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(54) Title: WEIGHING AND CHARACTERIZING MATERIALS BY ACOUSTIC LEVITATION

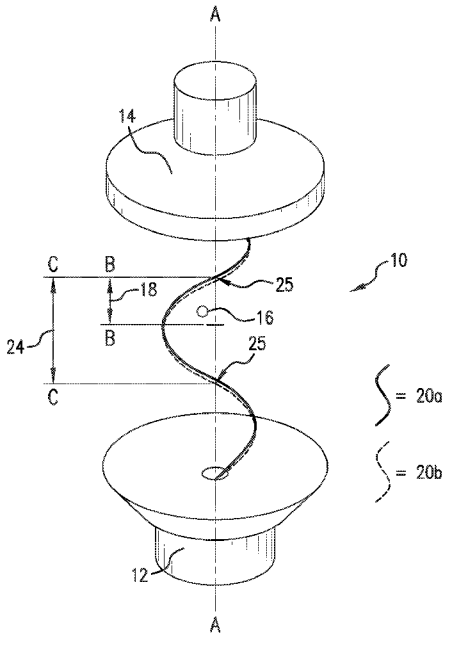

FIG.1

(57) Abstract: The invention relates to 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; 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; and to apparatus for use in the methods mentioned, as well as to related invention aspects.

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WEIGHING AND CHARACTERIZING MATERIALS BY ACOUSTIC LEVITATION

SUMMARY OF THE INVENTION

[001] Embodiments of the invention relate to a method or process for determining one or more of weight, mass, shape or other characteristics, of material, especially a material which is in the form of a solid particle or a liquid droplet, and to apparatus and devices designed and configured for that purpose.

BACKGROUND OF THE INVENTION

[002] In many fields of chemical, biological or medical research, for example pharmaceutical research companies often have substantial libraries of compounds or substances that require dispensing prior to testing or preparation. The most desirable way to store each of these compounds is as a solid because doing so 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.

[003] Additionally, pharmacies (hospital and retail) currently provide patients with formulations of active pharmaceutical ingredients (API) as dosage forms, typically oral. Moreover, drug products are developed for the average patient and in one or two or three fixed dosage forms to manage size or gender or age differences. The fixed dosage form does not take into account differences in the amount required by individuals due to metabolism, body size or other factors, and this may result in side effects or lack of efficacy.

[004] The fixed dosages require substantial storage area for the products at a pharmacy or distribution site, 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 $_{+/-}$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. This can require costly manufacturing facilities, process, resources and time to produce the finished product.

[005] During the manufacturing of the drug product (i.e. tablet capsule etc.) there may be often issues with homogeneity of the product or stability of the product with excipients or issues with packaging. Extensive time and effort is required to ensure the manufacturing equipment is clean correctly to avoid cross contamination of drugs and consequent potential harm to patients. Furthermore, customarily two 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.

[006] Recent genetic and biomarker products enable a specific, or personalized, dose and regime for a specific individual to reduce side effects and improve efficacy. Such specific dose(s) is not easily met by the conventional fixed dose formulation approach. A personalized dose can be performed manually but is labor intensive, and subject to dispensing errors. Problems with such manual formulation include the fact that materials are different and cause issues such as triboelectric interactions, electrostatic repulsion or attraction, the need to account for interparticle cohesive forces which can cause sticking together or to surfaces, or texture inconsistencies resulting in adhesion or repulsion. 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.

[007] In fields other than pharmaceutical (e.g. agriculture related chemistry, chemistry and fine chemistry), as well as in fields implicating radioactive materials (where the use of contactless methods is especially useful, allowing to characterize and dispense material minimizing loss and minimizing contamination from or between toxic or radioactive materials) or other fields wherein materials are used in trace amounts (e.g. antibodies, active proteins, nucleic acids), methods and apparatus for exact weighing

and distribution, especially contactless weighing and distribution, of materials is desirable.

[008] In view of these issues and limitations of drug or other material handling and dispensing, it is desirable to provide a method and apparatus which afford determination of exact amounts (for example, by weight, by physical size or shape or other characteristics or combinations thereof) of materials and which allow dispensing them, for example in containers or devices without having to touch them by any mechanical means during weighing and dispensing. Such a method and apparatus is particularly suitable and valuable for the preparation and handling of medicinal dosage forms, including without limitation oral, inhalation, intraperitoneally, subcutaneous, intravenous, intramuscular, intraocular and others.

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

[0010] US 2012/0197005 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.

[0011] US 7080556 describes an ultrasound apparatus and method for the monitoring of melting, mixing and chemical reaction processes.

[0012] WO2000019176 describes an ultrasonic measurement system with molecular weight determination. WO201481084 describes a method and apparatus for producing an acoustic field.

GENERAL DESCRIPTION OF THE INVENTION

[0013] Standing acoustic waves can be relatively powerful and can 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.

[0014] Accordingly, embodiments of the invention provide apparatus, devices and methods for acoustic levitation as a means to determine, assess, evaluate and/or quantify properties of materials, such as solid particles or liquid droplets Such

assessment, evaluation and/or quantification includes, but is not limited to weight and characteristics of the material. Accordingly, in embodiments of the invention the property comprises weight. In embodiments of the invention, the property comprises character of the material, for example: shape, form, density etc. Embodiments of the invention comprise apparatus, devices and methods wherein the material property comprises both weight and characteristics. Embodiments of the invention provide apparatus, devices and processes to dispense the weighed and/or characterized particles into appropriate containers or devices, making it possible to weigh and deliver exactly controlled amounts of such materials.

[0015] Embodiments of the invention provide apparatus, devices and process for acoustic levitation as a means to weigh, and to characterize, materials comprising solid particles or liquid droplets, and to dispense them into appropriate containers or devices, (for example tableting, capsule, syringe or ampoule filling) wherein the characterization includes (but is not limited to) one or more of determining shape, orientation, form, and density.

[0016] In embodiments of the invention, weight is determined by the material's (particle or droplet) position within the levitation field, such as by an optical means or system. In embodiments of the invention, characteristics of the material may also be determined optically, for example shape and size can be directly assessed. By applying a calculation to optically measured data, other characteristics can be determined. For example, density may be calculated as is known from a particle's weight and volume. In addition, the levitation field may be used in in combination with a spectroscopic technique, (for example Raman, infrared or near infrared) and obtained weight or density measurements to determine the solid-state form, or particle size, or morphology (i.e. amorphous, hydrate, polymorph, solvate, co-crystal, etc.) of an individual particle or group of particles in order to select and dispense only a a desired particle.

[0017] Embodiments of the invention provide apparatus for acoustic levitation comprising one or more acoustic transducers, such as those having an acoustic output in the ultrasonic range, for example greater than 20 kHz, and sound power in the range of 50-180 dBSPL (Decibel sound pressure level). In embodiments of the invention, the transducer or transducers may produce a sound pressure level in excess of 150 decibels (dBSPL).

[0018] The acoustic levitation apparatus and process of the present invention thus allows one or more of: separation of a particle or particles e.g. of an active pharmaceutical compound from a bulk reservoir either as individual particles or a group of particles; providing an accurate particle weight; moving, dispensing or transferring the particle or particles to a capsule or other formulation unit; and depositing the particle or particles in a controlled manner. Embodiments of the present invention allow the processing of materials with morphologies 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. Embodiments of the invention permit measuring the weight of individual particles or of a group of particles and/or determining the number of particles, and/or a distribution of particles.

[0019] In many embodiments, the invention comprises an acoustic levitation apparatus and method for 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 maintained in position (at least during weighing) 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. In many embodiments, the position is determined about a vertical axis and relative to the force of gravity.

[0020] In many embodiments, the invention relates to a method for 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: particle position; particle shape; particle weight; and particle orientation; and using the obtained feature to move, transfer or dispense the material into a further or final destination.

[0021] Generally as used herein, particle orientation means the alignment of the particle within the levitation field, for example in the case of a rod-like particle, whether it is aligned more vertically or more horizontally. “Position” generally is used herein to refer to the location of the material within the three-dimensional confines of the acoustic wave, for example a particle’s position within the node of a standing wave. Position is sometimes referred to herein in reference to proximity to an optical detection device.

[0022] In many embodiments, the invention describes an acoustic levitation apparatus (one or more devices) appropriate or equipped for carrying out said method, the apparatus comprising an acoustic levitation means, or acoustic levitation system, for generating an acoustic standing wave. In many embodiments the means, or system, for generating an acoustic standing wave comprises at least one pair of an acoustic transducer and acoustic reflector, or a pair of acoustic transducers - either or both are sometimes referred to herein as an acoustic transducer pair; together with a position sensing means, or device, 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.

DESCRIPTION OF THE DRAWINGS

[0023] The Figures show exemplary invention embodiments as follow:

[0024] Fig. 1 shows a schematic representation of an embodiment of an apparatus and system for the acoustic levitation of a material (here represented as a particle).

[0025] Fig. 2 is a plot showing the distribution of sound pressure level (in dB) within an acoustic levitation field versus vertical position (in millimeters from the transducer) within a transducer arrangement according to an embodiment of the invention.

[0026] Fig. 3 is a calibration curve, according to an embodiment of the invention, for a determination of weight of a particle and its vertical position in an acoustic levitation field.

[0027] 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.

[0028] Fig. 5 schematically illustrates, in an embodiment of the invention, how material levitation is detected and converted to weight measurement.

[0029] Fig 6 illustrates an embodiment of an apparatus and system for the acoustic levitation of a particle, showing an embodiment of both a singulation subsystem and a material transfer and/or dispensing subsystem.

[0030] Fig 7 is a schematic representation of an embodiment of apparatus and method for a material weighing and/or characterizing and dispensing system, wherein multiple particles may be levitated and characterized simultaneously, and shifted or dispensed.

DETAILED DESCRIPTION OF THE INVENTION

[0031] In embodiments of the invention, there is provided a system (apparatus) and method for acoustic levitation, wherein the apparatus comprises an acoustic transducer system. A transducer configuration designed to acoustically levitate a particle may comprise a single transducer, or may comprise two transducers in parallel, that is, in a spaced-apart, co-axial arrangement, or may comprise a transducer and reflector (also in a spaced-apart axially concentric arrangement). In embodiments of the invention, the two transducers, or transducer and reflector, are oriented vertically. In embodiments of the invention, the transducers, or transducer and reflector, may be oriented at some angle with respect to vertical.

[0032] The transducer pair preferably has an acoustic output in the ultrasonic range, for example, 10 kHz or greater, or 15 kHz or greater, or 20 kHz or greater, or 25 kHz or greater. Use of frequencies below 10 kHz, or even below 1 kHz is feasible, however efficiency may be low and energy requirements are generally higher.

[0033] 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. For purposes of the present invention, a node is a point along a standing wave where the wave has minimum amplitude. These occur at equally spaced intervals. The opposite of a node is an anti-node, a point where the amplitude of the standing wave is a maximum. These occur midway between the nodes.

[0034] In addition to the frequency and amplitude of the wave, other factors are also important. Such factors include, for example, the size, such as a geometric diameter, and/or length of the object or material being levitated. The material maximum dimension should preferably be less than about one quarter of the wavelength of the sound energy used to levitate; and/or the transducer or transducers must produce enough sound pressure to counteract the pull of gravity on the object or material in order to allow it to hover in the standing wave.

[0035] The method according to embodiments of the invention, especially is used for determining the weight where the material (particle or droplet) has a weight in the range from 0.1 ng to 10 g, or from 0.1 ng to 100 mg, or from 1 ng to 50 mg or 5 ng to 10 mg or from 10 ng to 1 mg.

[0036] In an aspect of the invention, the method is used where the solid material is a result of precipitating from a 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.

[0037] In an 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 be substantially amorphous, partially amorphous, substantially glassy, partially glassy, substantially crystalline or partially crystalline or a mixture of various solid states. In embodiments of the invention, the dry form may depend upon the speed of evaporation, which may be supported by supplying energy, e.g. thermal energy, inductive or conductive heating, radiation, infrared, radiofrequency energy for example microwave radiation.

[0038] In embodiments of the invention, the material comprises a solid or semisolid, and can be pulverous, crystalline, amorphous, a granule, a particle agglomerate, a mixture of solid states, 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), and may include dispersed entrapment material (e.g., coatings, nano- and microbeads, micelles, liposomes, nano- and microcapsules, nano- and microspheres). Entrapment material may include proteins, lipids, surfactants, polymers, and saccharides. As used herein, the term “solid” includes “semisolids,” unless otherwise clear from context.

[0039] Embodiments of the invention are useful in agriculture related chemistry, fine chemistry or other chemistry, and/or the material may comprise 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.

[0040] In embodiments of the invention the material comprises a liquid, such as a droplet.

[0041] In another aspect of the invention, the invention relates to a method according to any of the aspects or embodiments described herein, 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.

[0042] In another aspect of the invention, the invention relates to the method according to any of the aspects or embodiments described herein, where the material (e.g. particle or droplet) position is determined by an optical system, especially including any form of an image capture device, such as a camera, or a laser detection system, e.g. a laser interferometer; or by an acoustic system for example one that can detect and measure reflected sound energy e.g. sonar, or radiofrequency system that measures reflected radiofrequency energy e.g. radar.

[0043] Yet another aspect of the invention relates to the method according to any of the aspects or embodiments described herein, comprising further determining the shape of the material, especially where liquid droplet materials are used and more especially where solid materials are involved. In aspects of the invention, an acoustic particle levitation method is employed to determine the particle or form (e.g. crystal shape) and/or size in order to permit a conclusion, or decision on a physical or functional attribute of the particle, such as bioavailability and/or processability. Such conclusion or decision may be particularly relevant during the manufacture of a pharmaceutical or agrochemicals or cosmetic or other formulation.

[0044] In aspects of the invention, characteristics of the material may be used to sort, or to eliminate, particles having a characteristic which is out of specification. For example, a spherical particle having a diameter, size or weight larger than desired may be transferred to a reject container.

[0045] Another aspect of the invention refers to the method according to any of the aspects or embodiments described herein comprising further determining the position and/or orientation of the material. A further specific aspect relates to controlling (for example moving modifying or adjusting) either or both of position and orientation of the material (e.g. particle or droplet).

[0046] Another aspect of the invention relates to the method according to any of the invention aspects or embodiments described herein, 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.

[0047] Another aspect of the present invention relates to the method according to any of the aspects or embodiments described herein, 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 particle or droplet takes place simultaneously (in parallel) or sequentially. In this aspect, multiple standing waves can be configured or set up in parallel as well, to measure or assess properties of particles or droplets in each standing wave.

[0048] In aspects of the invention, particle introduction may occur in the same step, for example simultaneously or nearly simultaneously as particle formation. For example, particles may be created by a particle precipitation process, and the precipitated particles introduced directly into the acoustic levitation system. In aspects of the invention, particles may be created by precipitation from a solvent, such as by spray drying, or by precipitation from an anti-solvent. In one more embodiments of the invention, the precipitated particles may be subjected to one or more intermediate processes after their introduction into the acoustic levitation system, for example: inspection for size, shape, color or orientation in the levitation field

[0049] An important aspect of the invention relates to the method according to any aspect or embodiment described herein wherein the material is a drug, an excipient, a drug formulation, or intermediate, or placebo or inactive material. The method may comprise determining the weight of a material by a method according to any of the aspects or embodiments of the invention.

[0050] In embodiments of the method of the invention especially any aspects or embodiments of the method wherein the material is weighed, the method further comprises dispensing one or more material particles or droplets into one or more further or final destinations.

[0051] Embodiments of the invention comprise any method described herein wherein the particle or material is transported to a further or final destination which is selected based on information comprising one or more of the features selected from the position, the shape, the weight, or form (e.g. liquid, solid crystalline, amorphous etc.) and/or the orientation of the material, especially one or more of a combination of these features including at least the weight. It may be noted that as a general (and non-limiting) summary of the capabilities of the acoustic levitation system described herein, that a material may be assessed, determined or evaluated in one or more of the following respects: weight, position, orientation and characteristics (individually and collectively referred to sometimes herein as properties). Such assessment determination or

evaluation may arise directly from one or more sensor measurements or inputs, or maybe a combination of sensor measurements, inputs and computed values.

[0052] Embodiments of the present invention further comprise selecting the further or final destination based upon the weight, (for example liquid, solid, amorphous, Crystal polymorphs, solvate, hydrates variations), structure, size and/or shape of the material. In embodiments of the present invention, polymorphic forms may be evaluated for example by assessing packing differences owing to the polymorphic form as measured by density differences and/or in conjunction with some form of imaging, such as spectroscopy.

[0053] The method according to any aspect or embodiment 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 1 or 2 or 3 or 4 or 5 or 10 g or more of material at the same destination.

[0054] The method according to any aspect or embodiment described herein, wherein the material (particle or droplet) which is weighed and/or characterized comprises two or more different materials. In particular in the case where the material is a drug, the material may comprise two or more drugs, and/or in the case of a drug formulation one or more excipients with one or more drugs.

[0055] An aspect of the invention relates to any method described herein, wherein the dispensing of the material comprises shifting the position of said material so that it enters a device or container as a further or final destination, especially comprising using a solid particle as material and shifting the position of the material so that it enters a device which is selected from a tableting machine and a capsule filling machine, more especially comprising shifting the position of the material into a container. The container may be 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.

[0056] An aspect of the invention relates to any method described herein, further comprising shifting the material to a 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 from 0 ° relative to a positive pressure node levitating a material (particle or droplet) within the acoustic standing wave, or comprising shifting the material to the destination by weakening or removing the acoustic levitation field, allowing the material

to fall (e.g. by gravity) into a destination positioned below the acoustic standing wave, such as below the transducer.

[0057] The method according to any aspect or embodiment described herein, comprising supplying specific amounts or dosages into the device or container by dispensing or shifting the material. In a further aspect of the invention the material is shifted, moved or affected using a mechanical means or device to transport the material into the device or container. In a further aspect, the material is shifted, moved or affected acousticly, for example by shifting or moving the position of the transducer pair, and/or by applying a transverse acoustic wave.

[0058] The method according to any aspect or embodiment, comprising using mechanical means to move the receiving device and container under the material while it is in the levitating field, and subsequently disabling the levitating field, allowing the particle to fall by gravity into an appropriate container or destination.

[0059] An aspect of the invention relates to any method described herein, comprising determining the vertical position of the material in order to determine the weight of the material. This can be 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 thus enables more precision compared to other weight determination methods.

[0060] Another aspect of the invention relates to a method, wherein the position of the material is determined by an optical detection system or by an audio detection system, or both.

[0061] Any method described herein may further comprise measuring the environment in which the levitation takes place, for example within a column of space formed by a pair of transducers, or by a transducer and reflector, in respect of one or more parameters which may comprise temperature, charge (ambient or particle), humidity and pressure. In such embodiment, appropriate sensors are deployed to detect and/or measure such parameters. The results of such sensor measurements provide data which are inputted to an appropriate computing system and may be used as additional or alternative data to control the system, aspects thereof, and/or in calibration, for example by compensating for environmental variables.

[0062] The method according to any one of the aspects or embodiments described herein comprising determining the weight of the material (e. g. particle or droplet) by

calibration with particles or droplets of known weight. For example, this could be accomplished by means of a calibration curve, which itself may be implemented in programmed form, in software, hardware or firmware.

[0063] The present invention also, in a further 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 embodiments defined herein.

[0064] In embodiments of the invention, the invention relates to an apparatus (device) comprising at least one acoustic transducer pair, and at least one position sensing device or means for determining the position of a material which is in the form of a solid particle or a liquid droplet. The position sensing device preferably is an optical system, especially comprising a high-speed image capture device, for example a digital imaging system.

[0065] In some embodiments, the apparatus for acoustic levitation comprises a material input system, also sometimes referred to as a singulation system or element. Such material input system 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.

[0066] The apparatus, according to any one of the invention embodiments defined herein, further preferably comprises a material transport system or element for shifting the position of the material within an acoustic node to another location, for example a container. In embodiments of the invention, the material transport system comprises an acoustic aperture. As used herein, a material transport system may be used to refer to either or both of shifting material to a different location, or dispensing.

[0067] The apparatus according to any one of the preceding embodiments may, in a further invention embodiment, comprise a material collecting device or means to collect material positioned, characterized and/or weighed in an acoustic node. This material collecting means may be a device or a container. The material collecting device may be passive, or may be an active device.

[0068] Embodiments of the apparatus and method of the invention can be used in conjunction with generating a material with a certain (e.g., desired) size and morphology, for example by crystallizing or precipitating from a solvent or anti-solvent. In such

embodiments, material may be crystallized or precipitated in situ within the levitating node, or may be precipitated or crystallized conventionally and fed directly into a bulk dispenser for subsequent singulation. This can eliminate conventional processing steps such as milling, and thus may be more efficient with both respect to material and processing time. Such an in situ crystallization or precipitation may also eliminate undesirable chemical or pharmacological impurities and/or undesirable solid state polymorphs which can occur during conventional manufacturing, as well as mitigating or eliminating processing and material transportation errors.

[0069] Embodiments of the apparatus and method of the invention afford advantages in manufacturing, for example in fixed dose manufacturing wherein the present invention affords consistency and reliability and can improve homogeniety. In particular, various dosage strengths may be readily manufactured and without the need for revalidation efforts. The use of the present invention in manufacturing also can eliminate the need to mechanically weigh active materials, and in particular when dispensing small doses of highly potent materials, can eliminate requirements for mixing actives with excipients, and consequently heterogenous material errors.

[0070] Embodiments of the system and method of the present invention offer point of care manufacturing capability at a hospital, pharmacy or medical center, thus avoiding high levels of inventory of drug product in distribution sites, packaging process and costs of an analytical testing during and after manufacture, and further can eliminate the need for identity testing after packaging.

[0071] The definitions given in the following may be applied as appropriate or desired to replace one or more or all general terms of each invention aspect or embodiment in which they appear by the more specific definitions, thus further defining specific and preferred invention embodiments.

[0072] Unless otherwise clear from the context, the terms “aspect” and “embodiment” including their plurals, are used interchangeably.

[0073] Where a “material” is mentioned, this especially refers to a (relatively small) portion. A material may be either solid, semi-solid, or liquid, and in the form of a particle or droplet.

[0074] “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. The term "particle" may include nanoparticles.

[0075] "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 entrapment material) 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.

[0076] 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.

[0077] A "liposome" material is especially a material comprising spherical vesicles having at least one lipid bilayer, and may have a single, or multiple concentric or nonconcentric chambers.

[0078] A "nanosphere" or "microsphere" material is especially a hollow material comprising a spherical shell.

[0079] A "nanocapsule" or "microcapsule" material is especially a liquid core material surrounded by a membrane.

[0080] A "nanobead" or "microbead" material is especially a solid core material surrounded by a shell or coating.

[0081] 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).

[0082] A "cell component" may e.g. comprise membrane vesicles from organelle or the outer membrane of cells, or complete organelles, such as mitochondria.

[0083] A "cell material" preferably comprises 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.

[0084] An "optical system" (or "optical unit or element") may be any system, device, component or arrangement which utilizes some form of electromagnetic radiation to

detect a physical object. Examples of an optical system comprise a camera or a laser detection system. A camera system is preferably a high speed camera system. A "camera" is an optical instrument allowing recording of 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 (also referred to as a digital imaging system) 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. Suitable imaging protocols include, for example, optical coherence tomography, phase contrast and differential interference contrast microscopy, angle-resolved low-coherence interferometry and phase-contrast X-ray imaging. The optical system preferably has a resolution sufficient to be able to adequately image and characterize particles of the size desired, for example those in the 10 to 20 micron size range. In embodiments of the invention, a magnification of the optical system is preferably around 400 times, or greater. A focal length of the system is of a nature such that the lens remains out of the acoustic levitation field.

[0085] Generally, in embodiments of the present invention, a digital imaging system has three components; an image sensor, a lens and body, and software for processing the image. The image sensor is a digital integrated circuit that senses light projecting onto the surface of the device. The light is converted into electrical digital pixels. The pixels are arrayed and sent to the software for processing into an image on a computer monitor. Light enters the lens and travels through the body to the digital image sensor. Two important parameters of the imaging system are magnification and focal length. The magnification is the ability of the lens, image sensor, and software to increase the viewable size of the object. The focal length is the distance from the object to the lens. The lens must be far enough away from the acoustic field so as not to interfere with the acoustic standing wave in any way while providing sufficient focal range to bring the object into focus for imaging. In embodiments of the invention, a focal length may be at least 50 mm from the lens to the edge of the transducer to prevent interference with the acoustic standing wave. The magnification requirement for the levitation system should be sufficient to clearly resolve the smallest size particle being weighed by the apparatus. For example, a 20um diameter particle preferably takes a minimum resolution of 100x100 pixels at 100x magnification to produce a ½" object on a 10"x10" image on the

monitor screen with a 5 megapixel image sensor. This magnification provides sufficient resolution to measure the levitation height of the 20um particle.

[0086] A “laser detection system” is any laser system that allows determining 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.

[0087] In addition to determining a particle’s weight, in embodiments of the invention a particle characterization system may be supplied to determine properties and characteristics of a particle for example size, shape, density, surface properties, refractive index, spectral properties (e.g. infrared or raman) and others. Such a particle characterization system may also function as an optical detection system for determining particle position, or may be independent of or in addition to a particle position detection system. Laser detection systems can be used both as a particle position detection system and is a particle characterization system. Other systems which may be primarily particle characterization includes optical systems which utilize a speckle decorrelation our time of flight algorithm. Such systems allow, for example, so 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.

[0088] Characterization of a particle, as used herein, includes determining shape, size, morphology, surface texture, rugosity density and weight. Such features are properties of a particle may be additionally used to classify, sort, or dispense. By applying an acoustic wave at any angle to the levitation wave, particles may be rotated, turned or aligned in a particular manner, and ultimately transferred or dispensed based upon such alignment and/or characterization features. Thus, the standing acoustic levitating wave may be viewed as having an angle of 0° (purely vertical), and the angled acoustic wave may be positioned anywhere between 0 and 180°. Multiple angled waves may be employed to particular benefit. The angled wave may sometimes be referred to herein as a wave having a transverse component, or a transverse wave. In some embodiments, the transverse wave is orthogonal to the levitating wave.

[0089] In embodiments of the invention, application of a transverse of wave can rotate a levitated particle, that is, change its orientation, which can assist in obtaining a better image by the optical detection system. Additionally, a transverse wave may be employed to position a particle within a standing node, thus enabling the apparatus to

perform an operation on the particle. For example repositioning a particle within the standing node may enable the optical detection system to better focus thereon. In embodiments of the invention, a transverse wave may be used to manipulate or extract particles having a specific response thereto. For example application of a transverse wave may be used to reposition and thereby deselect or reject particles which are non-uniform or which have a shape which is not desired.

[0090] The term “dispense” or “dispensing” of a material especially relates to its contactless transfer to and deposition at a desired destination. Thus in embodiments of the invention, the material (e.g. particle or droplet) can be delivered in a precise amount and/or with precise characterization knowledge to a desired destination, without the need for the material to contact (or be contacted by) any intermediate surfaces other than those at the destination.

[0091] 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.

[0092] 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.

[0093] 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).

[0094] Drugs comprise, for example, antibodies, antibody fragments, nucleic acids, peptides, vaccines, enzymes, small molecules, organic drugs or other therapeutically active molecules.

[0095] The active ingredient(s) may, for example, comprise (non-limiting) 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, aminosalicylates, 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 thiazidesangiotensin receptor blockers, angiotensin receptor blockers and neprilysin inhibitors, anorectal preparations, anorexiants, antacids, anthelmintics, anti-angiogenic ophthalmic agents, anti-CTLA-4 monoclonal antibodies, anti-infectives, anti-adrenergic 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 thiazidesbeta-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 indandionescox-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, glycylcyclines, 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, insulininsulin-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, neuromascular 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, ophthalmic 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, oxazolidinedione anticonvuls, antsoxazolidinone 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 thiazidespotassium-sparing diuretics, probiotics, progesterone receptor modulators, progestinsprolactin 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, serotoninergic 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, sulfonylureas, synthetic ovulation stimulants, tetracyclic antidepressants, tetracyclines, therapeutic radiopharmaceuticals, therapeutic vaccines, thiazide diuretics, thiazolidine diones, thioxanthenes, third generation cephalosporins, thrombin inhibitors, thrombolytics, thyroid drugs, TNF alfa inhibitors, tocolytic agents, topical acne agents, topical agent, stopical anesthetics, topical anti-infectives, topical anti-rosacea agents, topical antibiotics, topical antifungals, topical antihistamines, topical antineoplastics, topical antipsoriatics, topical antivirals, topical astringents, topical debriding 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.

[0096] Embodiments of the present invention relate to pharmaceutical formulations or 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 a disease or condition.

[0097] The material of the present invention may be used, for example, for the preparation of pharmaceutical compositions that comprise a pharmaceutically effective amount of the material.

[0098] 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).

[0099] 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.

[00100] The pharmaceutical compositions may comprise from approximately 0.0001% to approximately 100% (% referring to weight percent) active ingredient. Single-dose administration forms may comprise, in embodiments herein, from approximately 0.001% to approximately 100% active ingredient and forms that are not of single-dose type may comprise, in embodiments herein, 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.

[00101] The pharmaceutical compositions of the present invention are, taking reference to the inventive weighing, characterizing, manipulating or dispensing, may otherwise be prepared in a manner as known to the art, for example by means of conventional mixing, granulating, coating, dissolving or lyophilizing processes or by a method or device according to the present invention, or by a combination of conventional preparing and methods of the present invention.

[00102] Embodiments of the present invention comprise 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, carboxy-methylcellulose, dextran, polyvinylpyrrolidone or gelatin.

[00103] 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, ß-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 C_8 to C_{12}, 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.

[00104] 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. In embodiments of the invention, the process may be coupled directly to a filling device under sterile conditions such that as a particle is weighed and/or characterized, it may be directly and contactlessly introduced into an ampoule or vial. By use of the term “contactless” it is meant that no human contact is required and minimal or no machine or surface contact, as once levitated, the particle may be directly transferred to its final destination, such as an ampoule or vial.

[00105] 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.

[00106] 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.

[00107] 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.

[00108] 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.

[00109] Pharmaceutical compositions suitable for rectal administration are, for example, suppositories that consist of a combination of the active ingredient and a suppository base.

[00110] 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.

[00111] Solutions such as are used, for example, for parenteral administration can also be employed as infusion solutions.

[00112] 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.

[00113] 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.

[00114] 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 10,000 mg, such as from 0.001 to 5 mg, e.g. from 0.001 to 1 mg.

[00115] Placebo formulations may comprise solely the excipient material(s) and may be useful in the placebo treatment or in clinical trials.

[00116] Diseases (including disorders) may, for example, comprise 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, heart attacks and stroke,

premature birth and other perinatal deaths, gastrointestinal disorders, and cancer. Any disease or disorder is encompassed by these general terms.

[00117] 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.

[00118] In accordance with the foregoing, the present invention also comprises the following embodiments, each of which can be claimed:

[00119] A material obtained (especially weighed, characterized and/or 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 herein.

[00120] A pharmaceutical or neutraceutical composition comprising a material obtained (especially weighed, characterized and/or 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.

[00121] A method for the treatment of a disorder, especially any one or more disorders, e.g. as set forth herein, in a subject in need of such treatment, comprising administering a pharmaceutically effective amount of a material obtained (especially weighed, characterized and/or dispensed) according to a method of the invention, especially to an individual in need thereof.

[00122] The use of a material obtained (especially weighed, characterized and/or dispensed) according to a method of the invention, for the manufacture of a medicament, nutraceutical, or food supplement for the treatment or prevention of a disease or disorder e.g. as mentioned herein.

[00123] A method as defined above comprising co-administration, e.g. concomitantly or in sequence, a therapeutically effective amount of a material obtained (especially weighed, characterized and/or 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 herein.

[00124] A combination product comprising a therapeutically effective amount of a material obtained (especially weighed, characterized and/or 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.

[00125] In many embodiments, the invention comprises at least one acoustic transducer pair; together with at least one position sensing means 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.

[00126] Referring to Figure 1, an apparatus **10** illustrating the principle of acoustic levitation is represented. A transducer **12** and a reflector **14** are positioned to be coaxial about a center axis **AA** at a distance that allows an acoustic standing wave to be formed between them. A material (here in a non-limiting way - a particle **16**) is held in a hovering position (in levitation) within a capture node **18** (also sometimes referred to as a positive pressure node, and/or a positive sound pressure zone) of a standing acoustic pressure wave **20**. Standing wave **20** is comprised of a direct acoustic wave **20a**, and a corresponding reflected acoustic wave **20b.** Direct and reflected acoustic waves **20a** and **20b** are essentially superimposed over one another. However solely for clarity in the Figure the two are shown slightly displaced from one another. Wave **20** represents the relative amplitude of the sound pressure relative to ambient pressure. When viewing the Figure, the portion of wave **20** left of center axis **AA** represent an acoustic pressure range from positive to ambient and the portion of the wave **20** right of axis **AA** represent an acoustic pressure range from negative to ambient. The capture node **18** is the zone in which particle levitation occurs, and is defined by the region **BB** as shown in the Figure. The capture node **18** is a subset (in this example, the upper half) of a positive pressure zone **24** formed within region **CC** in the Figure. Generally, capture node **18** is bounded by a midpoint (viewed along axis **AA**) of the capture zone **18** and a zero pressure boundary **25** above. A zero pressure boundary **25** (also referred to as an anti-node) is found at each point wherein the standing acoustic wave **20** intersects with the center axis **AA**.

[00127] Thus, the particle **16** is kept in the capture node **18** (levitation zone) by acoustic pressure. For a given acoustic pressure level (above the threshold required to levitate a particle), a particle having a relatively higher weight will sink lower in the capture node **18** compared to a relatively lighter particle. Put alternately, the heavier the particle, the higher the pressure is required to keep it in a fixed hovering position. If the particle is (e.g. by shift of the position of the node **18** or by decreasing the energy of the sound wave) reaching the lower half of the node **18**, it may drop through this lower part (with declining pressure) and antinode **25** and then be held by the next node **18** in a hovering position or drop e.g. through a hole in the transducer to a desired destination. This is one exemplary way to deliver a material without touching (hence contactless) and thus preventing or mitigating contamination or otherwise unwanted surface contact as the particle **16** is delivered to a desired destination. In particular, contactless dispensing is a benefit for materials which require special containment environments to prevent contamination of material/and or of containment, for example with toxic and or radioactive materials.

[00128] Figure 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). A capture node **18** and an antinode **25** of the sound pressure wave **20** and their height relative to a datum (a maximum sound pressure position, i.e. a node) are shown. For Figure 2, the datum was based upon the top surface of the transducer. The sound pressure level can, for example, be determined with a sound pressure calibration sensor (see Figure 4). Figure 2 represents measurements of the sound pressure level within the standing acoustic wave. The sound pressure amplitude follows a sinusoidal shape which matches the electrical signal used to drive the transducer. Real world effects, including but not limited to, sound harmonics from the transducer, air pressure variation, and ambient noise levels should be considered when calibrating the system to achieve accurate weight measurements.

[00129] Figure 3 depicts a graph of levitation height above a datum versus weight, wherein levitation height corresponds to the particles weight (according to an embodiment of the invention). In the Figure, the X axis represents distance from the datum in millimeters and the Y axis is weight in kilograms. For a given sound pressure, the particles levitate at different heights depending on their size and hence weight. The

particles levitate at the height at which acoustic pressure forces are balanced by the force of gravity. The "y" equation defines the line and R^2 refers to a statistical measure.

[00130] Therefore, in embodiments in the invention, a calibration curve (represented in Figure 3) is established by actually determining the material's (droplet or particle) position relative to a datum. The datum is a predetermined location – for example the surface of the transducer - and can be used for a range of particles with known weights to generate a calibration plot. Calibration (and consequent weight determination) may be accomplished using particles or droplets, or combinations thereof.

[00131] In order to perform a calibration, in the example represented in Figure 3 several different particle diameters were levitated within the acoustic particle levitator at the same time. The nominal particle diameters used were 20 µm, 50 µm and 100µm. The sizes of all three particle species were known because they are NIST-standard calibration particles of known weight and density (and hence weight) to within 1%. This information was provided by the manufacturers: Thermo Scientific and Cospheric. These particle diameters were chosen based upon a particle size range of interest, and do not represent the maximum or minimum particle diameters that can be levitated.

[00132] In one embodiment of the invention, weight of a particle is determined by determining the vertical position, that is, a height of the particle relative to a lower sound transducer surface or any other reference height or datum, and comparing the determined height to a calibration plot in order to determine the weight of the particle.

[00133] It is also within the scope of the present invention 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, as defined, for example, by an audio detection system, or to use a combination of any of the methods mentioned herein for determining the weight of a material.

[00134] Additionally, or alternatively also theoretical predictions of the weight/height (position) of the material particles can be used (e.g. weight can be based on a determination of the sound pressure level at specific heights), or by combinations of calibration and theoretical prediction. In aspects of the system and method, an audio detection system may comprise a microphone or other sound sensing means as a sensing element, and sound pressure may be measured periodically or continuously. By this method, sound pressure stability can be used as an internally calibrated method to accurately weigh particles. For example, a target sound pressure may be determined

experimentally or by reference to an external standard, and this target sound pressure is maintained via a microphone or sound sensing element coupled to an appropriate internal electronic control system.

[00135] Where a material is "dispensed" into one or more 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. A destination may be ultimate or final, that is, the end product of the method or process, or intermediate, that is some point before the ultimate or final point in the method or process. Such dispensing is useful for materials which require precise weighing a small amounts for example certain biological materials as well as certain highly potent materials. Embodiments of the invention provide methods and apparatus for dispensing genetic and biomarker materials and products that enable a specific dose and regimen for a specific individual, and further which can be performed in a highly automated manner. Embodiments of the invention also provide consistent product benefits when used with or in novel drug delivery systems which otherwise require a matrix or formulation of very small amounts of material.

[00136] 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.

[00137] 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.

[00138] In embodiments of the invention, material is shifted to the destination by using multiple sound transducers, which 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. Alternatively or in addition, superimposing a slow acoustic wave oriented in an angle different from 0° relative to the levitating wave may allow for such shift in the position of the material.

[00139] Additionally or alternatively, embodiments of the invention may use gas (e.g. air) streams or blasts, acting upon a material particle or droplet to create a force allowing the material to be dispensed or moved to a desired destination.

[00140] 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.

[00141] 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 or additionally, the mechanical means may comprise a manipulator, for example a robot manipulator (e.g. equipped with forceps), plungers, e.g. in rod shape, threads, wires, filaments, sheet-like materials or the like.

[00142] In embodiments of the invention, the mechanical means used to move shift or dispense the material may comprise 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 from which the levitation field has been can be adjusted to deliver the material to them, e.g. to a position below the transducer of the apparatus in which acoustic levitation is effected, for example through a hole in said transducer.

[00143] 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 reducing risks of contamination or material loss on such surfaces.

[00144] A further aspect of the invention relates to any method described herein, comprising providing units of the materials (that is, individual particles or droplets) with an electric charge of identical polarity in order to inhibit its or their aggregation or to move or 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 move or dispense them by means of electric field(s). 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. Particles may also be moved by applying electrical fields, e.g. using two or more electrodes of appropriate charge.

[00145] Figure 4 shows a schematic representation of an embodiment of the apparatus **10** 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 **30** on an output device **32,** here in the exemplary form of a conveyor or collection device. The standing wave **20** (see Figure 1) in this example is produced by lower and upper sound transducers **12**.

[00146] In this embodiment of the apparatus **10** a particle **16** of material (e.g. a particle or droplet of a drug material, such as an ibuprofen particle) is provided from a material introducing means **34** (here represented as an arrow). The material introducing means **34** is in communication with an input drop tube **36** which passes through a center of the upper transducer **12**. The particle **16** travels via the force of gravity to one or more capture nodes **18** (as shown also in Figures 1 and 2). By varying the strength of the acoustic levitation field, the particles **16** may be delivered to a specific capture node **18**. Arrow **40** represents particle flow in the Figure. Capture nodes **18** are represented schematically as ovals with a plus sign (positive pressure). Negative pressure zones, or anti-nodes, **25** are represented schematically as ovals with a negative sign. In this example, one of the capture nodes **18** may function as the weighing node, and one or more other capture nodes **18** may function to characterize the particle **16,** and/or to trigger shifting or dispensing of the particle **16**.

[00147] A position sensing device or system **42** (which may comprise, for example. a camera) determines the position of a material portion (e.g. particle **16**) at a capture node **18** and thus provides the information required to determine its weight (e.g. from a calibration curve as shown in Figure 3). A sound pressure level calibration sensor **44** may be provided e,g, in order to allow for calibration based on sound pressure and/or to control the sound pressure. Control of sound pressure, for example, lowering the sound intensity (energy) or momentarily switching it off entirely, may be used to dispense the particle(s) to a desired destination, such as the capsule halves **30** shown paradigmatically in Figure 4. The switching of sound energy may be controlled, for example, by appropriate switching elements and processor (not shown). In

embodiments of the invention, the apparatus is configured such that the particle may simply fall through, e.g., an output drop tube **46**, disposed, for example within the central aperture of the lower transducer **12** (or reflector) and through which the material portion, e.g. particle **16**, may fall without contacting the transducer **12**. The output may be controlled by an optional output position sensing system (not shown) which may interface with a defective material detection device **49**. If employed, the output position sensing system may serve to verify that the weighed and/or characterized particle is dispensed into the appropriate container. In embodiments of the apparatus and method of the present invention, the defective material detection device **49** may be configured to detect and to divert an out of specification particle. This aspect affords a significant benefit in enabling continuous quality control and continuous manufacturing, for example of drug particles.

[00148] Defective material (e.g. of undesired shape, size, weight, form or density) may (for example by use of a sound wave applied in a non-vertical, for example orthogonal or perpendicular direction to the standing acoustic wave **20** (represented also by nodes **18** and antinodes **25** in Figure. 4) be dispensed or transferred to a collection vessel **50** under the control of the defective material detection device **49**. It is noted that detection device **49** and collection vessel **50** are shown schematically in the figure and thus not intended to be limiting in terms of position or configuration.

[00149] In addition to the position sensing system **42**, and optional output position sensing system, an optional input position sensing system (not shown) may be positioned near the top of the process flow schematic, for example, near the material introducing means **34,** for example, a singulation system. This input position sensing system, in embodiments of the invention, may be used to confirm particle entry.

[00150] Alternatively or additionally, in embodiments of the invention the dispensing of material portions (e.g. particles or droplets **16**) may take place laterally (horizontally, e.g. perpendicular to a vertical wave axis) to a position other than the output drop tube **46**. In in embodiments of the invention, this may be achieved by applying electrical field (in which case, the material portions are preferably provided in a charged form); or by superimposing a transverse sound wave configured to shift the particles laterally, or combinations thereof.

[00151] Figure 5 shows another schematic representation of the system **10** forming an embodiment of the present invention, for weighing a material particle **16**, also

schematically depicting the sound pressure wave **20** and showing the particle position relative to a datum **60** which, in this example, is a position of maximum sound pressure in the corresponding capture node **18**. In general, a datum may be "N" multiples of a wavelength of sound from the top surface of the transducer. "N" may thus be any whole number up to a physical maximum of about fifty. An optical position sensing system **42** is shown diagrammatically as a camera, and is used as described herein to determine the position of the material particle **16**, here represented as levitating at a height x above the datum **60**. A computing system **62** allows for determining the weight of the particle **16** and for controlling the system **10**.

[00152] In general, devices, apparatus subsystems and means for particle introduction comprise those which achieve particle singulation, that is, in this context, selecting and introducing individual particles, as from a plurality of particles.

[00153] In aspects of the invention, one or more particles may be introduced (or singulated) by one or more mechanical, electrical, or fluidic means or devices. For example, a particle may be introduced by means of a vibrating mesh conveyor, or by a screw or auger type feed. A fluidized bed particle introducing means, or other microfluidic apparatus or device may serve as the particle introduction means or device. It is to be noted that various geometries of particle introduction may be contemplated and are within the scope of the present invention, and that particles may be introduced singly and/or multiply by acoustic manipulation, for example weighing performed as a batch process, or particles may be introduced sequentially and acoustic manipulation be performed on a continuous basis, or particles may be introduced in multiples (either single multiples are sequential multiples) and acoustic manipulation performed on the batch of particles, or sequential steps may separate multiple particles into individual manipulators. In embodiments of the invention, determination of particle characteristics such as weight may occur sequentially, in parallel, or both.

[00154] In embodiments of the invention, a device or means for particle singulation, that is the introduction of a single particle from a bulk source to enable the determination of particle weight and/or characteristics is useful for the practice of the process of the invention. Figure 6 shows an example of a particle singulation subsystem or apparatus. Additionally, Figure 6 shows a more discreet example of a subsystem or apparatus for moving and dispensing particles which have been characterized and/or weighed.

[00155] The basic elements of the apparatus **10** are as shown in Figure 1 and comprise, generally a transducer **12** and reflector **14** and associated control devices. In addition, there is a particle singulation system **70** which comprises an embodiment of the particle introduction means **34** (shown schematically in Figure 4). Particle singulation system **70** comprises a material input tank **72** which may be fitted with a cap **74** and which feeds a screw or auger feeder **76**.

[00156]. Screw or auger feeder **76** is driven by a motor **78**, in embodiments a stepper motor, and motor **78** is controlled by a controller **80**. The output of the singulation system **70** is designed to output particles **16** sequentially, and is aligned with the input drop tube **36**. In embodiments of the invention, the particle simulation system **70** may be controlled by a general or specific purpose computer, CPU or processor **81**.

In Figure 6 is also shown position sensing means or unit **42**, in this example, comprising an optical imaging device, communicating electrically with the computing system or computer **62**. Additionally shown in this figure are details of a drive system for the transducer **12**. The drive system comprises a power amplifier **84** electrically coupled to the transducer **12**. A signal generator **86**, which may generate a variety of waveforms supplies appropriate waveform information to the power amplifier **84**. Also electrically coupled to power amplifier **84** is a power supply **88**. In embodiments of the invention, the output of signal generator **86** may be controlled by a general or specific purpose computer, CPU or processor **90**.

Figure 6 further illustrates one embodiment of a subsystem and method for moving and/or dispensing into a desired further or final region or container a particle **16** or a plurality of particles **16** which have been weighed and/or characterized. Thus an embodiment of the output device **32** holding a plurality of capsules **30** is illustrated. In this embodiment, the output device **32** and capsules **30** are positioned upon an X-Y gantry **100**, which is one known to the art to be configured for an adopted to translate in one or more directions so as to be able to position each individual capsule **30** directly under the output drop tube **46**. The output device **32** comprises a capsule tray having a plurality of capsule wells **101**. In embodiments of the invention, the position of the gantry **100** with respect to output drop tube **46** may be controlled by a general or specific purpose computer, CPU or processor **104**. In this embodiment, it can be seen that the weighed and/or characterized material comprising particle **16** would fall in the ordinary manner through drop tube **46** but the dispensing location is changed by virtue of the

ability to move the gantry **100**, to locate each individual well **101** sequentially under the output drop tube **46**. Movement of the gantry **100** may be accomplished by any means known to the art such as mechanical, electromagnetic, electrical fluidic etc.

[00157] Alternatively or additionally, multiple standing waves can be set up over a single transducer, for example by providing a sound opaque mask, also referred to herein as an acoustic aperture, having a plurality of apertures within which the standing wave is allowed the form, thus generating a number of standing wave columns above a given transducer. In embodiments of the invention, an acoustic aperture is a structure configured and designed to reduce a size of the sound field generated by the transducer pair and/or to separate the sound field into multiple parallel sound fields within a single transducer pair. An acoustic aperture is comprised of a mask of a sound reflecting material including but not limited to glass, plastic, metal, stone, or wood. The shape of the mask may be, in embodiments of the invention, congruent with the sound producing surface of the transducer, and may be for example, circular, rectangular, elliptical, or triangular. The mask is positioned in close proximity to the transducer (but not in contact) so that sound wave emissions contacting the mask in non-aperture areas are reflected back to the transducer.

[00158] The mask is placed between the transducer and the reflector or two transducers so as to reflect the sound back toward the transducer. An aperture is made through the mask to allow the sound wave emanating from the transducer to pass through the mask and move on to the reflector. When the sound wave reflects back toward the transducer from the reflector a standing acoustic wave is established through the aperture. The size and shape of the aperture is designed to reduce the size of the acoustic standing wave and contain particles in a smaller area, and may serve, for example, to ease the depth of field focusing requirements of the digital imaging system. The shape of the aperture can be but is not limited to circular, rectangular, elliptical, or triangular. The size of the aperture is preferably determined by the size of the particle and by the wavelength of the frequency of sound from the transducer. The aperture preferably should be a minimum of three times the particle diameter or 3mm whichever is greater. In embodiments of the invention, the size of the aperture may be varied with a mechanical iris to provide a highly accurate position of the particle. The thickness of the mask, is that which is sufficient to mask the sound, and may be as little as 1mm as long as the sound reflectivity coefficient of the mask is sufficient to reflect most of the sound energy. In

embodiments of the invention, it has been found that reflecting about greater than 80% or 90% or 95% provides a practical optimum. The maximum thickness of the mask has no theoretical limit and is practically limited by the number of sound wavelengths spacing between the transducer and reflector (i.e. the mask thickness may be equal to one wavelength if the spacing between transducer and reflector is two wavelengths leaving one wavelength above the aperture for inspection and weighing in free space. Multiple apertures may be placed in the mask to allow formation of parallel acoustic standing waves.

[00159] Apertures formed within the sound mask preferably a minimum spacing that prevents the acoustic standing waves from interacting with each other and to allow spacing sufficient such that optical and mechanical instruments are able to operate on the particles hovering within the individual acoustic standing waves. A minimum spacing between apertures is preferably equal to or greater to the aperture size. The mask may be mounted such that it can rotate or translate in an X-Y orthogonal manner to move the acoustic standing wave(s) to desired position above the transducer. Motorized mechanisms can be used to provide exact positioning of the acoustic standing wave(s) to present hovering particles before digital imaging systems for weighing and inspection, defect extraction, or the output mechanism. Multiple instruments may be positioned in a radial fashion, subject to instrument spacing requirements, such that the acoustic aperture rotates the acoustic standing wave(s) into positions in front of each instrument for processing.

[00160] One illustrative embodiment in which this may be accomplished is illustrated, for example, in Figure 7. In such embodiments, a single particle may be manipulated within each standing wave column, or multiple particles may be manipulated within one or each standing wave column as described.

[00161] Figure 7 illustrates an example embodiment of an apparatus **10** and method for moving and/or dispensing levitated particles comprises a moving (rotating or translating) capture window **112** dispensed above the levitation transducer **12**. In embodiments of the invention, this capture window **112** comprises an “acoustic aperture” to localize the acoustic field to a diameter which is much smaller than that of the acoustic field produced by the transducer. In one aspect, the acoustic aperture comprises sound mask, which may be implemented as a rotatable plate **114** with a plurality of apertures **116** (preferably circular) formed therethrough. The plate **114** is configured and

suspended between the transducer **12** and the reflector **14**, such that the apertures **116** are positioned over the transducer so that the sound is reflected by the plate **114** back to the transducer, except in the apertures **116**, where sound energy passes through and hits the reflector **14** to form a plurality of standing waves **20**. At least one particle **20** is stably levitated in each of the aperture **116** regions. The aperture size may be determined by the particle size to be manipulated; in embodiments of the invention, these apertures may range in size from about 10 to 30 mm in diameter. Levitated particles can be moved radially by moving the position the apertures **116**. In embodiments of the invention, the plate **114** (and corresponding apertures **116**) may be rotated around a center of the transducer sound field by means of a drive motor **118** mounted upon a support member **120** and mechanically communicating with a gear system **122**. In embodiments of the invention, the acoustic aperture system may be controlled by a general or specific purpose computer, CPU or processor **124**.

[00162] While Figure 7 depicts the acoustic window as implemented with a rotatable disk, other configurations are possible and intended, for example the acoustic window could comprise a plate comprising a sound mask, which plate is translatable in an XY direction, in addition to or alternatively to being rotatable. Additionally, the plate comprising the sound mask could be offset from a center of transducer **12** such that rotation of the plate could be used to sequentially carry a particle or particles entrained in one of the acoustic standing waves **20** to a location where the particle can be dispensed, for example by further masking the standing wave **20**, or simply by moving the plate sufficiently out of range of the sound energy generated by the transducer **12**.

[00163] Figures 1, 6 and 7 illustrate the apparatus in stylized schematic form. An implementation of the apparatus could include a housing or enclosed structure for mounting the various components. The reflector may include a fine adjustment mechanism (i.e. a threaded rod connecting the reflector to a horizontal brace structure within the housing). If supplied, the calibration microphone may include a mechanical means to position it. Other components which could be mounted to the housing may comprise the optical imaging lens, body and sensor; the defect extraction system; the transducer; the material transport system; and the output device(s). Other imaging systems may be supplied in mounted within the housing for inspection of particles or droplets.

[00164] In embodiments of the invention, within the housing may also be sensors for measuring temperature, humidity, and barometric atmospheric pressure within the housing. The location of the sensors would preferably be as close as possible to, but not interfering with, the acoustic sound wave. Outputs from one or more of these sensors could be used to control, via the computing system, or via a dedicated control system, elements of the levitation apparatus. For example, changes in temperature or pressure may be used to compensate the transducer drive levels to maintain calibrated acoustic sound pressure or to adjust the transducer and reflector spacing to maintain minimal phase differences in the acoustic standing wave. All electronic drive components for the input system, microphone, optical imaging, defect extraction, transducer, reflector adjustment, lateral transport, and sensors could be located outside the primary housing in a separate enclosure and may or may not be attached to the housing. The external electronic component enclosure may or may not include the computer control system as some embodiments may use a laptop computer and other embodiments may use an embedded host computer in the enclosure.

[00165] In embodiments of the invention, the apparatus has been described as controlled by a computing system **62** comprising a computer processor. The program environment in which one embodiment of the invention may be executed illustratively incorporates one or more general-purpose computers or special-purpose devices such hand-held computers. Details of such devices (e.g., processor, memory, data storage, input, and output devices) are well known and are omitted for the sake of clarity.

[00166] It should also be understood that the elements of controlling the apparatus and methods of the present invention may be implemented using a variety of technologies. For example, aspects of methods described herein may be implemented in software running on a computer system, and/or implemented in hardware utilizing one or more processors and logic (hardware and/or software) for performing operations of the method, application specific integrated circuits (ASICs), programmable logic devices such as field programmable gate arrays (FPGAs), and/or various combinations thereof.

[00167] Accordingly, computing system **62** may be used to control some, a portion, or all elements of the apparatus **10** which require or benefit from computer control. Thus in embodiments of the invention, one, two, three, or all of the dedicated computers **81, 90, 104** and **124** may be dispensed with and more than one, or each element of the apparatus **10** controlled by a single computing system **62**.

[00168] Whilst the examples herein have generally described the apparatus of the present invention in terms of levitating a single particle, the system and method is not so limited. Multiple particles can undergo one or more of the processes of levitation, weighing, characterization and dispensing. This can be accomplished, for example by levitating multiple particles or droplets into multiple nodes of a single standing wave, for example, as depicted schematically in Figure 4, wherein the particles can form a column within each capture node **18** of the standing wave **20** above transducer **12**. In such embodiments, particles can be moved up and down the column by manipulating sound pressure, for example by decreasing sound pressure to move particles downward towards the transducer, and increasing sound pressure to capture particles again within a capture node. Effectively, a pipeline of particles can be manipulated in this manner, and one or more of the steps comprising levitation, weighing characterizing and dispensing may be performed sequentially or simultaneously.

[00169] Examples: The following examples illustrate the invention without limiting its scope.

EXPERIMENTAL

[00170] By imaging with an optical system (see e.g. the camera in Fig. 5, the levitation heights tabulated in Table 1 were determined:

Example 1

Table 1. Particle levitation height versus weight

1	2	3	4	5	6
Particle diameter (µm)	Position (mm)	Mass (kg)	Mass trend (kg)	Abs err%	Mass (mg)
100	0.290244	5.49E-10	5.78E-10	5	5.492E-04
50	0.6033835	6.87E-11	6.24E-11		6.865E-05
20	0.9706452	4.39E-12	4.59E-12	4	4.394E-06

[00171] 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.

[00172] Standard statistical methods were used to correlate the measured data with actual values. In this example, a power law was used and resulted in a fit parameter that is very nearly 1.0, indicating an excellent fit. The particular statistical analysis employed was a two parameter to three 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. A parabolic fit could also be utilized, which would be expected to yield a fit parameter of exactly 1.0 because there would be three degrees of freedom in the data and three degrees of freedom in the model. In Table 1, column 1 is the diameter of the particles, column 2 is the levitation height in the positive pressure node, column 3 is the known weight of the particle, column 4 is the calculated weight (referred to as Mass Trend) of the particle based on mathematical curve fitting, column 5 is the absolute error percentage between the known weight and the calculated weight, and column 6 is the calculated weight in milligrams for reference. The average error for this measurement is 5.3%. Particles used to obtain the data of Table 1 were 100u particles (Dri-Cal DC-100); 50u particles (ChromoSpheres-T BK050T); and 20u particles (Dri-Cal DC-20); all from Thermo Scientific. While not shown in the table, actual drug particles (comprising ibuprofen) of different sizes, and of higher density than the test particles were successfully levitated as well.

Example 2

[00173] A Power Amplifier board from Power Amp Design, and a 120V Power supply was used to drive au ultrasonic transducer made by STEM, Inc. cleanly to a full 80 Watts of power. Expanded Styrofoam beads of 3mm diameter and weighing approximately 50 milligrams each were levitated. I can levitate multiple beads in a vertical stack. The number of beads is dependent on the number of wavelengths in the space between the transducer and the reflector. Multiple (at least four 4) beads were levitated simultaneously, that is each in a different vertical node.

Example 3

[00174] In this example, an “acoustic aperture” was made to localize the acoustic field to a relatively small diameter. An acoustically opaque plate, with a circular aperture about

twenty five mm in diameter, was suspended between the transducer and the reflector. The circular aperture was positioned over the transducer so that the sound was reflected back to the transducer except the where sound passed through the circular aperture and hit the reflector to form the standing wave. Styrofoam beads (as test particles) were introduced into the circular aperture and were stably levitated, as determined by the absence of visible movement to the naked eye. The aperture size may be determined by the particle size to be manipulated. In embodiments of the invention a minimum aperture size is 3x the diameter of the particle, for example a 3 mm aperture for a 1mm particle diameter. The bead's position can be altered by moving the position of the aperture around the transducer sound field. The purpose of this feature is to provide positioning of the particle within the apparatus for multiple operations while the particle is held in a relatively constant vertical position by the acoustic standing wave

Example 4

[00175] In this example, an embodiment of the apparatus was made wherein the reflector contains a plurality of small apertures designed and configured for dropping beads into the sound field for levitation. Expanded polystyrene test beads were dropped (manually) beads through one of the apertures in the reflector and were captured in an uppermost capture node of the levitation field in ten out of ten attempts. This experiment demonstrates that particles can be inputted into the levitation field by dropping them through the reflector. The size of the hole and the drop distance to the capture field are important. The size of the hole should be minimized to reduce impact on the acoustic standing wave because a hole allows some portion of the sound pressure to escape rather than be reflected back to the transducer. The drop distance is important because the acceleration of the particle due to gravity must be offset by the sound pressure to decelerate the particle to zero velocity and be captured in the capture node.

[00176] 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 a property of a particle of material, comprising: providing a levitation field comprising an acoustic standing wave; introducing said particle of material into the levitation field wherein the material is allowed to position itself at an acoustic pressure node of the standing wave; determining at least one of a position of the material and an orientation of the material the in the acoustic pressure node; and using the information to determine a property of the material.

2. The method of claim 1 wherein the material is a solid particle or a liquid droplet.

3. The method of claim 1 wherein the property comprises weight.

4. The method of claim 1 wherein the property comprises a characteristic.

5. The method according to claim 1 wherein said orientation is determined by subjecting the material to a transverse acoustic wave.

6. The method according to claim 5, further comprising determining a shape of the material by subjecting the material to the transverse acoustic wave.

7. The method according to any of claims 1 to 6, wherein the 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.

8. The method according to claim 7 wherein the material is solid and comprises pulverous, crystalline, amorphous, a granule, an agglomerate of particles, a mixture of solid states, micelle material, liposome material, a viral material, a cell component, cell material or entrapment material.

9. The method according to any of claims 1 to 6 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, a nutraceutical, or a radioactive material.

10. The method according to any of claims 1 to 9, wherein position is determined by an optical system.

11. The method according to any of claims 1 to 10, wherein multiple particles are introduced into multiple nodes of the same standing wave simultaneously or sequentially and the determination of the weight of each particle takes place in parallel.

12. A method of dispensing a material in the form of a solid particle or a liquid droplet or mixture, comprising: providing a levitation field comprising an acoustic standing wave; introducing said material into said levitation field, so that it is positioned and kept in position by an acoustic pressure node of the standing wave, determining information on one or more features selected from position, shape, weight and orientation of the material; and using the obtained feature to dispense the material into a destination.

13. The method according to claim 12, wherein the weight is determined by sensing the position of the material within the acoustic standing wave relative to a datum.

14. The method according to any of claims 12 or 13, wherein the destination is selected based on the information one or more of the features selected from position, shape, weight, form, size and orientation of the material.

15. The method according to claim 14, comprising dispensing more than one material particle or droplet to the same destination and thus accumulating the material at that destination.

16. The method according to any of claims 12 to 15 wherein the material comprises one or more drugs, a drug formulation comprising one or more drugs with one or more excipients, or a placebo.

17. The method according to any of claims 12 to 16, wherein the dispensing of the material comprises shifting the position of said material so that it enters a device or container as a final destination.

18. The method according to any of claims 9 to 17, wherein the shifting comprises applying one or more of; a transverse or superimposed acoustic wave, an electrical field, a gas or fluid stream, or an acoustic aperture.

19. The method according to any of claims 9 to 17, comprising shifting the material to the destination by weakening or removing the acoustic levitation field, allowing a particle or droplet of the material to fall into a destination positioned below the levitation field.

20. The method according to any of claims 12 to 17, wherein the position of the material within the acoustic standing wave is determined by an optical system or by an audio system, or both.

21. The method according to any of claims 12 to 20, comprising providing the material with an electric charge.

22. The method according to any of claims 1 to 21, comprising determining the weight of the material by calibration with particles or droplets of known weight.

23. A system for assessing properties of a particle or droplet, the system comprising an acoustic transducer pair, a particle singulation system, an optical position sensing device, and a computer processor.

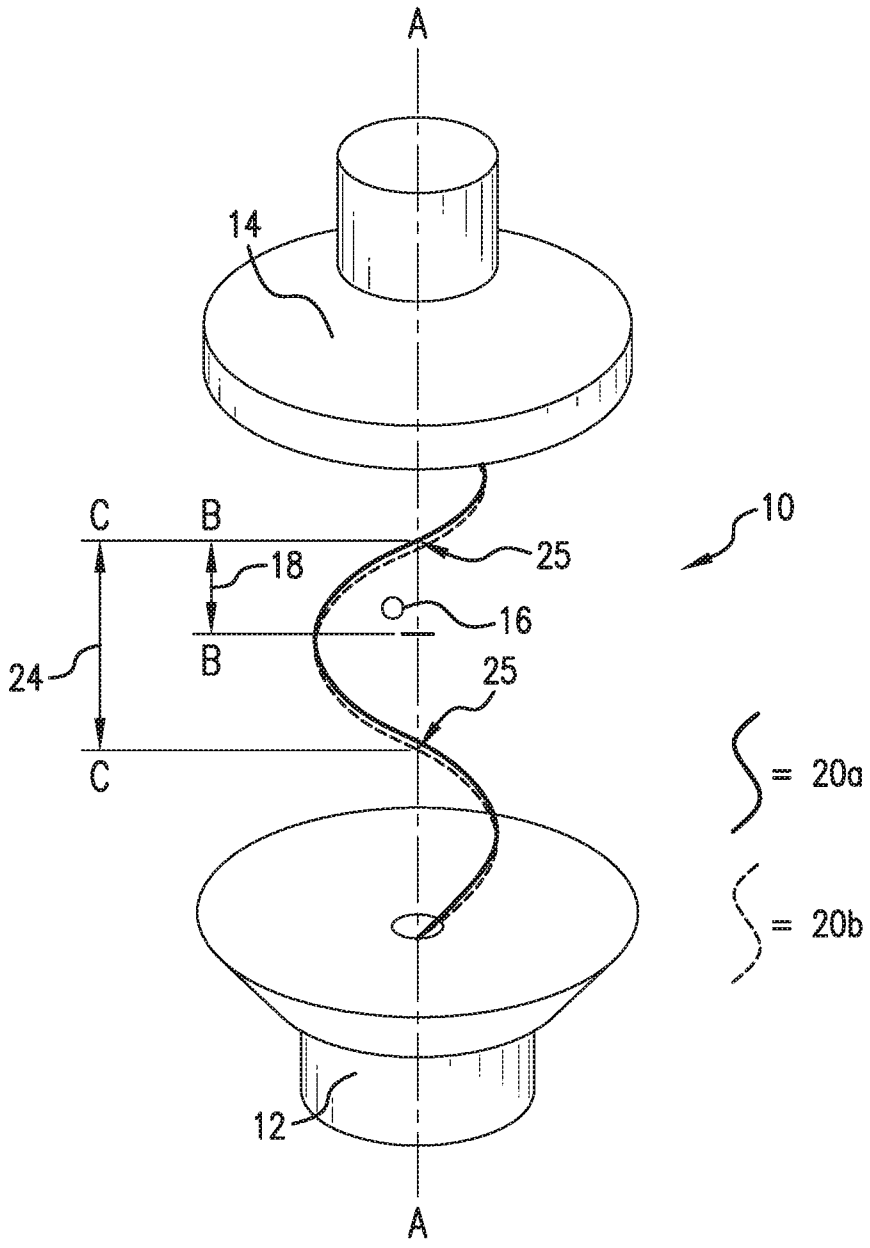
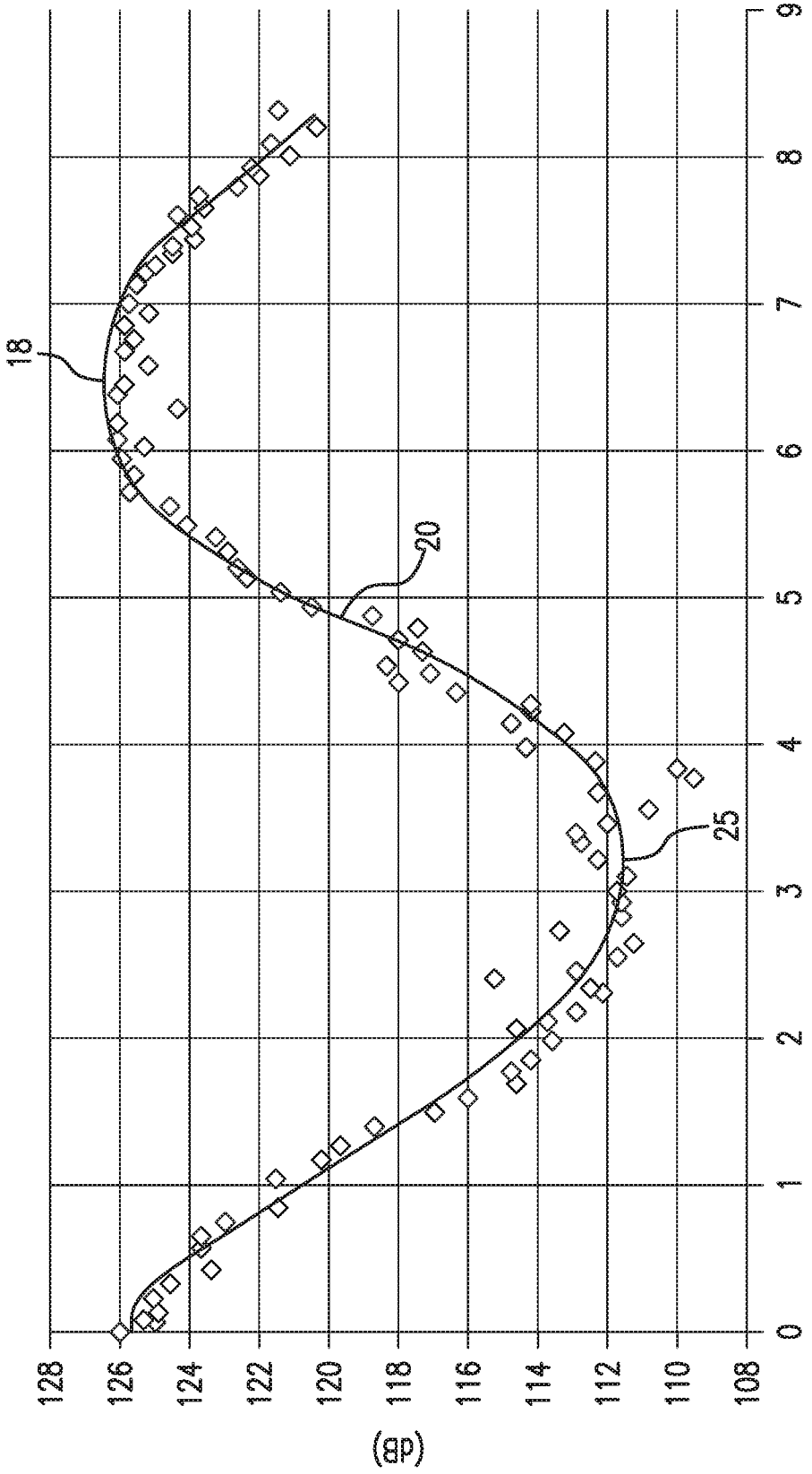


FIG. 1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25
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126
124
122
120
118
116
114
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110
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(dB)
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1
2
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4
5
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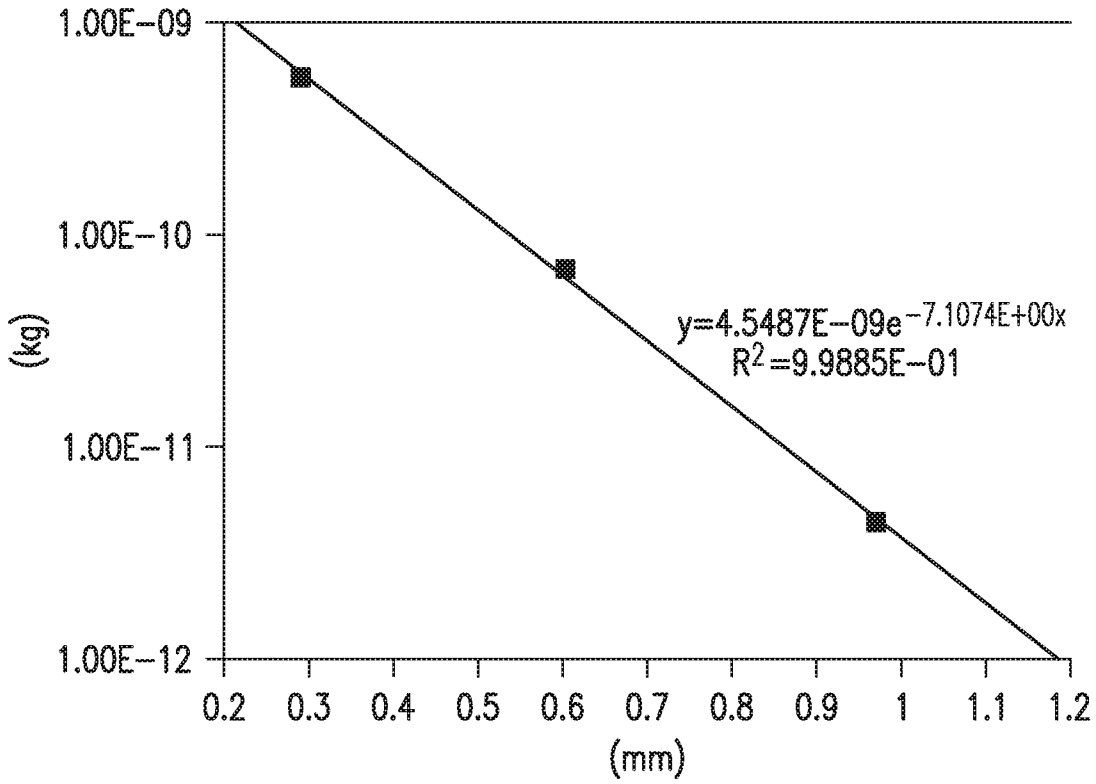
7
8
9
(mm)

FIG.2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0.7
0.8
0.9
1
1.1
1.2
(mm)

FIG.3

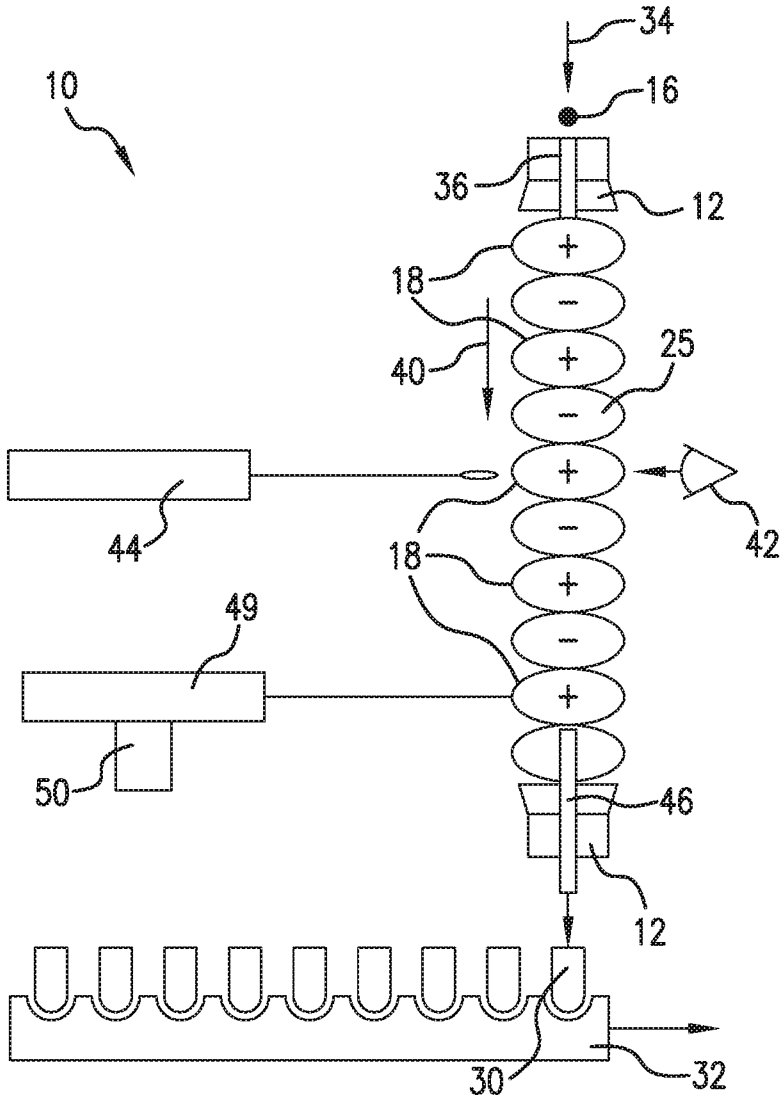

FIG.4

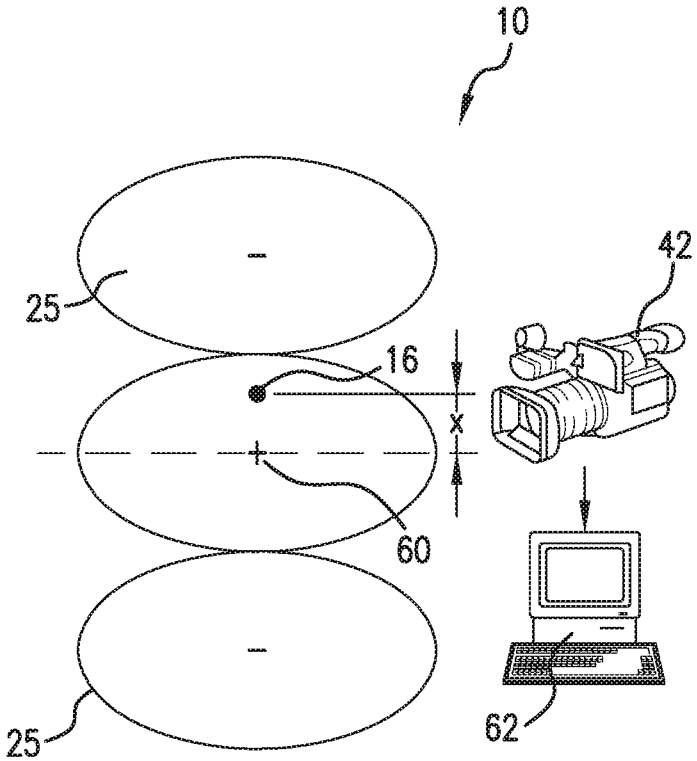

FIG.5

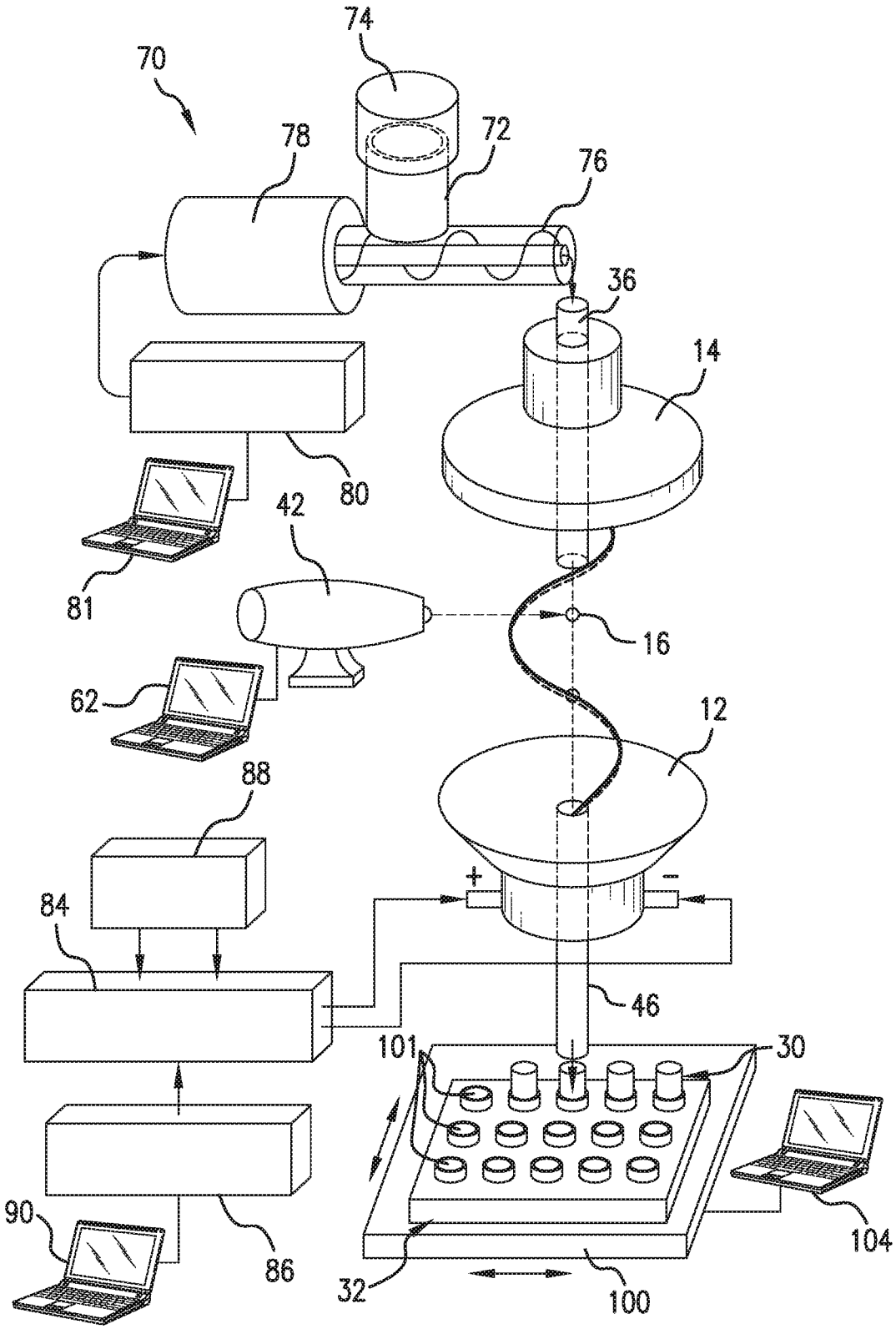

FIG.6

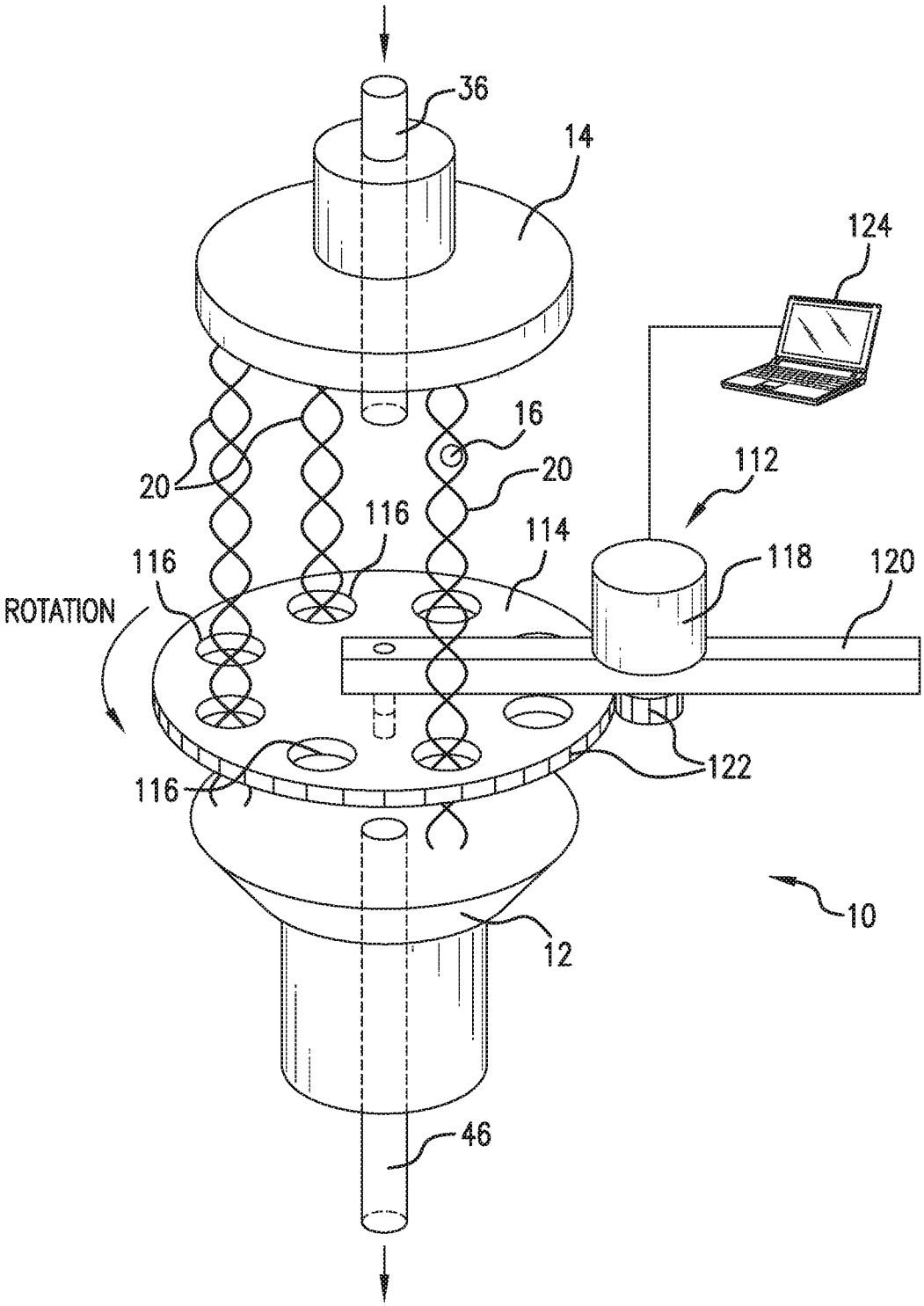
36
14
124
16
20
20
112
116
114
116
118
120
ROTATION
122
116
10
12
46

FIG. 7

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2016/056846

A. CLASSIFICATION OF SUBJECT MATTER
INV. G01N29/02 B01J19/10 B01L3/00 G01G7/00 G01N29/04
G01N15/02 G01N15/10 G01N21/03
ADD.
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)
G01N B01J B01L 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)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KAVOURAS A ET AL: "Ultrasonic levitation for the examination of gas/solid reactions", REVIEW OF SCIENTIFIC INSTRUMENTS, AIP, MELVILLE, NY, US, vol. 74, no. 10, 1 October 2003 (2003-10-01), pages 4468-4473, XP012040464, ISSN: 0034-6748, DOI: 10.1063/1.1606532	1-4,8,10
Y	the whole document	5,6
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[X] Further documents are listed in the continuation of Box C.

[X] 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

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 February 2017	03/04/2017

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Roetsch, Patrice

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2016/056846

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LEITERER J ET AL: "Structure analysis using acoustically levitated droplets", ANALYTICAL AND BIOANALYTICAL CHEMISTRY, SPRINGER, BERLIN, DE, vol. 391, no. 4, 30 March 2008 (2008-03-30), pages 1221-1228, XP019621388, ISSN: 1618-2650 the whole document	1,2,4, 8-10
Y	US 4 420 977 A (ELLEMAN DANIEL D [US] ET AL) 20 December 1983 (1983-12-20) column 1, lines 23-49; figures 1-3	5,6
Y	US 5 036 944 A (DANLEY THOMAS J [US] ET AL) 6 August 1991 (1991-08-06) column 4, line 60 - column 5, line 63; figures 3-6	5,6

2

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2016/056846

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4420977 A	20-12-1983	NONE	
US 5036944 A	06-08-1991	NONE	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2016/056846

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-6, 8-10

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-6, 8-10

   Method of determining weight of a particle of material with enhanced accuracy

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2. claim: 7

   Method of determining weight of a particle with the capability of producing amorphous compounds at high conversion rates

   ---

3. claim: 11

   Method of determining simultaneously weight of multiple particles of material

   ---

4. claims: 12-22

   Method of dispensing particles, droplets or mixture in a precise amount and/or with precise characterization knowledge to a desired destination, with a reduced contamination risk

   ---

5. claim: 23

   System for assessing properties of a particle or droplet with simplified handling of the material/system

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