown here paradigmatically. This may be controlled by a detection unit (not shown) or the particle may simply fall through, e.g., outdrop tube **19** through which the material portion, e.g. particle, may fall without contacting it. The output may be controlled by an optional optical system (not shown) which may interface with a detection unit 18. .

[00133] Defective material (e.g. of undesired shape, weight or density) may (for example by use of a sound wave used in perpendicular direction to the wave represented by the trap sites **11** in the Figure) dispensed (transferred) to a collection vessel **17** under the control of the detection unit (e.g. extraction tube) **18** for defective material.

[00134] Alternatively (not shown), the dispensing of material portions (e.g. particles or droplets) may take place laterally (horizontally, e.g. perpendicular to the vertical wave axis) to a position other than outdrop tube **19**, e.g. by electrical fields (then the material portions are preferably provided in a charged form) or superimposed sound wave allowing to shift the particles laterally (which can also be done as depicted here for defective particles only).

[00135] Fig. 5 shows another schematic representation of a device forming an invention embodiment for weighing a material particle **3**, also schematically depicting the sound pressure wave **7** and showing the particle position relative to a datum **24** which is the position of maximum sound pressure in the corresponding node. A camera is shown as an

example of an optical system **14**, and allows for the position determination of the material particle **3**, here represented as levitation height X above the datum **24**, and computer **25** allows for determining the weight of the particle **3** and for controlling the device.

[00136] While various embodiments have been described above, it should be understood that they have been presented by way of example only, and not limitation. Thus, the breadth and scope of a preferred embodiment should not be limited by any of the above-described exemplary embodiments, but should be defined only in accordance with the following claims and their equivalents.

Claims

1. A method of determining the weight of a material which is in the form of a solid particle or a liquid droplet, comprising introducing said material into an acoustic levitation field, so that it is positioned and kept in position by an acoustic node of a standing wave in the acoustic levitation field, determining the position of the material and using the position information to determine the weight of the material.
2. The method according to claim 1, wherein the material particle or droplet has a weight in the range from 0.1 ng to 5 g, e.g. from 0.1 ng to 100 mg, in particular from 1 ng to 5 or 1 mg.
3. The method according to any one of claims 1 or 2, wherein the solid material is a result of liquid material comprising a solution or dispersion, including a suspension of a solid material in a solvent or solvent mixture or an emulsion of a liquid material in a solvent or solvent mixture that is not miscible with the solvent.
4. The method according to claim 3, further comprising evaporating the solvent and forming the solid material in dry form.
5. The method according to claim 1 or claim 2 wherein the material is solid and can be pulverous, crystalline, amorphous, a granule, an agglomerate of particles, a mixture of solid states, micelle material, liposome material, a viral material, a cell component or cell material.
6. The method according to any one of claims 1 to 5 where the material comprises a drug, a drug and excipient combination, an excipient, an intermediate for the synthesis of a drug, a cell component or a cell, a food product, nutraceutical, or a material useful in agriculture related chemistry, other chemistry, . fine chemistry, a radioactive material or another material used in trace amounts,

7. The method according to any one of claims 1 to 6, wherein the position is determined by an optical system.
8. The method according to any one of claims 1 to 7, comprising further determining the shape of the material, especially where liquid droplet materials are used or alternatively where solid particle materials are used.
9. The method according to any one of claims 1 to 8, comprising further determining the orientation of the particle or droplet.
10. The method according to claim 9 wherein the orientation depends on the effect of the levitation field, acoustic node, or the material in the levitation field, or a combination of two or more of these parameters.
11. The method according to any one of claims 1 to 10, further comprising determining whether the material is in solid or in liquid form or mixture or an aggregate or a combination of two or more of these forms.
12. The method according to any one of claims 1 To 11, further comprising determining whether the material is in crystalline or amorphous form, or a combination thereof.
13. The method according to any one of claims 1 to 12, wherein multiple particles or droplets are introduced into multiple nodes of the same standing wave simultaneously or sequentially and the determining of the weight of each takes place in parallel.
14. The method according to any one of claims 1 to 13 wherein the material is a drug or a drug formulation, or placebo or intermediate.
15. A method of dispensing a material in the form of a solid particle or a liquid droplet or mixture, comprising introducing said material into an acoustic levitation field, so that it is positioned and kept in position by an acoustic node of a standing wave in the acoustic levitation field, determining information on any one or more features selected from the position, the shape, the weight and the orientation of

the material and using the obtained feature to dispense the material into a final destination.

16. The method according to claim 15, comprising determining the weight by a method according to any one of claims 1 to 14.
17. The method according to any one of claims 15 or 16, wherein one or more material particles or droplets are dispensed into one or more final destinations.
18. The method according to any one of claims 14 to 17, wherein the final destination is selected based on the information one or more of the features selected from the position, the shape, the weight and the orientation of the material.
19. The method according to claim 18 wherein the final destination is selected based on the weight, polymorphism, size and shape of the material.
20. The method according to any one of claims 14 to 18, comprising dispensing more than one material particle or droplet to the same final destination and thus accumulating the material at that destination.
21. The method according to claim 20, comprising accumulating up to 10 g of material at the same destination.
22. The method according to any one of claims 14 to 20, comprising using as the material a drug or drug formulation or placebo.
23. The method according to any one of claims 14 to 22, wherein more than one material is used. The method according to 22, wherein the more than one material is a drug or excipient, or both.
24. The method according to any one of claims 14 to 22, wherein the dispensing of the material comprises shifting the position of said material so that it enters a device or container as destination.

25. The method according to claim 24, comprising using a solid particle as material and shifting the position of the material so that it enters the device which is selected from a tableting and a capsule filling machine.
26. The method according to claim 24, comprising shifting the position of the material into a container which is selected from a capsule, an ampoule, a syringe, a bottle, an infusion container, a sachet, a vial, a spray container or a blister pack.
27. The method according to any one of claims 14 to 26, comprising shifting the material to the destination by using multiple sound transducers, applying electrical fields, using a gas stream or blast, moving the transducer(s) of the levitating wave or superimposing a slow acoustic wave oriented in an angle different from 0 ° relative to the levitating wave, or combinations thereof.
28. The method according to any one of claims 14 to 56, comprising shifting the material to the destination by weakening or removing the acoustic levitation field, and allowing the material to fall into a destination positioned below the material.
29. The method according to any one of claims 14 to 26, comprising, by shifting the material, supplying specific amounts or dosages into the device or container.
30. The method according to any one of claims 14 to 24, comprising affecting the material using mechanical means to transport it into the device or container.
31. The method according to any one of claims 14 to 24, comprising using mechanical means to move the receiving device and container under the material and subsequently disabling the acoustic field to capture the particle in the device.
32. The method according to any one of claims 1 to 26, comprising determining the vertical position of the material in order to determine the weight of the material.
33. The method according to any one of claims 1 to 27, wherein the position of the material is determined by an optical system or a sound system, or both.

34. The method according to any one of claims 1 to 28, wherein the position of the material is determined with a high-speed microscopic system.
35. The method according to any one of claims 1 to 34, comprising providing units of the material(s) with an electric charge of identical polarity in order to inhibit its or their aggregation.
36. The method according to any one of claims 1 to 34, comprising providing units of the material(s) with an electric charge of different polarity in order to promote its or their aggregation.
37. The method according to any one of claims 1 to 34, comprising controlling one or more parameters selected from the group consisting of temperature, charge, humidity, pressure, operating conditions of the device housing the material, characteristics of the levitation field, and combinations thereof.
38. The method according to any one of claims 1 to 37, comprising determining the weight by calibration with particles or droplets of known weight.
39. An apparatus, for carrying out a method according to any one of claims 1 to 37, comprising an acoustic transducer, an acoustic reflector, and a unit for determining the position of a material which is in the form of a solid particle or a liquid droplet.
40. The apparatus according to claim 39, wherein the unit for determining the position is an optical system.
41. The apparatus according to claim 40 wherein the optical system comprises a microscope and a high-speed imaging device.
42. The apparatus according to any one of claims 38 to 41, comprising a unit or element for shifting the position of the material in an acoustic node.

43. The apparatus according to any one of claims 38 to 42, comprising a unit to collect material positioned and/or weighed in an acoustic node.
44. The apparatus according to claim 43, wherein the unit to collect material is a device or a container.

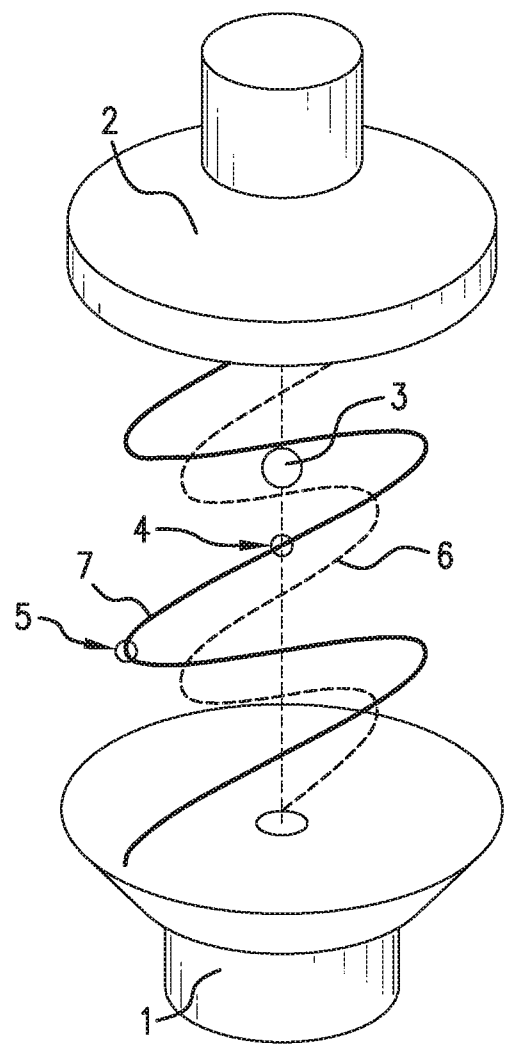


FIG.1

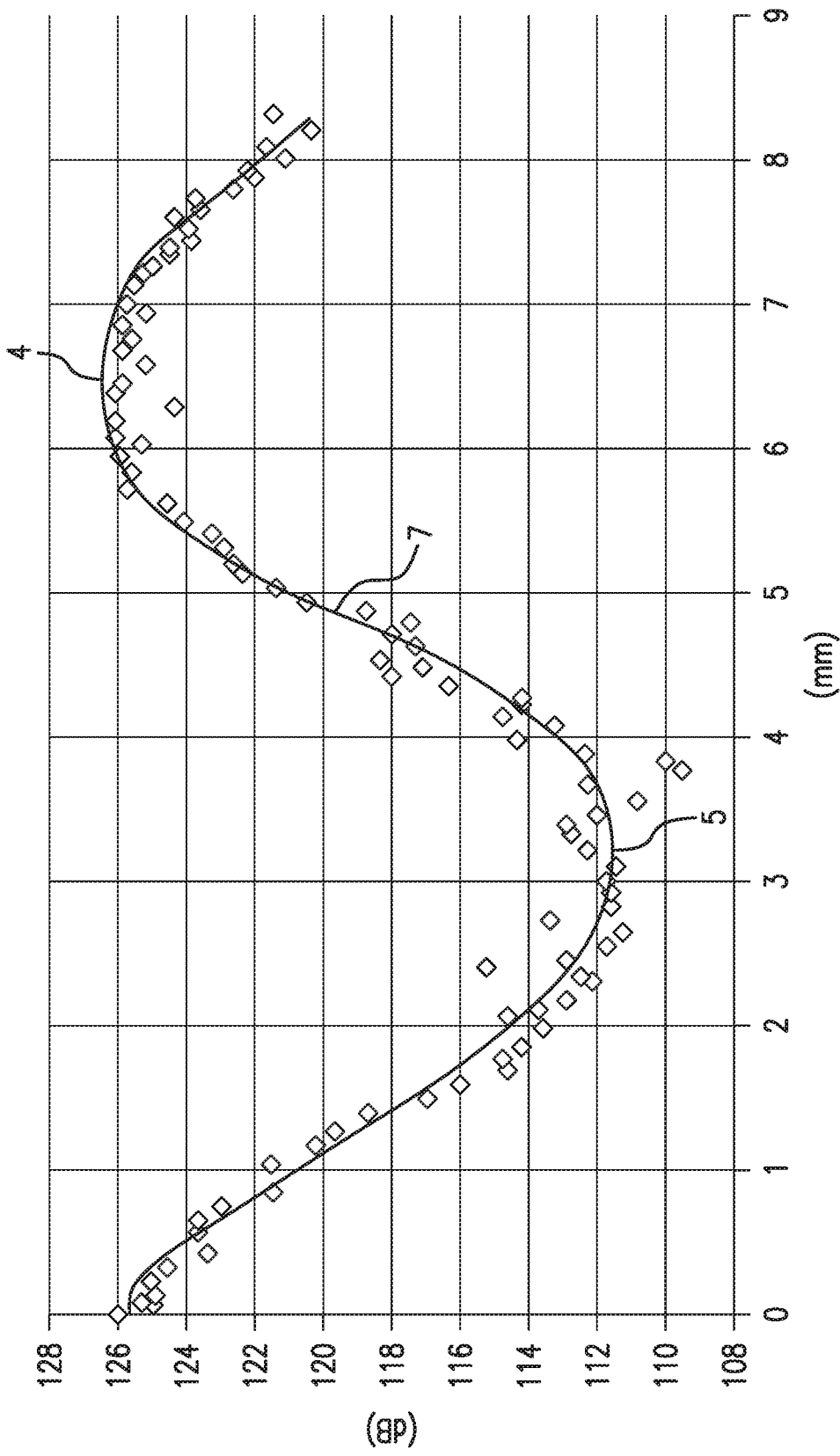


FIG.2

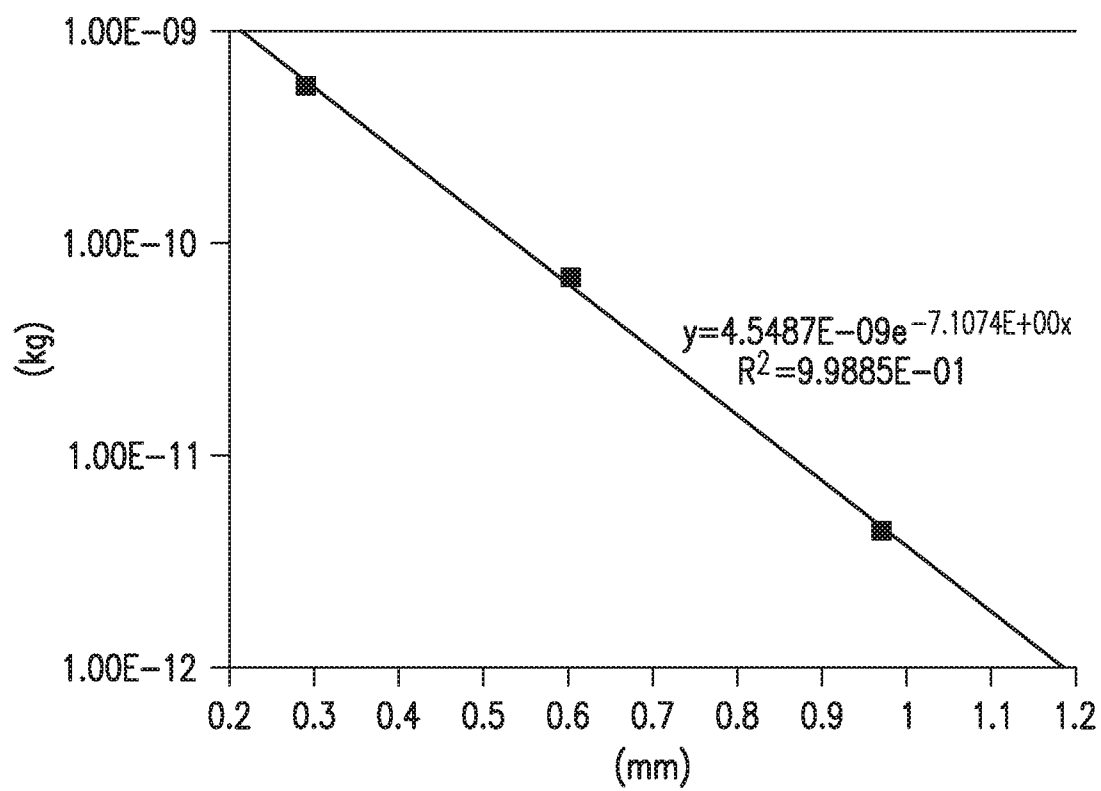


FIG.3

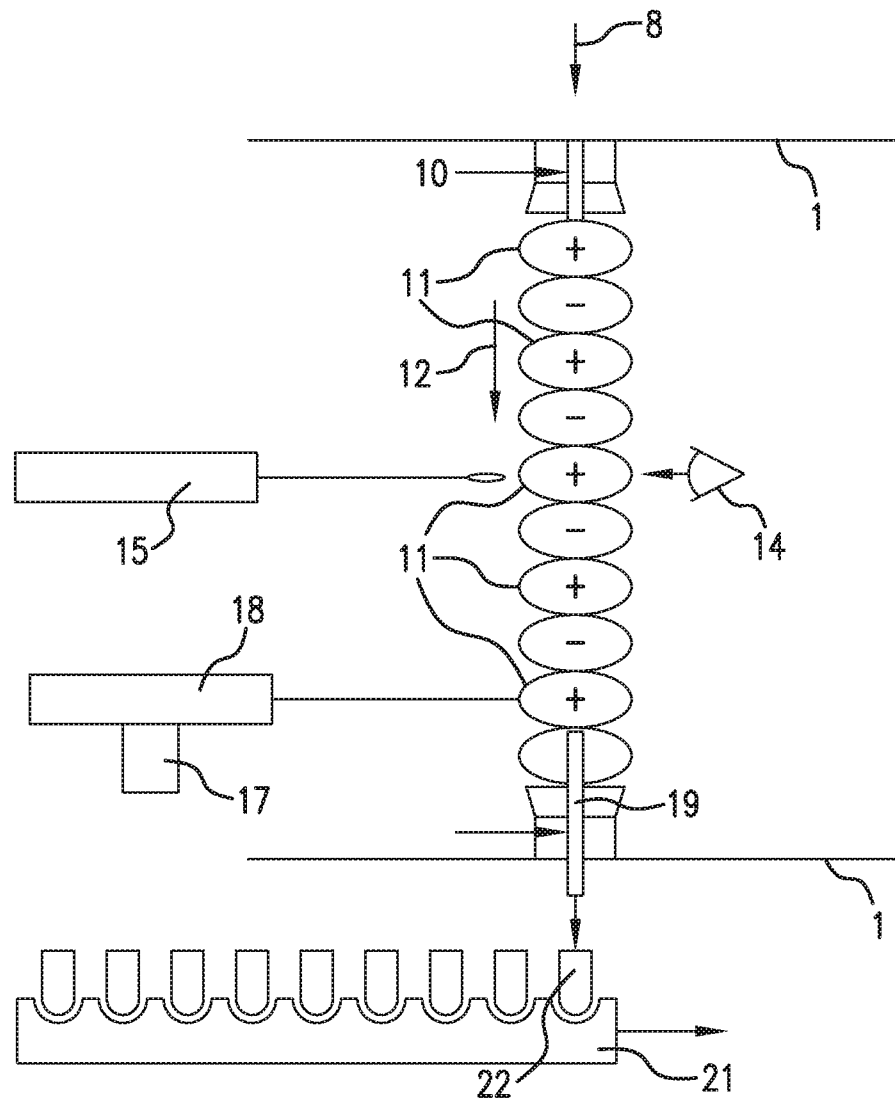


FIG.4

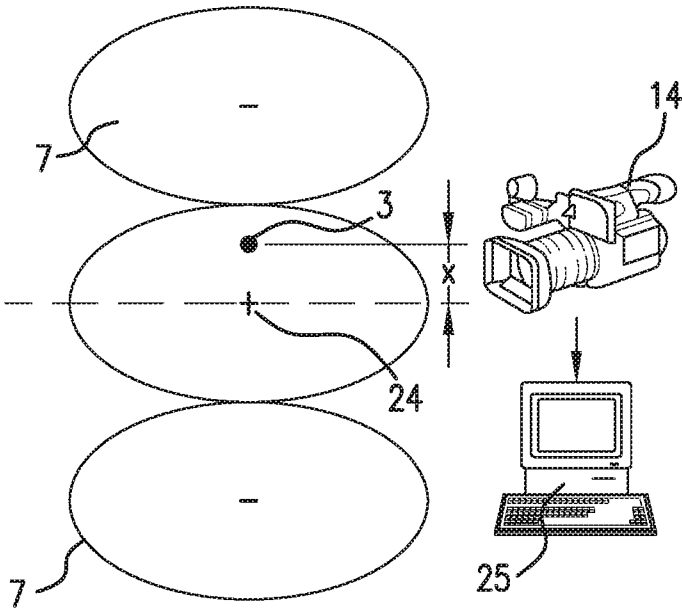


FIG.5

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2015/094697

A. CLASSIFICATION OF SUBJECT MATTER

G01G 9/00(2006.01)i

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)

G01G

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)

CNPAT, WPI, EPODOC, CNKI: acoustic+, sound, levitat+, weight, material, liquid, transport, dispens+

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Anonymous. "Experiment of Sound Levitation" <i>Retrieved from the Internet: URL: http://wenku.baidu.com/link?url=QZ5Vo3xJFs9WoDsTWZ-xLiXwtJ0IK9YPEd4jHLIEl42p9NS1nYR8HgkqJ0ZAs59mvtZu0xcyOGeWBrTO2v23X7kewYunIrx6lcffo4m3FiO retrieved on 2016-06-15</i> , 13 November 2013 (2013-11-13), the second section: experiment scheme	1-44
A	CN 104085691 A (UNIV. EAST CHINA SCIENCE & TECH.) 08 October 2014 (2014-10-08) the whole document	1-44
A	JP 2005239391 A (TOYOTA IND. CORP.) 08 September 2005 (2005-09-08) the whole document	1-44
A	US 5810155 A (KAJIO CORPORATION) 22 September 1998 (1998-09-22) the whole document	1-44
A	US 2012197005 A1 (UCHICAGO ARGONNE L.L.C.) 02 August 2012 (2012-08-02) the whole document	1-44
A	CN 202935948 U (UNIV. JILIN) 15 May 2013 (2013-05-15) the whole document	1-44

☐ 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
"E"	earlier application or patent but published on or after the international filing date	"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
"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)	"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
"O"	document referring to an oral disclosure, use, exhibition or other means	"&"	document member of the same patent family
"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

15 June 2016

Date of mailing of the international search report

08 July 2016

Name and mailing address of the ISA/CN

STATE INTELLECTUAL PROPERTY OFFICE OF THE
P.R.CHINA
6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing
100088, China

Facsimile No. (86-10)62019451

Authorized officer

LU,Hao

Telephone No. (86-10)62413602

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/CN2015/094697

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
CN	104085691	A	08 October 2014	None			
JP	2005239391	A	08 September 2005	None			
US	5810155	A	22 September 1998	US	5890580	A	06 April 1999
US	2012197005	A1	02 August 2012	US	9327264	B2	03 May 2016
CN	202935948	U	15 May 2013	None			