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(71) Applicant *(for all designated States except US)*: **MONASH UNIVERSITY** [AU/AU]; Wellington Road, Clayton, VIC 3168 (AU).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **FRIEND, James, Robert** [US/AU]; Unit 26, 15 Cochrane Street, Brighton, VIC 3186 (AU). **YEO, Lesile, Yu-Ming** [MY/AU]; 30 Vears Road, Glen Iris, VIC 3146 (AU).

(74) Agent: **WATERMARK PATENT & TRADEMARK ATTORNEYS**; 302 Burwood Road, Hawthorn, VIC 3122 (AU).

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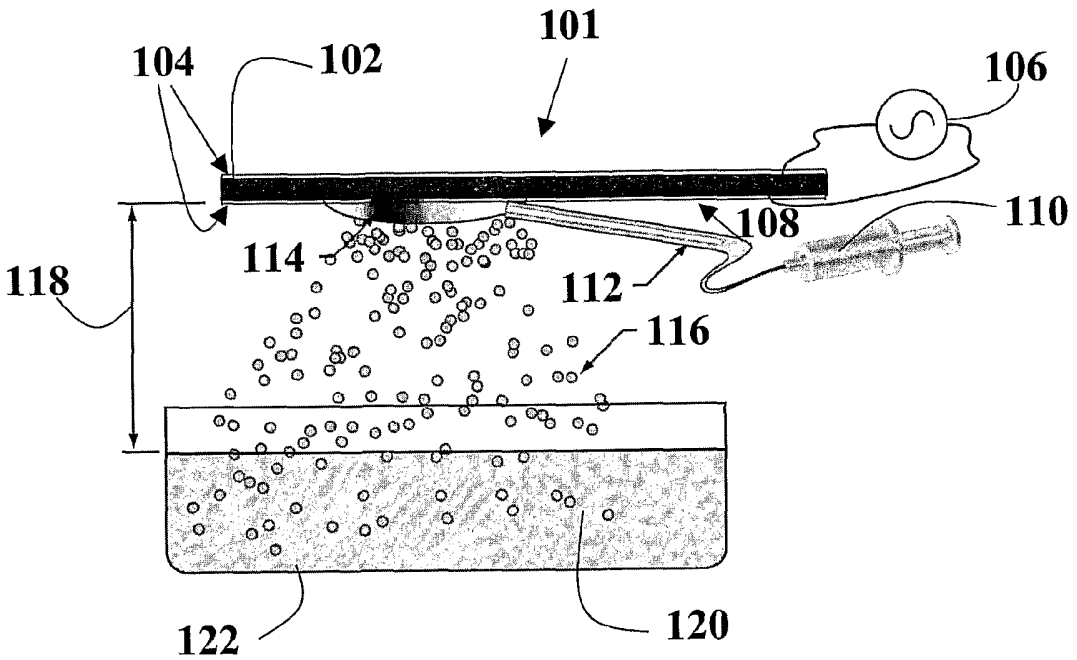

(57) Abstract: A process and apparatus for generating particles, including: applying an ultrasonic signal to at least one electrode (104, 502, 503, 504, 505) of a piezoelectric transducer element (101 , 501) to generate vibrations in said transducer element; and applying a liquid to a surface (108) of said transducer element, said liquid including a particle forming component and a carrier component; whereby the vibration of said transducer element generates droplets of said liquid to form substantially solid particles by evaporation of at least part of said carrier component.

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PROCESS AND APPARATUS FOR GENERATING PARTICLES

The present invention relates to a process and apparatus for generating particles.

BACKGROUND OF THE INVENTION

A new generation of therapeutics known as biopharmaceuticals includes biologic drugs, proteins, polynucleotides and liposomes. However, the efficiency of biopharmaceuticals is limited by their generally poor update in the human body. One approach to address the very low cell transection efficiencies of biopharmaceutical is to administer large doses. However, this can lead to unwanted side-effects such as toxicity and multidrug resistance, as well as the economic factors of higher expense per dose and the need for greater biopharmaceutical production.

The two steps that limit biopharmaceutical uptake in the body are: (i) the cellular uptake of the biopharmaceutical, and (ii) the migration of the biopharmaceutical into the cell nucleus. Both of these steps are particularly difficult to improve for molecules that are non-soluble, toxic or large. However, the delivery of biopharmaceuticals in nanoparticles, in particular particles having a diameter less than about 250 nm, can assist in overcoming both of these limiting steps. However, existing processes for generating nanoparticles suitable for drug delivery are cumbersome, time consuming, expensive, require the user of organic solvents, and are typically capable of producing only low yields of nanoscale particles. Moreover, the resulting particles can agglomerate into larger clusters shortly after formation, thus reducing the yield of nanoscale particles even further. There is thus a need for a simple process for producing unagglomerated nanoparticles in the absence of organic solvents, which would represent a major breakthrough for drug encapsulation and delivery.

It is desired to provide a process and apparatus for generating particles that alleviate one or more of the above difficulties, or at least provide a useful alternative.

SUMMARY OF THE INVENTION

With this in mind, in accordance with one aspect of the present invention, there is provided a process for generating particles, including:

applying an ultrasonic signal to at least one electrode of a piezoelectric transducer element to generate vibrations in said transducer element; and

applying a liquid to a surface of said transducer element, said liquid including a particle forming component and a carrier component;

whereby the vibration of said transducer element generates droplets of said liquid to form substantially solid particles by evaporation of at least part of said carrier component.

Preferably the ultrasonic signal has a frequency of at least about 1 MHz.

Preferably, said particles have a diameter of less than about 1000 nm.

Preferably, the carrier component is substantially volatile.

Preferably, the vibration of said transducer element is such that the formed particles have a substantially monodisperse size distribution.

Advantageously, the transducer element may include electrodes located on opposing surfaces of a piezoelectric material to excite piston mode vibration of said material.

Preferably, said vibration is at a frequency of at least about 100 to 500 MHz.

Preferably, said vibration is at a resonance frequency of said material.

Alternatively, the transducer element may include the electrodes located on one surface of said material to excite surface acoustic waves in said surface.

The ultrasonic signal applied to the electrode may be at a frequency of at least about 8 MHz.

Preferably, the diameter of said droplets is less than about 6000 nm.

Preferably, the diameter of said particles is less than about 250 nm.

Preferably, the diameter of said particles is less than about 50 nm.

Preferably, said particle forming component of said liquid includes a polymer.

Preferably, said polymer is suitable for drug delivery to a human being.

Advantageously, said particle forming component of said liquid may include a metal or ceramic.

Advantageously, said liquid may include a drug.

Advantageously, said liquid may include a biopharmaceutical substance.

Advantageously, said particles may include a liquid encapsulated within a solid.

The present invention also provides an apparatus for generating particles, including:

a transducer element including a piezoelectric material having at least one electrode located on one or more surfaces of said material;

a signal generator connected to said electrode to apply an ultrasonic signal to said electrodes, thereby generating vibrations in said material;

whereby the vibration of said material generates droplets of a liquid applied to a surface of said material, the liquid including a particle forming component and a carrier component such that the droplets form substantially solid particles by evaporation of at least part of said carrier component.

Preferably, the apparatus includes a dispensing component for dispensing said liquid to said surface.

Preferably the ultrasonic signal has a frequency of at least about 1 MHz.

Preferably, said particles have a diameter of less than about 1000 nm.

Preferably, the carrier component is substantially volatile.

Preferably, the vibration of said material is such that the formed particles have a substantially monodisperse size distribution.

Advantageously, the electrodes may be on opposing surfaces of said material to excite piston mode vibration of said material.

Preferably, said vibration is at a frequency of at least about 100 to 500 MHz.

Preferably, said vibration is a resonance frequency of said material.

Alternatively, the electrodes may be located on one surface of said material to excite surface acoustic waves in said surface.

The ultrasonic signal applied to the electrode may be at a frequency of at least about 8 MHz.

Preferably, the diameter of said droplets is less than about 6000 nm.

Preferably, the diameter of said particles is less than about 250 nm.

Preferably, the diameter of said particles is less than about 50 nm.

Preferably, said particle forming component of said liquid includes a polymer.

Preferably, said polymer is suitable for drug delivery to a human being.

Advantageously, said particle forming component of said liquid may include a metal or ceramic.

Advantageously, said liquid may include a drug.

Advantageously, said liquid may include a biopharmaceutical substance.

BRIEF DESCRIPTION OF THE DRAWINGS

It will be convenient to further describe the invention with respect to the accompanying drawings which illustrate preferred embodiments of the apparatus according to the present invention. Other embodiments of the invention are possible, and consequently, the particularity of the accompanying drawings is not to be understood as superseding the generality of the preceding description of the invention.

In the drawings:

Figure 1 is a schematic diagram of a preferred embodiment of an apparatus for producing nanoparticles;

Figure 2 is a flow diagram of a preferred embodiment of a process for producing nanoparticles using the apparatus;

Figures 3 and 4 are graphs of particle size distribution produced by the atomizer using vibration velocities of 1.0 and 1.4 m/s, respectively;

Figure 5 is a schematic diagram of a piezoelectric transducer of the SAW atomizer in accordance with a second preferred embodiment of the invention;

Figure 6 is an image of a photolithographic mask used to define electrodes of a SAW atomizer in accordance with Figure 5;

Figures 7 and 8 are images of portions of the photolithographic mask used to define pairs of interdigitated electrodes for the SAW atomizer;

Figure 9 is a graph of particle size distribution produced by the SAW atomizer; and

Figure 10 is a scanning electron microscope image of agglomerated particles of zeolite produced by the SAW atomizer, each particle having a diameter of about 100 nm.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

As shown in Figure 1, an apparatus for generating particles includes a piezoelectric transducer element 101 in the form of a cylindrical disc 102 of a hard piezoelectric material such as lead zirconate titanate (PZT) and having a diameter of about 20 to 30 mm and a thickness of about 1 mm. The apparatus, also referred to herein as an atomizer, is described herein in relation to an atomization process, as shown in Figure 2, that generates substantially solid particles, via the formation of nanoscale droplets of a liquid that includes a particle forming component and a carrier component.

At step 202, 500-nm thick layers of platinum (Pt) metal are deposited onto the opposing planar faces of the disc 102 to provide electrodes 104 for the atomizer. The PZT disc 102 is then polarized by applying a 20 kV/cm electric field to orient the electric domains within the ceramic PZT disc 102 along the thickness direction of the disc 102. The electrodes 104 are subsequently connected to outputs of respective polarities of a Radio Frequency (RF) signal generator 106. The RF signal generator 106 drives the PZT transducer element 101 with a sinusoidal signal having an ultrasonic frequency of at least about 1 MHz, thereby causing the opposing planar faces of the transducer element 101 to vibrate with a relatively constant and in-phase piston-like motion across each planar face of the transducer element 101. The disk 102 is preferably driven in either its fundamental (being in this case 1.645 MHz) or first harmonic (5.345 MHz) thickness mode of vibration.

At step 204, a drop of a desired fluid is applied to the underside or downward directed face 108 of the transducer element 101 from a syringe 110 or other form of liquid pump, using a supply tube 112 to conduct the fluid from the syringe 110 to the transducer element 101. The liquid applied to the face of the transducer element 101 includes a particle forming component and a carrier component. The particle forming component can be any substance that can be dissolved in the carrier component and that solidifies to a substantial extent upon removal of the carrier component. Examples of suitable particle forming components include polymers, metals, and ceramics. The particle forming component is preferably a polymer, and more preferably a polymer suitable for

drug delivery to a human being, being a physiologically acceptable polymer that biodegrades into non-harmful products such as natural metabolites or other materials that can be readily cleared from the body on an acceptable time scale. The liquid can also include chemical and/or biological markers to harness cellular transport mechanisms and thereby increase transfection efficiencies into cells. The liquid may also control the release of an encapsulated drug by selective degradation of the polymer matrix upon injection, ingestion or inhalation.

When the transducer element 101 is excited at an ultrasonic frequency at step 206, the liquid drop 112 on the lower face 108 of the transducer element 102 is atomized, whereby tiny droplets or particles of the liquid are emitted from the surface of the drop 112. The droplets are generated by acoustic radiation transmitted from the PZT element into the liquid applied to the transducer face 108, as described in Robert J. Lang, *Ultrasonic atomization of liquids*, Journal of the Acoustical Society of America Vol. 34, No. 1, 1962 ("Lang"). The droplets are believed to be generated by surface capillary waves at low power excitation of the PZT element, and by surface instabilities about the crests of these waves at higher power excitation. By vibrating the transducer element 101 at ultrasonic frequencies of at least about 1 MHz, nanometer-scale droplets can be formed.

The atomized droplets or particles 116 fall a distance 118 (being in this case about 8 cm) under gravity to a capture medium 120 contained in a vessel 122 located under the transducer element 101 at step 208, allowing for evaporation of the carrier component of the liquid within the atomized droplets to form substantially solid or hollow, fluid-containing particles. Depending on the atomization conditions, the particles can be monodisperse with diameters on a nanometer-scale. The capture medium contains chemicals to prevent agglomeration of the formed nanoparticles. In the described embodiment, the capture medium consists of deionized (DI) water and a hardening agent such as sodium dodecyl sulfate (SDS) at 1 mM, which facilitates the precipitation of the particles 116 in the capture medium 120.

The nanoparticle-containing capture medium and hardening agent is then centrifuged at approximately 2500 rpm for 10 minutes in a swinging bucket rotor to remove any large agglomerates that may have formed, due predominantly to accumulation of the hydrophobic polymer at the air-liquid interface. Measurement

of the particle size distribution both before and after centrifugation indicates that the distribution and yield of the nanoparticles was unaffected by the centrifuge.

To evaluate the performance of the atomizer, a polymeric solution was prepared by dissolving polycaprolactone (PCL), with a molecular weight of 65 000 Dalton in acetone (99.5% purity) to create a feedstock solution of 0.5% PCL weight per volume (w/v). The feedstock solution pumped onto the face 108 of the transducer element 102 forms a 10-mm diameter droplet with a wetting angle of approximately 30 degrees, maintained through controlled pumping rate of the feedstock solution. The acetone carrier component evaporates very rapidly upon atomization to produce solid particles of the polymer. The resulting particle sizes were measured using a Zetasizer instrument from the UK company Malvern Instruments with Dispersion Technology Software version 4.10b1. The Z-average particle size of each sample is defined as the diameter of the sphere that diffuses at the same speed as the particle being measured. The Malvern system determines Z-average particle size by measuring the Brownian motion of the particles in a sample using dynamic light scattering. The vibration velocity of the surface was monitored using a laser Doppler vibrometer during operation.

Particle size analysis obtained using the Zetasizer are shown in Table 1 for the ultrasonic atomization of 0.5% polycaprolactone in acetone at approximately 25 C and 45% relative humidity. Unless indicated otherwise in Table 1, the feedstock solution was pumped at a flow rate of 28 ml/h onto the bottom surface of the piezoelectric disk transducer running at an amplitude of 1.0 m/s vibration velocity and a frequency of 1.645 MHz into a hardening agent of 1 mM SDS in water located 8 cm beneath the transducer. Under most conditions, as shown in Table 1, an average particle diameter was found to be between 181 and 226 nm.

Table 1

Parameter		Z-Average Particle Diameter	Standard Deviation	Number of runs
Transducer	0.7 m/s	208	5.7	6
Vibration	1.0 m/s	186	5.7	6
Velocity	1.4 m/s	5641	6474.4	6
Excitation	1.645 MHz	186	5.7	6
Frequency	5.305 MHz	182	2.3	6
Flow rate	20 ml/hr	187	13.9	6
	28 ml/hr	186	5.7	6
	36 ml/hr	181	6.5	6
Atomizer height	8 cm	186	8.4	3
	12 cm	202	3.5	3
	16 cm	215	4.6	3
SDS Detergent	1 mM	186	5.7	6
Concentration	10 mM	226	21.4	6
	100 mM	3467	3692.7	6

Figure 3 is a log-linear graph of the particle size frequency distribution under the conditions which resulted in the smallest Z- average particle size observed, 181 nm, with a standard deviation (σ) of 6.5 nm. The distribution in Figure 3 is essentially a monodisperse, symmetrical (on a log-linear scale) frequency distribution 302. A small amount of larger agglomerations 304 which were not removed by the centrifuge are visible in the graph at diameters of approximately 500 to 700 nm.

Figure 4 is a graph of the bimodal particle size frequency distribution that was obtained when the vibration velocity was increased to 1.4 m/s. The reduced efficiency of the atomisation process may be caused by overheating of the liquid, causing it to boil away, or by the ejection of far larger droplets from the surface of the drop 114 than at the lower vibration velocity of 1.0 m/s.

The efficiency of the atomisation process is also reduced if the concentration of SDS in the capture solution hardening agent is increased to 100 mM. It is believed that the hydrophobic nature of the polymer prevents the creation of a stable emulsification in water, and hence a surfactant is added to

assist in stabilizing the nanoparticle/hardening agent solution. The critical micelle concentration (CMC) of SDS in water is approximately 2.5 g/l or 8.7 mM. It was observed that, at concentrations below and above the CMC of SDS in water, e.g. 1 mM and 10 mM, no sedimentation of the nanoparticles occurred. At much higher SDS concentrations, e.g. 100 mM or 11.5 CMC, the particles tended to form larger aggregates that varied greatly in size, as indicated by the larger Z-average particle diameter and larger standard deviation in column 3 of Table 1.

Analysis of variance (ANOVA) studies were performed for each of the process parameters of frequency, amplitude, flow rate, atomizer height and detergent concentration in the hardening agent. The ANOVA analysis (not shown) indicated that, for the conditions listed in Table 1, the parameters of amplitude, atomizing surface height and surfactant concentration in the hardening agent have statistically significant effects on the Z-average particle diameter of the PCL nanoparticles, using $p = 0.05$. In contrast, variations in the flow rate and frequency do not have statistically significant effects on the Z-average particle diameter ($p = 0.05$).

In an alternative embodiment, nanoparticles of fluid are generated by surface acoustic waves on the surface of a piezoelectric transducer, as described in M. Kurosawa, A. Futami, and T. Higuchi, *Characteristics of Liquids Atomization Using Surface Acoustic Wave*, Proc. of Transducer 97, Chicago, USA ("Kurosawa"), rather than by piston movement of the entire transducer, as described above. As shown in Figure 5, in this alternative embodiment, the transducer element 501 includes four interdigitated finger electrode pairs 502, 503, 504, 505 are formed on the surface of a generally parallelepiped piezoelectric substrate 506. The substrate 506 is cut from a 128 Y-X rotated $LiNbO_3$ crystal wafer sourced from Roditi UK, Ltd. The four electrodes 502, 503, 504, 505 form two pairs of electrically isolated and interdigitated or interleaved finger electrodes. Electrodes 502 and 503 are connected to respective polarity outputs of the signal generator 106, with the other pair of electrodes 504, 505 being left disconnected, short-circuited, or also connected to the signal generator 106 in the same manner as the first pair pf electrodes 502, 503 to obtain different forms of wave vibration along the crystal surface.

The electrodes are defined by photolithography using the quartz mask shown in Figure 6. The mask defines four sets of electrode pairs and thus can be used to produce four surface acoustic wave (SAW) atomizers. The horizontal direction in Figure 6 corresponds to the Y-axis of the $LiNbO_3$ wafer. The upper three rows of electrode pairs, as seen in Figure 6, are identical and define a simple interdigitated electrode pair configuration as shown in Figure 5. Each electrode is formed by depositing a 5-nm thick adhesion layer of titanium followed by a 250-nm-thick layer of aluminium. The black boxes 604 around the periphery of the mask are used to align cutting lines; the corner boxes 606 demarcate the sides of the top and bottom atomizers and ends of all four atomizers. The smaller boxes 604 along the left and right sides demarcated the dividing lines between the atomizers. Wires (not shown) are attached to the upper and lower bars 608 of each pair of interdigitated finger electrodes to conduct the ultrasonic driving signals to each of the electrode fingers. With respect to the vertical direction of Figure 6, the Rayleigh waves are essentially isolated to the region where the fingers overlap, and propagate in both directions from each electrode pair. Reflection of the Rayleigh wave generated from the electrodes off the left and right edges is reduced by coating the edges of the $LiNbO_3$ crystal with silicone rubber.

The left electrode pair and right electrode pair are used together to form (Rayleigh) surface acoustic waves (SAW) that propagate from one electrode pair to the other electrode pair. These waves are formed by the inverse piezoelectric effect among the fingers of each electrode pair, where a differential charge between fingers causes distortion of the surface at a speed which matches the speed of sound of the Rayleigh wave divided by the distance between the IDT fingers. For example, the speed of sound of Rayleigh wave along the y-axis of 128 Y-X $LiNbO_3$ material is 5112 m/s, and four times the 110-micron inter-finger width is 440 microns, giving a frequency of 11.6 MHz. The RF signal generator 106 drives the lithium niobate element 506 with a sinusoidal signal having an ultrasonic frequency of at least about 1 MHz, thereby causing the planar faces of the transducer element 506 to vibrate with a relatively constant sinusoidal motion between and within electrodes 502 to 505, perpendicular to the planar face and along a direction between the electrodes 502, 503 and electrodes 504, 505. The

piezoelectric substrate 506 is preferably driven in its fundamental (being in this case 8.611 MHz) surface acoustic wave (Rayleigh) mode of vibration.

Figure 7 shows a more detailed schematic of one of the left-hand upper pads 602 from Figure 6. The interlaced fingers are evenly spaced, with 110-micron wide fingers and 110-micron wide gaps between the fingers.

Excitation of the electrodes with a signal of ultrasonic frequencies generates surface acoustic waves that travel along the surface of the lithium niobate substrate 506. A liquid droplet is applied to the excited surface of the substrate 506 in an arrangement identical to that shown in Figure 1, thereby generating nanoparticles of fluid as described above for the first embodiment.

Figure 8 is an enlarged image of the lower left-hand electrode pair 610 of the mask shown in Figure 6. It will be apparent from Figure 6 that the lower set of electrodes 610, 612 are different from the other electrodes 602 on the mask. While the upper three sets of electrodes 602 are of a relatively simple and symmetrical design, and are all identical to each other, the two lower electrodes 610, 612 are more complex and are asymmetrical. Additionally, these two electrodes 610, 612 are not identical to each other but rather are mirror images of each other. This arrangement cancels out the left-ward propagation of the generated wave in the left electrode pair 610; and correspondingly, the right-ward propagation of the generated wave in the right electrode pair 612. The electrode pairs are therefore unidirectional, generating SAW radiation in only one direction. An additional feature of these electrodes 610, 612 is the ability to efficiently excite harmonic overtones of the fundamental resonance frequency of the electrode pattern which lies at approximately 10 MHz, permitting the use of higher-frequency resonances to atomize fluids placed between the two electrode pairs 610, 612.

To illustrate the performance of the SAW atomizer, the transducer element 501 was driven at 8.611MHz and used to atomise a fluid drop of polycaprolactone (PCL) dissolved at 5% w/v in acetone. As shown in Figure 9, this generates monodisperse particles with a range of diameters narrowly distributed around an average diameter of around 63 nm +/-8.188 nm; 96% of the particles were within this narrow range.

In another experiment, the transducer element 501 was again driven at 8.611 MHz at a minimum input power of 2W required for atomising the working fluid. The experiment used a weaker concentration of polycaprolactone (PCL) dissolved at 1% weight per weight (w/w) in acetone. The working fluid was supplied to the transducer element 501 using a syringe pump at a flow rate of 24 mol/hr. It was observed that the atomisation of the working fluid was difficult to achieve when the PCL concentration was higher than 1% w/w. Rapid evaporation of acetone prior to atomisation left a film of polymer which covered the surface of the transducer and consequently damped the capillary waves from where the microdroplets are understood to be generated. The size and shape of the produced nanoparticles were determined using a number of different techniques consisting of Dynamic Light Scattering (DLM), Atomic Force Microscopy (AFM) and Transmission Electron Microscopy (TEM). The results showed that nanoparticles of two different diameters were generated smaller than 50 nm and 130-220 nm. The results from the AFM imaging indicated that the larger nanoparticles might be agglomerations of nanoparticles smaller than 50 nm, although this finding does not appear to be supported by the DLS and TEM data. For studies are therefore required in this area.

Figure 10 is a scanning electron micrograph of zeolite particles generated by the SAW atomizer. The agglomerated zeolite particles each have a diameter of about 100 nm. The nanoparticles were generated by atomizing a rather caustic (pH 13) solution of zeolite in 25% ethanol, 50% acetone, and 25% NaOH. The ceramic zeolite dissolves in the caustic solution, but solidifies rapidly on atomization via evaporation of the acetone and ethanol carrier components. The particles are collected on a solid surface and heated at 250°C for 15 minutes to remove any residual solvent.

Modifications and variations as would be deemed obvious to the person skilled in the art are included within the ambit of the present invention as claimed in the appended claims.

CLAIMS:

1. A process for generating particles, including:

applying an ultrasonic signal to at least one electrode of a piezoelectric transducer element to generate vibrations in said transducer element; and

applying a liquid to a surface of said transducer element, said liquid including a particle forming component and a carrier component;

whereby the vibration of said transducer element generates droplets of said liquid to form substantially solid particles by evaporation of at least part of said carrier component.

2. A process according to claim 1, wherein the ultrasonic signal has a frequency of at least about 1 MHz.

3. A process according to claim 1 or 2, wherein said particles have a diameter of less than about 1000 nm.

4. A process according to any one of the preceding claims, wherein the carrier component is substantially volatile.

5. A process according to any one of the preceding claims, wherein the vibration of said transducer element is such that the formed particles have a substantially monodisperse size distribution.

6. A process according to any one of the preceding claims, wherein the transducer element includes electrodes located on opposing surfaces of a piezoelectric material to excite piston mode vibration of said material.

7. A process according to claim 6, wherein said vibration is at a frequency of at least about 100 to 500 MHz.

8. A process according to claim 6, wherein said vibration is at a resonance frequency of said material.

9. A process according to any one of claims 1 to 5, wherein the transducer element includes at least one electrode located on one surface of said material to excite surface acoustic waves in said surface.

10. A process according to claim 9, wherein the ultrasonic signal applied to the electrode is at a frequency of at least about 8 MHz.

11. A process according to any one of the preceding claims, wherein the diameter of said droplets is less than about 6000 nm.

12. A process according to any one of claims 1 to 11, wherein the diameter of said particles is less than about 250 nm.

13. A process according to claim 12, wherein the diameter of said particles is less than about 50 nm.

14. A process according to any one of the preceding claims, wherein said particle forming component of said liquid includes a polymer.

15. A process according to claim 14, wherein said polymer is suitable for drug delivery to a human being.

16. A process according to any one of the preceding claims, wherein said particle forming component of said liquid includes a metal or ceramic.

17. A process according to any one of the preceding claims, wherein said liquid includes a drug.

18. A process according to any one of the preceding claims, wherein said liquid includes a biopharmaceutical substance.

19. A process according to any one of the preceding claims, wherein said particles include a liquid encapsulated within a solid.

20. An apparatus for generating particles, including:

a transducer element including a piezoelectric material having at least one electrode located on one or more surfaces of said material;

a signal generator connected to said electrodes to apply an ultrasonic signal to said electrodes, thereby generating vibrations in said material;

whereby the vibration of said material generates droplets of a liquid applied to a surface of said material, the liquid including a particle forming component and a carrier component such that the droplets form substantially solid particles by evaporation of at least part of said carrier component.

21. An apparatus according to claim 20, wherein the apparatus includes a dispensing component for dispensing said liquid to said surface.

22. An apparatus according to claim 20 or 21, wherein the ultrasonic signal has a frequency of at least about 1 MHz.

23. An apparatus according to any one of claims 20 to 22, wherein said particles have a diameter of less than about 1000 nm.

24. An apparatus according to any one of claims 20 to 23, wherein the carrier component is substantially volatile.

25. An apparatus according to any one of claims 20 to 24, wherein the vibration of said material is such that the formed particles have a substantially monodisperse size distribution.

26. An apparatus according to any one of claims 20 to 25, wherein the electrodes are on opposing surfaces of said material to excite piston mode vibration of said material.

27. An apparatus according to claim 26, wherein said vibration is at a frequency of at least about 100 to 500 MHz.

28. An apparatus according to claim 26, wherein said frequency is a resonance frequency of said material.

29. An apparatus according to any one of claims 20 to 25, wherein the electrodes is located on one surface of said material to excite surface acoustic waves in said surface.

30. An apparatus according to claim 29, wherein the ultrasonic signal applied to the electrode is at a frequency of at least about 8 MHz.

31. An apparatus according to any one of claims 20 to 30, wherein the diameter of said droplets is less than about 6000 nm.

32. An apparatus according to any one of claims 20 to 31, wherein the diameter of said particles is less than about 250 nm.

33. An apparatus according to claim 32, wherein the diameter of said particles is less than about 50 nm.

34. An apparatus according to any one of claims 20 to 33, wherein said particle forming component of said liquid includes a polymer.

35. An apparatus according to claim 34, wherein said polymer is suitable for drug delivery to a human being.

36. An apparatus according to any one of claims 20 to 35, wherein said particle forming component of said liquid includes a metal or ceramic.

37. An apparatus according to any one of claims 20 to 36, wherein said liquid includes a drug.

38. An apparatus according to any one of claims 20 to 37, wherein said liquid includes a biopharmaceutical substance.

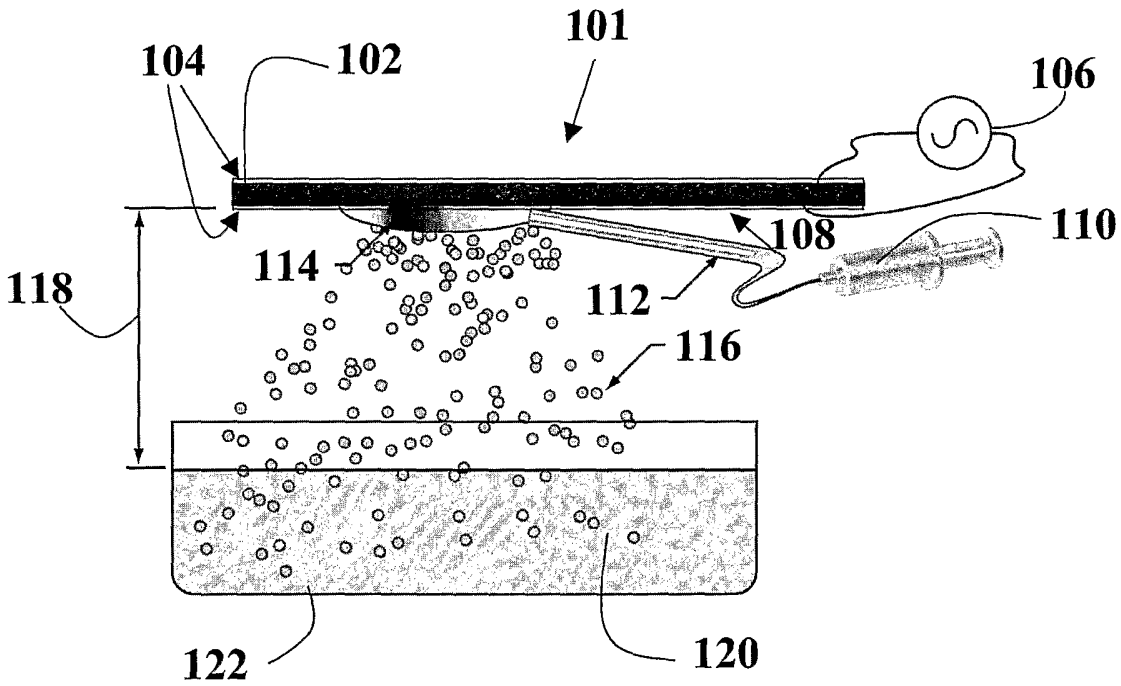


FIGURE 1

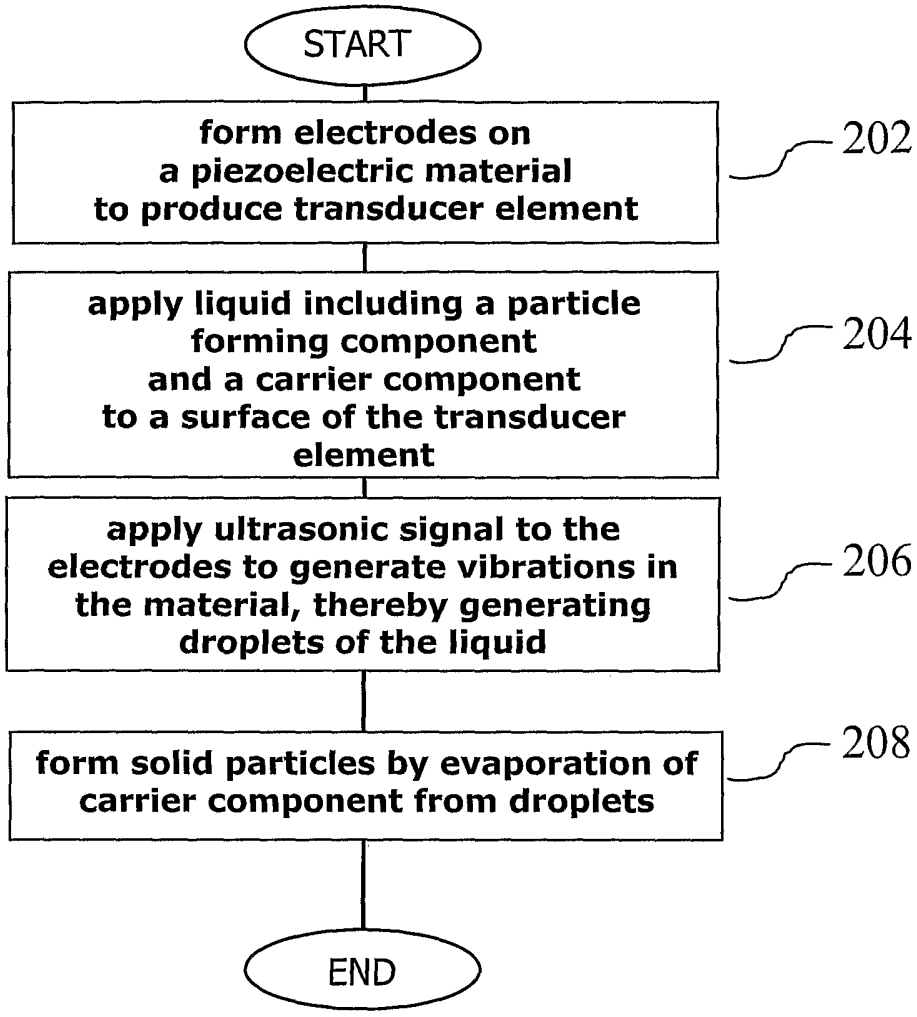

START
form electrodes on a piezoelectric material to produce transducer element
202
apply liquid including a particle forming component and a carrier component to a surface of the transducer element
204
apply ultrasonic signal to the electrodes to generate vibrations in the material, thereby generating droplets of the liquid
206
form solid particles by evaporation of carrier component from droplets
208
END

FIGURE 2

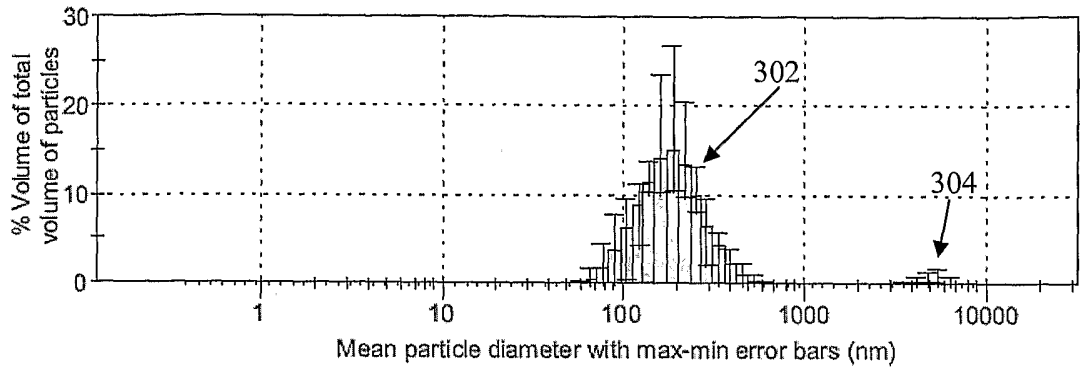


FIGURE 3

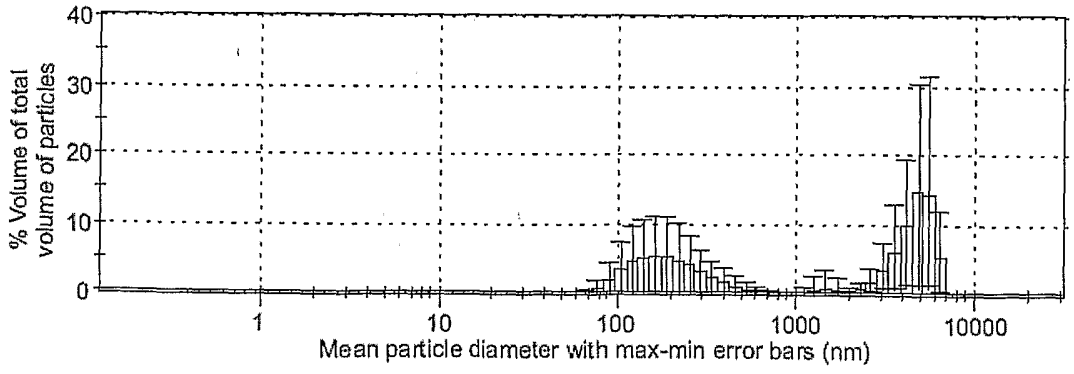


FIGURE 4

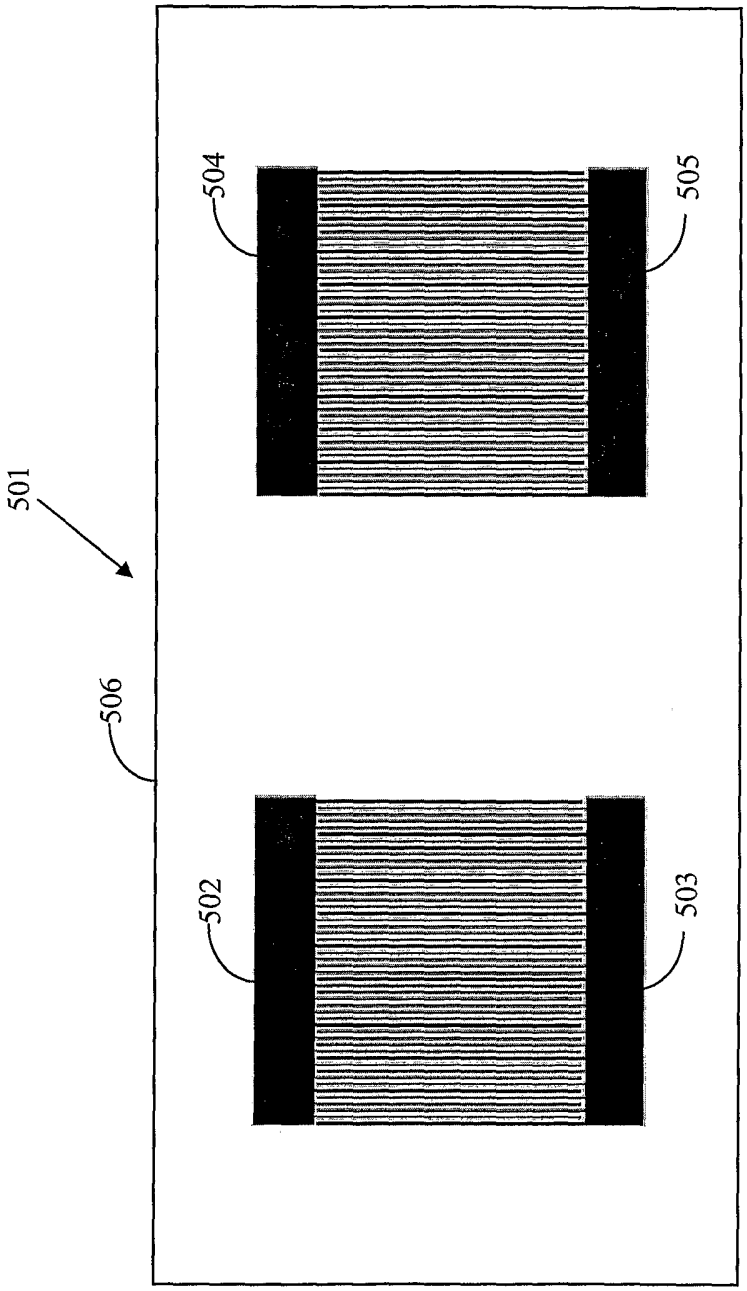


FIGURE 5

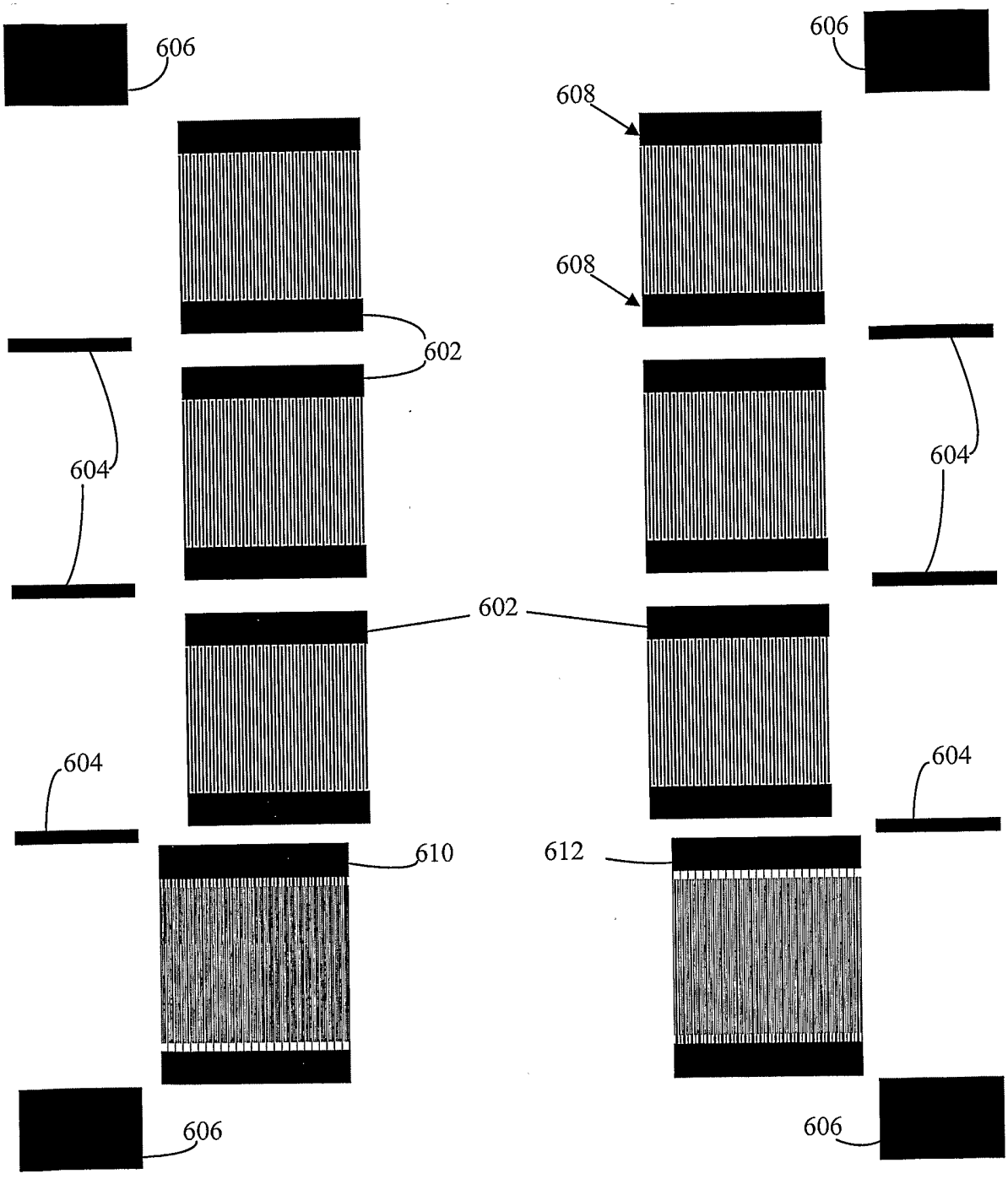


FIGURE 6

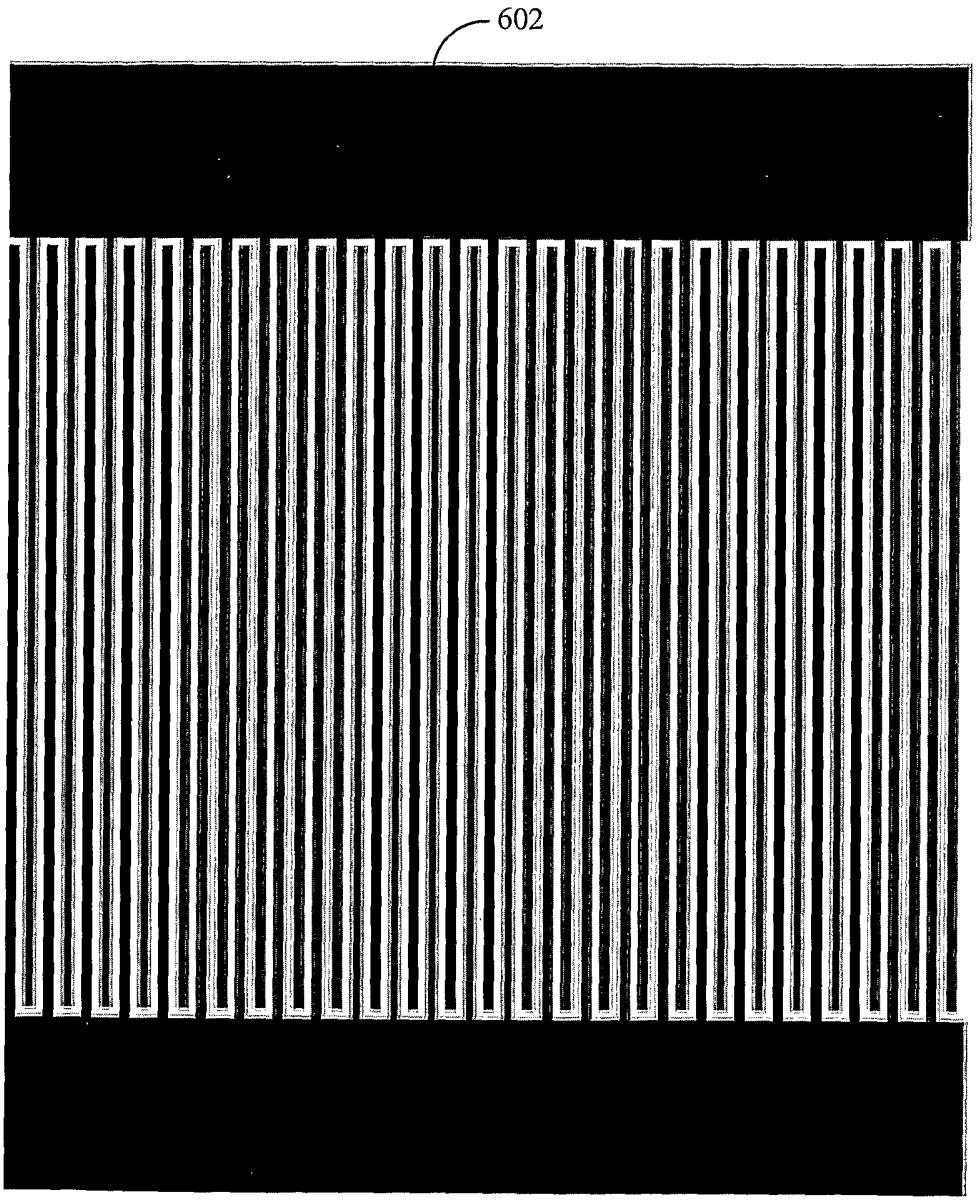


FIGURE 7

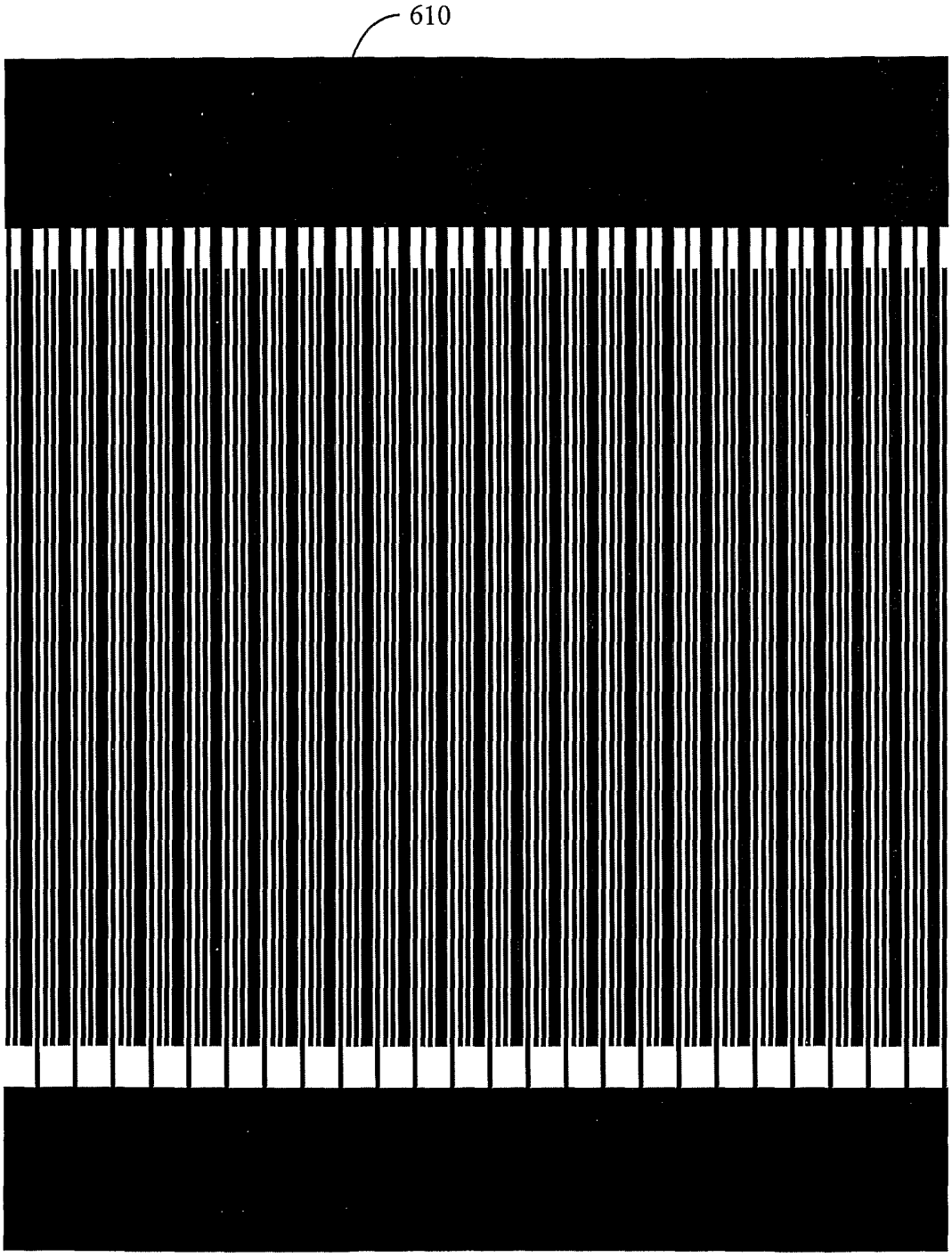
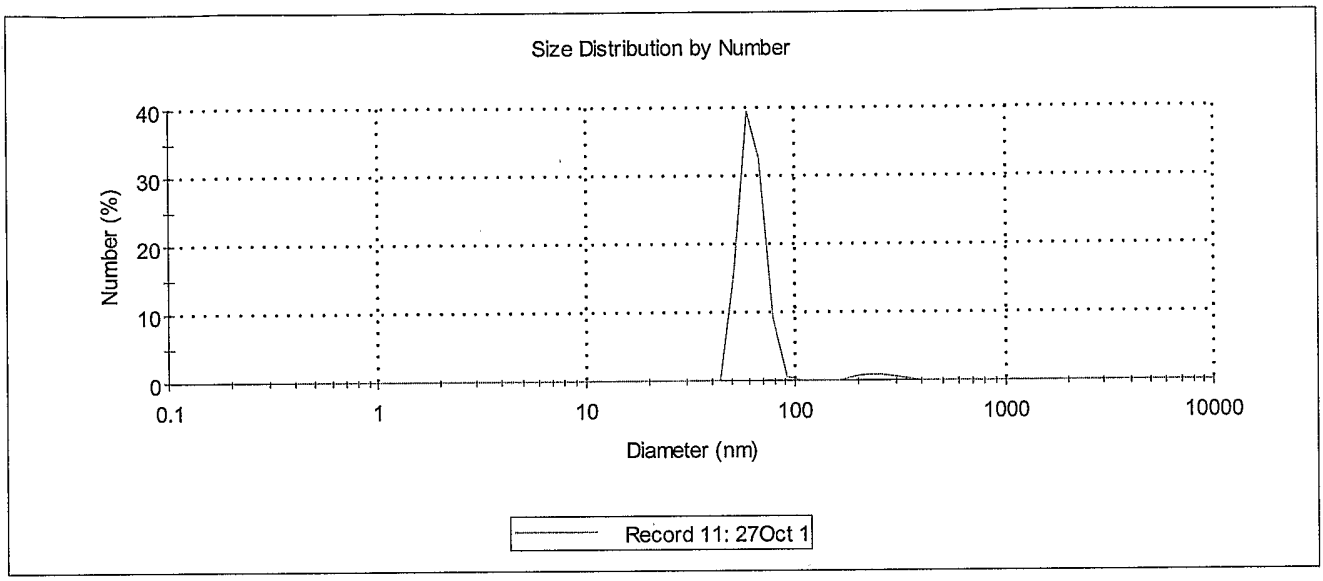


FIGURE 8


Size Distribution by Number
Number (%)
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30
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10
0
0.1
1
10
100
1000
10000
Diameter (nm)
Record 11: 27Oct 1

FIGURE 9

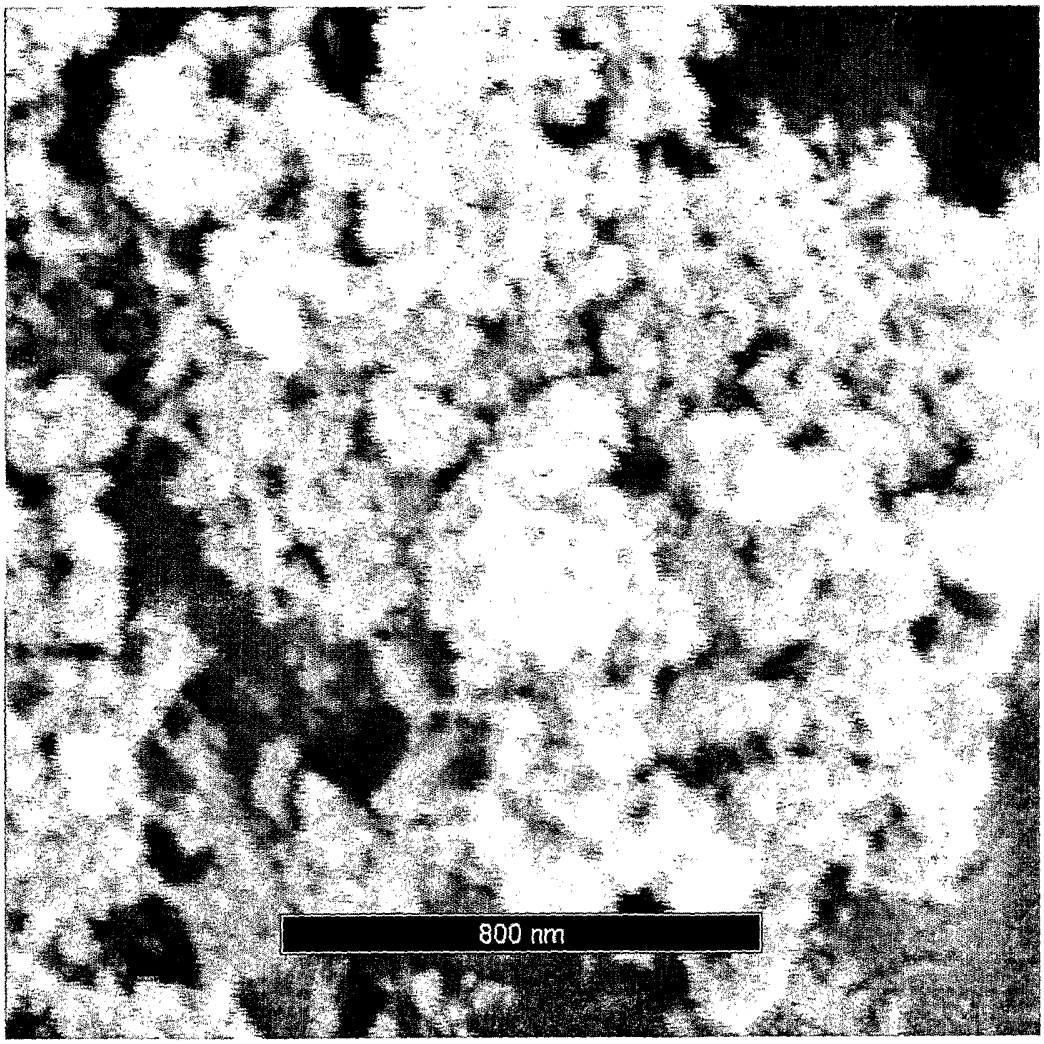

FIGURE 10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2006/001951

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.

B05B 17/06 (2006.01) ***B01J 2/02*** (2006.01)
B01D 1/18 (2006.01) ***B81C 5/00*** (2006.01)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
DWPI, JAPIO - Keywords ultrasonic, vibration, particles, atomization, evaporation, piezoelectric, liquid and like terms

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1452239 A1 (RIKEN et al.) 1 September 2004 See entire document	1-38
X	EP 512394 A2 (MILLIPORE CORPORATION) 11 November 1992 See entire document	1, 3-6, 9, 11, 12, 14-21, 23-26, 28-29, 31, 32, 34-38
X	Patent Abstracts of Japan, JP 62149331 A (SHINRYO AIR CONDITIONING CO LTD) 3 July 1987 See abstract	1, 20

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

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"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
15 February 2007	12 APR 2007
Name and mailing address of the ISA/AU	Authorized officer
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	**GREG POWELL** Telephone No : (02) 6283 2308

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2006/001951

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5297734 A (TODA) 29 March 1994 See entire document	1-38
X	US 6601581 B1 (BABAEV) 5 August 2003 See entire document	1-38
X	US 5389379 A (DIRIX et al.) 14 February 1995 See entire document	1-38

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/AU2006/001951

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
EP	1452239	JP	2003136005	US	2005126480	WO	03039759
EP	0512394	JP	5180802	US	5526682		
JP	62149331	NONE					
US	5297734	EP	0480615	JP	4150968	JP	4207798
		JP	4207799	JP	4207800		
US	6601581	AU	2002245165	WO	02055131		
US	5389379	AU	33134/93	CA	2089354	EP	0556917
		FI	930672	JP	5337360	MX	9300851
		NO	930557	NZ	245914	ZA	9300929

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

END OF ANNEX