(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 October 2006 (05.10.2006)

PCT

(10) International Publication Number
WO 2006/103671 A1

(51) International Patent Classification:
B01J 19/10 (2006.01) ***B02C 19/18*** (2006.01)
B01J 19/00 (2006.01)

(21) International Application Number: PCT/IL2006/000403

(22) International Filing Date: 30 March 2006 (30.03.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

167772	31 March 2005 (31.03.2005)	IL
60/708,766	17 August 2005 (17.08.2005)	US
60/708,765	17 August 2005 (17.08.2005)	US

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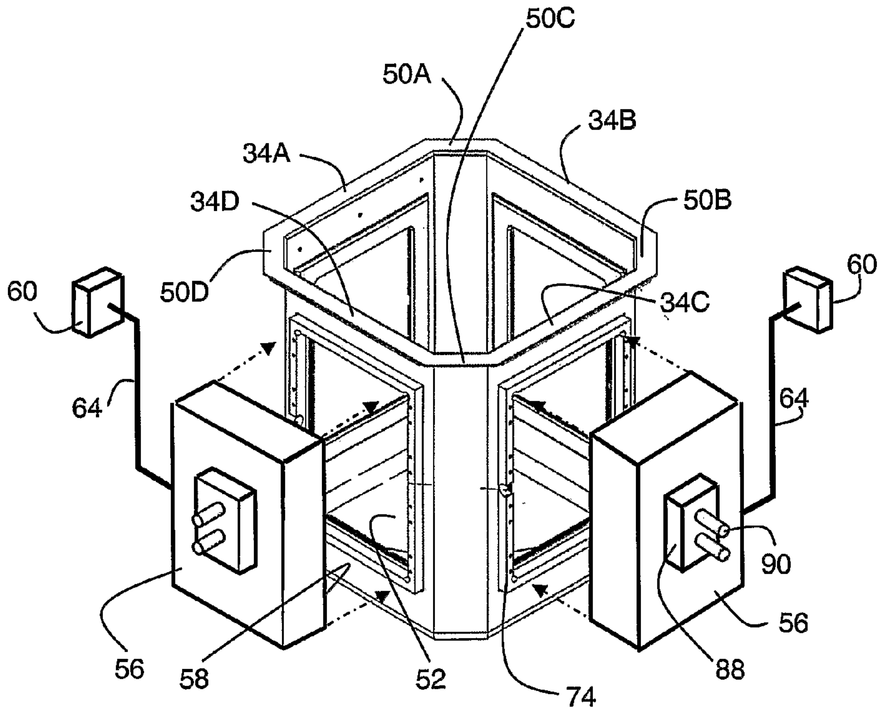
(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ,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

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) **Title:** APPARATUS FOR TREATING PARTICLES AND LIQUIDS BY ULTRASOUND



(57) **Abstract:** Apparatus for treating solid particulates and/or liquids by ultrasound is disclosed. The apparatus comprises a plurality of ultrasonic transducer elements, and a liquid receiving container. The liquid receiving container has a plurality of side walls, each formed with at least one window, such that each window is sealingly engaged with one ultrasonic transducer element.

WO 2006/103671 A1

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

APPARATUS FOR TREATING PARTICLES AND LIQUIDS BY ULTRASOUND

FIELD AND BACKGROUND OF THE INVENTION

The present invention relates to ultrasound, and more particularly, to an apparatus for treating particles and liquids by ultrasonic cavitation.

Prior techniques for physicochemical treatment of various liquids and liquid mixtures by acoustic cavitation are well known. These processes are carried out in acoustic cavitation vessels that are generally of two types. Generally, in these acoustic cavitation vessels, an intense acoustic field is produced by means of ultrasound transducer coupled to the liquid volume to be processed.

When the acoustic intensity produced in the liquid exceeds a certain threshold which depends on the nature of the liquid, temperature, pressure and gases in solution, a spontaneous production of cavitation bubbles happens in a few microseconds. The implosion of these bubbles produces a phenomenon of extreme violence called cavitation. Within the cavitation bubbles, the temperature can be rather large (a few thousands of degrees), and the implosion produces spherical shock waves with large acoustic pressure (several hundreds to a few thousands of atmospheres). These extreme conditions are the sources of diverse physical phenomena, including rupture of molecules, formation of free radicals, ionization of water and the like.

Ultrasound, therefore, has many practical applications. For example, U.S. Patent No. 4,156,593 discloses a technique for size reduction of coal particles for separating contaminants in the presence of ultrasonic cavitation.

U.S. Patent No. 5,035,363 discloses a system wherein the particle size of energetic explosive materials is reduced by subjecting slurry containing the explosive materials in an inert liquid to intense acoustic cavitation from an ultrasound generator for a short time. Particulates of the explosive materials are rapidly ground to a small particle size while minimizing the danger of detonation.

Experience has shown that the shape of the particles is of significant importance, and more precisely, it is highly desirable that the ground particles have smooth surfaces and a generally rounded shape, so as to improve the flowability of the particles. For example, when a dry powder is used in the preparation of a formulation, the quality of the formulation as well as its preparation efficiency, depends, not only on the production process and machinery, but also on the physical characteristics of the particles in the powder. This is due to the known processing difficulties associated with powder materials, including adherence of cohesive materials to containing surfaces, consolidation during transportation and storage and the like.

Thus, in order to utilize mass-production technology in the encapsulation of dry powder, it is necessary that such compositions have desirable flow characteristics permitting rapid flow through high speed encapsulators without clumping or aggregation.

It is further desired that the powder will exhibit enhanced packing characteristics to allow the use of automatic machinery. Good packing characteristics can facilitate the production of relatively high-potency formulations.

The above characteristics are also desirable when the substances are marketed as powder or granular composition, as in the case of, for example, food products (*e.g.*, table sugar, cocoa, coffee, pediatric formulas) cosmetic products and the like. For example, high flowability facilitates efficient production of beverages from the powder or granular composition. In the pharmaceutical industry, the above characteristics are desirable in the production of suspensions or formulations containing excipients or carriers, *e.g.*, preparations of controlled release products.

A method and apparatus for shaping solid particulate material by ultrasonic cavitation is disclosed in U.S. Patent No. 6,669,122 to Kaully et al. The method comprises forming raw slurry of the starting material, in a liquid which is a partial solvent of said material, and submitting the slurry to treatment by ultrasound transducers to produce therein ultrasonic vibrations. The ultrasonic shaping occurs within a cavitation vessel, provided with a stirrer which stirs the slurry during treated. The transducers are mounted by means of hooks on a cavitation vessel.

Experiments performed by the Inventors of the present invention, revealed, however, that the shaping capability of this apparatus is not satisfactory. For example, it was found that the distribution of ultrasonic energy with the slurry is not uniform, leaving a certain amount of particles less or not affected by the cavitation.

The present invention provides solutions to the problems associated with prior art techniques aimed at treating particles by ultrasound.

SUMMARY OF THE INVENTION

According to one aspect of the present invention there is provided an apparatus for treating solid particulates and/or liquids by ultrasound. The apparatus comprises a plurality of ultrasonic transducer elements; and a liquid receiving container, having a plurality of side walls, each formed with at least one window, such that each window is sealingly engaged with one ultrasonic transducer element.

According to further features in preferred embodiments of the invention described below, each of the side walls is flat, and each the ultrasonic transducer elements comprises a flat front surface, such that the flat front surface is substantially parallel to an inner surface of a respective side wall. According to still further features in the described preferred embodiments the flat front surface is substantially coplanar with the inner surface of the respective side wall.

According to still further features in the described preferred embodiments each of the side walls is curved, and each the ultrasonic transducer elements comprises a curved front surface, such that a curvature of the curved front surface substantially matches a curvature of an inner surface of a respective side wall. According to still further features in the described preferred embodiments the curved front surface is substantially flush with the inner surface of the respective side wall.

According to still further features in the described preferred embodiments the receiving container is substantially devoid of any laterally extending surfaces, such that when slurry is applied therein, a uniform dispersion of particles being present in the slurry is maintained.

According to still further features in the described preferred embodiments the apparatus further comprises a stirring mechanism, for establishing a motion of a liquid or slurry present in the receiving container.

According to still further features in the described preferred embodiments the apparatus further comprises a temperature reducing arrangement being in thermal communication with an outside surface of the plurality of side walls and the plurality of ultrasonic transducer elements.

According to still further features in the described preferred embodiments the liquid receiving container is a double walled vessel having an inner wall and an outer wall, and further wherein the temperature reducing arrangement comprises a conduit defined between the inner wall and the outer wall.

According to still further features in the described preferred embodiments the conduit is filled with a chilling liquid capable of absorbing heat from the inner walls and the at least one ultrasonic transducer element.

According to still further features in the described preferred embodiments the apparatus further comprising a fluid circulation mechanism being in fluid communication with the conduit, and operable to establish circulation of the chilling liquid between the conduit and a chilling zone thereby to repetitively chill the chilling liquid.

According to still further features in the described preferred embodiments the liquid receiving container comprises a base formed with at least one draining port. According to still further features in the described preferred embodiments the base inclined downwards towards the draining port.

According to still further features in the described preferred embodiments the apparatus further comprising a support framework for securing the ultrasonic transducer element to the window.

According to still further features in the described preferred embodiments the support framework comprises an external support rim sealingly bearing against an inner surface of a respective side wall and an inner support rim supporting the ultrasound transducer element.

According to still further features in the described preferred embodiments the apparatus further comprising a sealing gasket extending between the support framework and the ultrasound transducer element.

According to still further features in the described preferred embodiments the support framework has inner and outer chamfered or rounded edges so as to minimize or eliminate substantially laterally extending surfaces within the receiving container.

According to still further features in the described preferred embodiments the apparatus further comprising at least one ultrasound generator operatively associated with at least one ultrasound transducer element for producing ultrasonic vibrations within the receiving container.

According to still further features in the described preferred embodiments each ultrasonic transducer element is secured to the support framework by a securing flange embracing the ultrasonic transducer element.

The present invention successfully addresses the shortcomings of the presently known configurations by providing apparatus for treating solid particulates and/or liquids by ultrasound which enjoy properties far exceeding the prior art.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. In case of conflict, the patent specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is herein described, by way of example only, with reference to the accompanying drawings. With specific reference now to the drawings in detail, it is stressed that the particulars shown are by way of example and for purposes of illustrative discussion of the preferred embodiments of the present invention only, and are presented in the cause of providing what is believed to be the most useful and readily understood description of the principles and conceptual aspects of the invention. In this regard, no attempt is made to show structural details of the invention in more detail than is necessary for a fundamental understanding of the invention, the description taken with the drawings making apparent to those skilled in the art how the several forms of the invention may be embodied in practice.

In the drawings:

FIGs. 1A-B are schematic illustrations of a prior art apparatus, for shaping slurry by ultrasound;

FIG. 2 is a schematic illustration of an apparatus for treating particles and liquids by ultrasonic cavitation, according to a preferred embodiment of the present invention;

FIG. 3 is a schematic illustration of a double walled vessel of the apparatus, according to a preferred embodiment of the present invention;

FIG. 4 is a schematic illustration of a liquid receiving container of the apparatus, according to a preferred embodiment of the present invention;

FIGs. 5A-B are schematic illustrations of a support framework, supporting ultrasound transducer elements of the apparatus, according to a preferred embodiment of the present invention;

FIG. 6 is a schematic illustration of a side view of a ultrasound transducer element secured to one of the walls of the liquid receiving container, according to various exemplary embodiments of the present invention;

FIGs. 7A-B are schematic illustrations of a perspective bottom view (Figure 7A) and a side view (Figure 7B) of the double walled vessel, according to various exemplary embodiments of the present invention

FIG. 8 is a schematic illustration of a prototype apparatus manufactured according to the teachings of preferred embodiments of the present invention and used for the production of various types rounded particles;

FIGs. 9A-C are images of: the raw sucrose particles (Figure 9A), sucrose particles of the present embodiments (Figure 9B) and the prior art particles (Figure 9C);

FIGs. 10A-D are images of: 200-600 micrometer (Figures 10A-B), 600-1200 micrometer (Figures 10C) and 100-250 micrometer (Figures 10D) raw fructose particles;

FIG. 11A is an image of 200-600 micrometer rounded fructose particles prepared in a slurry of methanol and fructose, according to a preferred embodiment of the present invention;

FIG. 11B is an image of 200-600 micrometer rounded fructose particles prepared in a slurry of ethanol and fructose, according to a preferred embodiment of the present invention;

FIG. 11C is an image of 600-1200 micrometer rounded fructose particles prepared in a slurry of methanol and fructose, according to a preferred embodiment of the present invention;

FIG. 11D is an image of 600-1200 micrometer rounded fructose particles prepared in a slurry of ethanol and fructose, according to a preferred embodiment of the present invention;

FIG. 11E is an image of 100-250 micrometer rounded fructose particles prepared in a slurry of ethanol and fructose, according to a preferred embodiment of the present invention;

FIG. 12 is an image of raw diltiazem hydrochloride particles;

FIG. 13 is an image of rounded smooth diltiazem hydrochloride particles produced according to a preferred embodiment of the present invention;

FIG. 14 is an image of raw metformin particles;

FIG. 15 is an image of rounded smooth metformin particles produced according to a preferred embodiment of the present invention;

FIG. 16 is an image of raw oxcarbazepine particles;

FIG. 17 is an image of rounded smooth oxcarbazepine particles produced according to a preferred embodiment of the present invention;

FIGs. 18A-C are images of three samples of particles used as an input to image processing software;

FIG. 19 is an image showing raw sucrose particles after image processing; and

FIGs. 20A-C are histograms describing the sphericity for the particles of Figures 18A-C, respectively.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present embodiments comprise an apparatus which can be used for treating particles and liquids by ultrasonic cavitation. Specifically, the apparatus of the present embodiments can be used for size reduction, disintegration or shaping of particles and expediting chemical reactions and other crystallization or precipitation processes for production of micro- or nanoparticles.

The principles and operation of present embodiments may be better understood with reference to the drawings and accompanying descriptions.

For purposes of better understanding the present invention, as illustrated in Figures 2-20 of the drawings, reference is first made to the construction and operation of a conventional (*i.e.*, prior art) apparatus as illustrated in Figures 1A-B.

Before explaining at least one embodiment of the invention in detail, it is to be understood that the invention is not limited in its application to the details of construction and the arrangement of the components set forth in the following description or illustrated in the drawings. The invention is capable of other embodiments or of being practiced or carried out in various ways. Also, it is to be understood that the phraseology and terminology employed herein is for the purpose of description and should not be regarded as limiting.

Referring now to the drawings, Figures 1A-B illustrates a prior art apparatus **1**, for shaping slurry by ultrasound. Apparatus **1** includes a cavitation vessel **10** in which the cavitation and the shaping of the slurry occurs. Cavitation vessel **10** is provided with double wall **11**, forming a space for a cooling fluid introduced through an inlet **12** and discharged through an outlet **13**. Bottom **14** of vessel **10** is slanted to facilitate discharge of the slurry of shaped particles from the latter. An outlet **15** is provided in the center of slanted bottom **14**. Numeral **16** designates posts which occupy spaces that are not in the effective zone for the cavitation process. Ultrasound transducers **18** are mounted by means of hooks **19** on cavitation vessel **10**. The ultrasound generators may be of any type, such as known in the art. The ultrasonic vibrations gradually transform the raw slurry to a shaped slurry.

A major limitation of prior art apparatus **1** is that the anterior of vessel **10** is not adapted to allow uniform distribution of ultrasound energy therein. Particles present in the slurry oftentimes reach regions in which the energy density is rather low, and are therefore not affected by the cavitation. In particular, the existence of "dead zones" (posts **16**) presents a drawback, whereby particles may accumulate therein and not participate in the process. Even when transducers **18** are positioned closely to one another, they do not completely block the flow of slurry into posts **16**. Moreover, as the transducers are mounted by hooks to the upper side of vessel **10**, the dynamic process of ultrasonic cavitation together with rapid stirring, generates vibrations which in turn dislocate the transducers. As a result of the dislocation, gaps are formed between the transducers, and more slurry is accumulated in the "dead zones".

While conceiving the present invention it has been hypothesized and while reducing the present invention to practice it has been realized that the above limitations can be overcome by forming windows at the walls of the vessel and introducing ultrasonic transducer elements in the windows.

Figure 2 illustrates an overall view of an apparatus **20** for treating particles and liquids by ultrasonic cavitation, according to a preferred embodiment of the present invention. Apparatus **20** can be used in many applications, including, without limitation, grinding and shaping of particles, ionization of liquids (*e.g.*, water), degrading of organic compounds, cleaning and erosion of surfaces, acceleration of the chemical reactions, melting of particulates, crystallization and precipitation of micro and/or nanoparticles, and the like.

Apparatus **20** preferably comprises a double walled vessel **24** which is optionally mounted on a support structure **26**. Vessel **24** is better illustrated in Figure 3. According to a preferred embodiment of the present invention vessel **24** comprises a liquid receiving container **34** surrounded by an exterior container **36** with a chilling liquid conduit **38** extending therebetween. Conduit **38** is preferably liquid tight and has a temperature reducing arrangement, *e.g.*, in the form of a coil extending within conduit **38** for heat exchange via a cooling liquid flowing through the coil (not seen but only an inlet segment thereof **40** in Figure 2). Extending between containers **34** and **36** are a plurality of supporting and reinforcing ribs **41**. Preferably, receiving container **34** is substantially devoid of any laterally extending surfaces, such that when slurry or liquid is applied therein, a uniform dispersion of particles present in the slurry or liquid is maintained. Containers **34** and **36** preferably coaxially extend within one another such that container **34** gives rise to a treating zone **44**.

Container **34** is better illustrated in Figure 4. In the preferred embodiment illustrated in Figure 4, container **34** has four side walls, designated **34A, 34B, 34C** and **34D**, interconnected to one another with chamfered wall portions **50A-50D**. However, this need not necessarily be the case as for some applications it may be desired to manufacture container **34** with a different number of side walls and/or different number of chamfered wall portions. The inner surfaces of the side walls and interconnecting chamfered wall portions of container **34** are substantially smooth. Additionally, the walls and the chamfered wall portions are preferably made of an acoustically reflective material. Preferably, the material is also selected so as not to interact with the liquid in the container. A representative example of a material suitable for the walls of the container is stainless steel metal or like material.

According to a preferred embodiment of the present invention at least one of the number, shape and orientation of the walls and chamfered wall portions is designed and constructed such that the acoustic reflections therefrom result in a substantially uniform distribution of acoustic field within the container. This embodiment is particularly advantageous because it prevents the formation of "dead zones" at the corners of the container.

Formed in each side wall there is a window **52** which accommodates an ultrasonic transducer element **56**. Two transducer elements are shown in the schematic illustration of Figure 4, but this should not be considered as limiting as the ordinary skilled person would know how to use the illustration to construct an apparatus having more transducer elements. Windows can also be formed in one or more of the chamfered wall portions, if desired. Transducer elements **56** are each associated with an ultrasound generator **60** extending outside of vessel **24** by means of conduit **64**.

According to a preferred embodiment of the present invention, apparatus **20** comprises a stirring mechanism, generally shown by **27**, for establishing a motion, typically rotary motion, of the slurry or liquid so as to ensure homogeneous dispersion of the particles within container **34** and uniform exposure of said particles to ultrasonic energy. The stirring mechanism is shown in Figure 2 in a form of a bridge **25** supporting a motor **28** coupled to a gear unit **30** from which extends downwardly an axle **32** fitted with one or more steering blades (not shown). Axle **32** is preferably detachable so as to allow the replacement of the steering blades and/or for maintenance. Alternatively or additionally, the stirring mechanism can provide a stream of gas which is circulated in the slurry or liquid.

Elements **56** are preferably supported by means of a support framework **74**, secured to the respective windows of container **34**. Support framework **74**, is better illustrated in Figures 5A-B (see also Figure 6). In various exemplary embodiments of the invention support framework **74**, comprises an external support peripheral rim **76** fitted for comfortably receiving within the window and secured in place by means o

f bolts **78**. An inner peripheral rim **79** is fitted for receiving transducer element **56** which tightly bears against a sealing gasket **80** received within a suitable peripheral groove **82**. Transducer element **56** is preferably secured to framework **74** by means of a bracing plate **88** tightened to framework **74** by bolts **90**. The arrangement is such that fastening bolts **90** increases tight bearing of the front surface **58** of transducer element **56** against gasket **80** to thereby ensure a liquid tight engagement therebetween. In accordance with a different embodiment (not shown), the assembly comprises the support framework and the associated transducer elements **56** are tightly secured in place by means of a support flange secured directly to the outer surface of the side wall of the receiving container by means of suitable tightening bolts.

The periphery of framework **74** preferably has a slanted inner edge **96** (chamfered in the schematic illustrations of Figures 5A and 6 but it may just as well be rounded). The width, *W*, of the portion projecting inward from the inside surface of side walls **34A-34D** is preferably of minimal dimensions so as to eliminate or reduce the problem of particles of material accumulating thereon during the process.

In the schematic illustrations of Figures 4 and 6, transducer elements **56** have a flat front surface **58**. However, this need not necessarily be the case, since, for some applications, it may be desired for the transducer elements to have curve front surfaces. In such cases, the side walls of container **34** are preferably also curved.

In any event, the front surfaces of the transducer elements are preferably flush with the inner surfaces of the side walls, such that inner surface of the container is substantially smooth. Thus, according to a preferred embodiment of the present invention the cross section of container **34** is shape-wise compatible with the shape of elements **56**. Specifically, when front surfaces **58** of elements **56** are flat, the inner surface of the walls of container **34** are also flat, whereby front surface **58** is substantially parallel, more preferably coplanar with the inner wall of container **34**. Alternatively, when front surfaces **58** are curved, the containers have a generally round cross section (*e.g.*, cylindrical containers), such that the curvatures of front surface **58** substantially match the curvature of the inner wall of container **34**. In this embodiment, front surfaces **58** are substantially co-surfaced with the inner wall of container **34**. In other words, elements **58** are positioned such that there is a minimal or no protrusion of front surface **58** inwards into container **34**.

Figures 7A and 7B schematically illustrate a perspective bottom view (Figure 7A) and a side view (Figure 7B) of containers **36** and **34**, according to various exemplary embodiments of the present invention. The base **46** of container **34** preferably has downwardly inclined surfaces extending towards a draining port **48** which, at the assembled position of apparatus **20**, can extends above a collecting container **18**. A spigot **49** preferably accommodates port **48** so as to allow control over liquid flow out of container **34**. In use, the slurry or liquid to be treated can be poured directly into treating zone **44** of liquid receiving container **34**, while spigot **49** is in a closed state preventing the slurry or liquid from exiting container **34**. In this embodiment, once the ultrasound treatment is completed, spigot **49** is brought to an open state and the treated slurry or liquid is allowed to flow into collecting container **18**.

In alternative embodiment, an additional container, such as, but not limited to, an erlenmeyer flask (not shown, see Figure 8) can be secured to base **46** or rim **76**, and the slurry or liquid is poured into the additional container. In this embodiment, the volume between the additional container and the walls of container **34** is preferably filled with a liquid medium (*e.g.*, water), mediating transducer elements **56** and the slurry or liquid to be treated. The mediating liquid medium facilitates propagation of the acoustical field from transducer elements **56** to the slurry or liquid.

The ultrasound treatment of the slurry or liquid is preferably performed by activating the ultrasound generators to produce ultrasonic vibrations in the slurry or liquid. At the same time, the stirring mechanism is preferably activated to generate rotary motion to the process medium, *e.g.*, particles in slurry, emulsion *etc.*, while being subjected to the acoustic field. Preferably, but not obligatorily, the stirring speed should be from about 100 to about 800 rpm.

The generation of ultrasonic vibration field in the slurry or liquid results in cavitation and in the production of high local pressures. The high pressure in the cavities, near the particles in the slurry, produces various effects including grinding or shaping of particles, enhancement of chemical reactions, ionization, erosion and the like.

Thus, in one embodiment apparatus **20** is used for shaping particles made of any substance, including, without limitation, food (*e.g.*, nutritional or nutraceutical) substances, pharmaceutical substances, cosmetic substances and the like. Representative examples of suitable substances, include, without limitation, disaccharide (*e.g.*, sucrose, lactose), monosaccharide (*e.g.*, fructose), vitamin (*e.g.*, folic acid, ascorbic acid), mineral (*e.g.*, calcium carbonate, magnesium hydroxide), spice (*e.g.*, peppercorn, salt), cocoa, instant coffee component, soy, pharmaceutically active ingredients (*e.g.*, Diltiazem Hydrochloride, Metformin, Oxcarbazepine), and various other substances including substances suitable for the preparation of cosmetic powders (*e.g.*, magnesium stearate). As demonstrated in the Examples section that follows, apparatus **20** is capable of manufacturing generally round particles with a substantially smooth surface.

In another embodiment, apparatus **20** is used for enhancing chemical or biological reactions. Apparatus **20** can increase the conversion, improve the yield, change the reaction pathway and/or initiate the reaction. For example, apparatus **20** can be used to enhance reactions with single electron transfer mechanisms. When a highly supersaturated solution is fed into apparatus **20**, the ultrasound induces a very large number of nuclei for crystal growth. Moreover, the ultrasound suppresses the formation of agglomerates of small crystals. Thus, apparatus **20** enables formation of small (less than 10 μm) crystals of a material. Such small crystals may be of a suitable size for use in, *e.g.*, inhalers.

In an additional embodiment, apparatus **20** is used for removing organic compounds from a liquid medium. In this embodiment, apparatus **20** the stirring mechanism generates or deliver a stream of gas to be circulated in the liquid medium. The combination of ultrasound waves and gas circulation leads to a selective removal of functionalized organic compounds, substantially without the constituents of the liquid medium, such as a solvent, other than the functionalized organic compounds to be removed, being in any way affected, degraded or destroyed. The circulation of the gas is conducive to cavitation and to evacuating the compounds to be removed, and also the gases derived from the decomposition of the functionalized organic composition.

In still another embodiment, apparatus **20** is used for inducing hydrogen desorption from a metal hydride. Thus, slurry containing a hydride powder and a liquid medium can be subjected to ultrasound of adjusted intensity. Hot spots created by acoustic cavitation release hydrogen, without significant increase of the total temperature of the system. Apparatus **20** thus facilitates an easy and efficient hydrogen desorption.

The preferred ultrasound energy density within container **34** is from about 1 to about 100 watts per liter. The frequency of the ultrasound waves produced by the transducer elements is preferably selected in accordance with the application for which apparatus **20** is employed. For example, when apparatus **20** is used for grinding, relatively low ultrasound frequencies are preferably used (say, below 25 KHz). When apparatus **20** is used for shaping particles, higher frequencies (above 25 KHz) are more preferred. It is to be understood, however, that these values should not be considered as limiting. In particular, when apparatus **20** hosts a particular chemical reaction, the ultrasound frequency is selected to enhance this specific chemical reaction.

As used herein the term "about" refers to ± 10 %.

Additional objects, advantages and novel features of the present invention will become apparent to one ordinarily skilled in the art upon examination of the following examples, which are not intended to be limiting. Additionally, each of the various embodiments and aspects of the present invention as delineated hereinabove and as claimed in the claims section below finds experimental support in the following examples.

EXAMPLES

Reference is now made to the following examples, which together with the above descriptions illustrate the invention in a non limiting fashion.

EXAMPLE 1

Production of Rounded Sucrose Particles

A prototype apparatus was built according to the teaching of the present embodiments and used for producing rounded particles of various substances. In the present Example, the prototype apparatus was tested for the production of rounded sucrose particles.

Figure 8 illustrates the experimental system, which included a liquid receiving container **150**, made of stainless steel and formed with windows **152** on its side walls. The windows accommodated flat ultrasonic transducers **154** extending coplanar with the surfaces of the side walls.

Liquid receiving container **150**, was surrounded by an exterior container **160** so as to form a conduit **162** between the walls of the inner and exterior containers. Through an inlet **163**, conduit **162** was filled with a chilling liquid which was continuously circulated via outlet **164** so as to maintain a constant temperature of about 30 °C within container **150**.

150 liter of 90 % methanol and 10 % water were poured into container **150**, and 50 Kg. of sucrose were added to the liquid in the container thus forming sucrose slurry by stirring.

The ultrasonic transducers were activated while stirring the slurry at a frequency of 25 kHz and a power of 2.5 kW, thus generating a power density of 0.015 kW/liter within the container. Following about 8 hours of treatment, the slurry was filtered under vacuum, and the sucrose was washed in methanol and dried at room temperature. A powder consisting of rounded smooth sucrose particles having average size of 300-600 micrometer was formed.

Following drying, a sample of the formed sucrose particles was subjected to BET measurement using a TriStar 3000 analyzer (Micromeritics, Georgia, USA), to obtain a specific surface area for the particles (surface area per unit mass). An averaged value of 0.03 m^2/gr was measured. For comparison, the specific surface area of a sample of prior art particles of similar size (355-500 micrometer Suglets®, purchased from NP Pharm, France), was also measured. The specific surface area of the particles of this sample was 0.27 m^2/gr. Thus, the sucrose particles produced according to the teaching of the present embodiments of the invention are characterized by a specific surface area which is about 9 times smaller than the specific surface area characterizing the prior art. As the average size of the samples was similar, the specific surface was used as a measure of the smoothness of the particles. Thus, it was demonstrated that the particles produced according to the teaching of the present embodiment are 9 times smoother than the prior art particles.

An additional estimate of the particles' smoothness was performed by analyzing the samples via Scanning Electron Microscopy (SEM).

Figures 9A-C are images of the raw sucrose particles (Figure 9A), sucrose particles of the present embodiments (Figure 9B) and the prior art particles (Figure 9C). Whereas the prior art particles revealed an average surface roughness of several micrometer, the surface of the particles prepared according to the teaching of the present embodiments was substantially smooth.

EXAMPLE 2

Production Rounded Fructose Particles

Rounded fructose particles were prepared in two experiments, using an experimental system similar to the system shown in Figure 8 and described in Example 1 hereinabove. In this example, erlenmeyer flask **156** was fastened to a external support peripheral rim **159** mounted above container **150**.

In the first experiment, a 500 ml erlenmeyer flask was used. 200 ml of methanol were poured into the erlenmeyer flask, and the volume **158** between the erlenmeyer flask and the inner walls of container **150** was filled with water. 70 gr. of fructose were added to the liquid in the erlenmeyer flask, thus forming fructose slurry. Two sizes of raw fructose particles were used: 200-600 micrometer, and 600-1200 micrometer.

The ultrasonic transducers were activated while stirring the slurry. It was found by the inventors of the present invention that frequencies from about 16 kHz to about 60 kHz, and power densities from about 0.005 to about 0.05 kW/liter are suitable. Yet, higher efficiency was achieved at a frequency of about 25 kHz and a power density of about 0.01 kW/liter. During the process, a constant temperature of about 30 °C was maintained in liquid receiving container.

Following about 3 hours of treatment, the slurry was filtered under vacuum, and the fructose was washed in methanol and dried at room temperature. A powder consisting of rounded smooth fructose particles was formed.

In the third experiment, a 3 liter erlenmeyer flask was fastened to the rim of the liquid receiving container. 1.5 liters of ethanol were poured into the erlenmeyer flask, and the volume between the erlenmeyer flask and the inner walls of the liquid receiving container was filled with water. 500 gr of fructose were added to the liquid in the erlenmeyer flask, thus forming fructose slurry. Three sizes of raw fructose particles were used in the first experiment: 100-250 micrometers, 200-600 micrometers and 600-1200 micrometers.

The ultrasonic transducers were activated while stirring the slurry, as in the first and second experiments. Following about 3 hours of treatment, the slurry was filtered by centrifuge and dried by rotary drum supplied with dry air. Powders consisting of rounded smooth fructose particles were formed.

Figures 10A-D are images of the 200-600 (Figures 10A-B), 600-1200 (Figure 10C) and 100-250 (Figure 10D) micrometer raw fructose particles.

The rounded smooth fructose particles are shown in Figures 11A-E.

Figures 11A-B are images of 200-600 micrometer rounded fructose particles of the methanol experiment (Figure 11A), and the ethanol experiment (Figure 11B).

Figures 11C-D are images of 600-1200 micrometer rounded fructose particles of the methanol experiment (Figure 11C), and the ethanol experiment (Figure 11D).

Figure 11E is an image of 100-250 micrometer rounded fructose particles of the ethanol experiment.

EXAMPLE 3

Production of Rounded Diltiazem Hydrochloride Particles

Rounded dilitiazem hydrochloride particles were prepared using an experimental system similar to the system shown in Figure 8 and described in Examples 1 and 2 hereinabove.

A 3 liter erlenmeyer flask was fastened to the rim of the liquid receiving container. 1.5 liter of propanol was poured into the erlenmeyer flask, and the volume between the erlenmeyer flask and the inner walls of the liquid receiving container was filled with water. 400 gr. of raw diltiazem hydrochloride particles were added to the liquid in the erlenmeyer flask to form slurry. The size of the raw particles was 20-45 micrometer. Figure 12 is an image of the raw diltiazem hydrochloride particles.

The ultrasonic transducers were activated while stirring the slurry. It was found by the inventors of the present invention that frequencies from about 20 kHz to about 60 kHz, and power densities from about 0.005 to about 0.05 kW/liter are suitable. Yet, higher efficiency was achieved at a frequency of about 47.5 kHz and a power density of about 0.01 kW/liter. During the process, a constant temperature of about 30 °C was maintained in liquid receiving container.

Following about 2.5 hours of treatment, the slurry was filtered through a 20 micrometer sieve and a 45 micrometer sieve, and the particles were dried by air. A powder consisting of rounded smooth diltiazem hydrochloride particles was formed.

Figure 13 is an image of 45 micrometers rounded smooth diltiazem hydrochloride particles produced in the experiment. As shown, the surface of the particles prepared according to the teaching of the present embodiments was substantially smooth.

The diltiazem hydrochloride particles were subjected to an angle of repose test. The particles were placed on a smooth tile positioned horizontally. The tile was tilted slowly each time at 1° about the horizontal axis. The angle of repose was defined as the angle at which the first particles had slide. The measured angle of repose was 48° for the powder containing the raw particles, and 38° for the powder containing the rounded smooth diltiazem hydrochloride particles, demonstrating a significant improvement of flowability in the rounded particles, compared to the raw particles.

EXAMPLE 4

Production of Rounded Metformin Particles

Rounded metformin particles were prepared using an experimental system similar to the system shown in Figure 8 and described in Examples 1 and 2 hereinabove.

A 3 liter erlenmeyer flask was fastened to the rim of the liquid receiving container. 2.5 liter of methanol was poured into the erlenmeyer flask, and the volume between the erlenmeyer flask and the inner walls of the liquid receiving container was filled with water. 700 gr. of raw metformin particles were added to the liquid in the erlenmeyer flask form slurry. The size of the raw particles was 300-600 micrometer. Figure 14 is an image of the raw metformin particles.

The ultrasonic transducers were activated while stirring the slurry. It was found by the inventors of the present invention that frequencies from about 16 kHz to about 60 kHz, and power densities from about 0.005 to about 0.05 kW/liter are suitable. Yet, higher efficiency was achieved at a frequency of about 25 kHz and a power density of about 0.01 kW/liter. During the process, a constant temperature of about 30 °C was maintained in liquid receiving container.

Following about 2 hours of treatment, the slurry was filtered under vacuum and the powder was dried at room temperature. A powder consisting of rounded smooth metformin particles was formed.

Figure 15 is an image of 300-600 micrometers rounded smooth metformin particles produced in the experiment. As shown, the surface of the particles prepared according to the teaching of the present embodiments was substantially smooth.

The metformin particles were subjected to a flow rate test using a Hall flow meter having a 5 millimeter diameter nozzle. The nozzle was tilted at an angle of 30°. For the powder containing the raw metformin particles, no flow was observed (zero flow). For the powder containing the rounded metformin particles, a flow rate of 10.2 gr/($cm^2 \times s$), was measured, demonstrating a vast improvement of flowability in the rounded metformin particles, compared to the raw particles.

EXAMPLE 5

Production of Rounded Oxcarbazepine Particles

Rounded oxcarbazepine particles were prepared using an experimental system similar to the system shown in Figure 8 and described in Examples 1 and 2 hereinabove.

A 1.5 liter erlenmeyer flask was fastened to the rim of the liquid receiving container. 2.5 liter of acetone was poured into the erlenmeyer flask, and the volume between the erlenmeyer flask and the inner walls of the liquid receiving container was filled with water. 600 gr. of raw oxcarbazepine particles were added to the liquid in the erlenmeyer flask to form slurry. Figure 16 is an image of the raw oxcarbazepine particles.

The ultrasonic transducers were activated while stirring the slurry. It was found by the inventors of the present invention that frequencies from about 16 kHz to about 60 kHz, and power densities from about 0.005 to about 0.05 kW/liter are suitable. Yet, higher efficiency was achieved at a frequency of about 25 kHz and a power density of about 0.01 kW/liter. During the process, a constant temperature of about 30 °C was maintained in liquid receiving container.

Following about 3.5 hours of treatment, the slurry was filtered under vacuum and the powder was dried at room temperature. A powder consisting of rounded smooth oxcarbazepine particles was formed.

Figure 17 is an image of rounded smooth oxcarbazepine particles produced in the experiment. Micronized particle population formed during the rounding process is also seen in the image.

EXAMPLE 6

Sphericity and Shape Factor

The sphericity and shape factor of several samples of particles produced in various exemplary embodiments of the invention were measured.

The samples were imaged through a transmission optical microscope (magnification: ×12.5).

Figures 18A-C show the images of raw sucrose particles (Figure 18A), 300-600 micrometer sucrose particles prepared as descried in Example 1 above (Figure 18B), and 355-500 micrometer prior art Suglets® particles, purchased from NP Pharm, France (Figure 18A).

The images were analyzed by image processing software (Buehler Omnimet®). Each image processing comprised the following steps. In a first step the particles were delineated for 1 cycle; in a second step, dark areas were defined by thresholding; in a third step, the dark areas were filled; in a fourth step, particles smaller than 20 $\times$ 20 pixels were eliminated; in a fifth step border particles were eliminated; and in a sixth step the delineation of the non-eliminated particles were processed by the octagonal kernel of the software for 3 cycles. Figure 19 is an image showing the raw sucrose particles after image processing.

Following image processing the area, A, and perimeter, P, of each particle was measured from the images. The sphericity of each particle was defined as $4\pi A/P^2$.

Figures 20A-C are histograms describing the sphericity as defined above for the samples shown in Figures 18A-C, respectively. The results of the three samples are summarized in Table 1, below.

Table 1

Sample	**No. of particles**	**sphericity**
raw sucrose	75	0.773 ± 0.05
rounded 300-600 μm sucrose	51	0.875 ± 0.027
355-500 μm Suglets® (prior art)	98	0.862 ± 0.019

As shown in Table 1, the present embodiments successfully produce round particles whose shape is sphere-like.

The sphericity of the particles was also measured using a DSA-10 image analyzer (Ankersmid Ltd., Israel). The analysis was performed during constant flow of slurry containing the particles. Images of about 1000 particles were analyzed by the image analyzer to determine the sphericity of the particles. In these measurements the sphericity was also as defined $4\pi A/P^2$. To distinguish between the sphericity values obtained as determined using the image processing software and the sphericity values obtained using the image analyzer, the latter are referred to below as "shape factor".

Beside sphericity, the DSA-10 image analyzer was used to characterize the shape of the particles by their aspect ratio, defined as the ratio between the minimal Feret and the maximal Feret of the particles.

Particles prepared in accordance with the teachings of the present embodiments shown improved shape characteristics in all categories. On the average, the particles prepared according to the teaching of the present embodiments shown a 5-20 % enhancement of the shape factor and aspect ratio and a 10-35 % enhancement of the sphericity, compared to the raw particles, demonstrating, again, the spherical nature of the particles of the embodiments.

Table 2 below summarizes the shape factor, aspect ratio and sphericity of several samples prepared in various exemplary embodiments of the invention.

Table 2

Material	Sample	No. of particles	shape factor	aspect ratio	sphericity
raw dilitiazem hydrochloride	(i)	110	0.7032	0.5416	0.5278
	(ii)	197	0.7056	0.5442	0.4773
	(iii)	226	0.6847	0.5293	0.4954
rounded dilitiazem hydrochloride above 45 μm	(i)	80	0.8211	0.6986	0.6601
	(ii)	33	0.8368	0.7053	0.6940
	(iii)	84	0.8229	0.7015	0.6572
rounded dilitiazem hydrochloride 20-45 μm	(i)	164	0.8426	0.6915	0.5106
	(ii)	61	0.8168	0.6935	0.5220
	(iii)	90	0.8467	0.6947	0.5139
rounded dilitiazem hydrochloride mix 20-45μm + 45μm	(i)	73	0.8383	0.6828	0.5315
	(ii)	92	0.8419	0.6923	0.6004
	(iii)	164	0.8279	0.6731	0.5942
raw metformin	(i)	40	0.8244	0.6900	0.6146
	(ii)	107	0.8214	0.6434	0.5675
	(iii)	85	0.8404	0.6420	0.5720
rounded metformin	(i)	54	0.8719	0.6791	0.7634
	(ii)	63	0.8739	0.6740	0.7676
	(iii)	122	0.8843	0.6904	0.7344
raw oxcarbazepine	(i)	141	0.7789	0.6102	0.4997
	(ii)	59	0.7908	0.6062	0.4760
	(iii)	177	0.7886	0.6221	0.4144
rounded oxcarbazepine	(i)	69	0.8138	0.5875	0.6103
	(ii)	102	0.7996	0.5887	0.5707
	(iii)	78	0.8174	0.5829	0.4969

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination.

Although the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all such alternatives, modifications and variations that fall within the spirit and broad scope of the appended claims. All publications, patents and patent applications mentioned in this specification are herein incorporated in their entirety by reference into the specification, to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein by reference. In addition, citation or identification of any reference in this application shall not be construed as an admission that such reference is available as prior art to the present invention.

WHAT IS CLAIMED IS:

1. An apparatus for treating solid particulates and/or liquids by ultrasound, comprising:

a plurality of ultrasonic transducer elements; and

a liquid receiving container, having a plurality of side walls, each formed with at least one window, such that each window of said at least one window is sealingly engaged with one ultrasonic transducer element of said plurality of ultrasonic transducer elements.

2. The apparatus of claim 1, wherein each of said side walls is flat, and each said ultrasonic transducer elements comprises a flat front surface, such that said flat front surface is substantially parallel to an inner surface of a respective side wall.

3. The apparatus of claim 2, wherein said flat front surface is substantially coplanar with said inner surface of said respective side wall.

4. The apparatus of claim 1, wherein each of said side walls is curved, and each said ultrasonic transducer elements comprises a curved front surface, such that a curvature of said curved front surface substantially matches a curvature of an inner surface of a respective side wall.

5. The apparatus of claim 4, wherein said curved front surface is substantially flush with said inner surface of said respective side wall.

6. The apparatus of claim 1, wherein said receiving container is substantially devoid of any laterally extending surfaces, such that when slurry is applied therein, a uniform dispersion of particles being present in said slurry is maintained.

7. The apparatus of claim 1, further comprising a stirring mechanism, for establishing a motion of a liquid or slurry present in said receiving container, while said liquid or slurry is applied with ultrasonic energy.

8. The apparatus of claim 1, further comprising a temperature reducing arrangement being in thermal communication with an outside surface of said plurality of side walls and said plurality of ultrasonic transducer elements.

9. The apparatus of claim 8, wherein said liquid receiving container is a double walled vessel having an inner wall and an outer wall, and further wherein said temperature reducing arrangement comprises a conduit defined between said inner wall and said outer wall.

10. The apparatus of claim 8, wherein said conduit is filled with a chilling liquid capable of absorbing heat from said inner walls and said at least one ultrasonic transducer element.

11. The apparatus of claim 9, further comprising a fluid circulation mechanism being is in fluid communication with said conduit, and operable to establish circulation of said chilling liquid between said conduit and a chilling zone thereby to repetitively chill said chilling liquid.

12. The apparatus of claim 1, wherein said liquid receiving container comprises a base formed with at least one draining port.

13. The apparatus of claim 12, wherein said base inclined downwards towards said draining port.

14. The apparatus of claim 1, further comprising a support framework for securing said ultrasonic transducer element to said window.

15. The apparatus of claim 14, wherein said support framework comprises an external support rim sealingly bearing against an inner surface of a respective side wall and an inner support rim supporting said ultrasound transducer element.

16. The apparatus of claim 15, further comprising a sealing gasket extending between said support framework and said ultrasound transducer element.

17. The apparatus of claim 14, wherein said support framework has inner and outer chamfered or rounded edges so as to minimize or eliminate substantially laterally extending surfaces within said receiving container.

18. The apparatus of claim 1, further comprising at least one ultrasound generator operatively associated with at least one ultrasound transducer element for producing ultrasonic vibrations within said receiving container.

19. The apparatus of claim 15, wherein each ultrasonic transducer element is secured to said support framework by a securing flange embracing said ultrasonic transducer element.

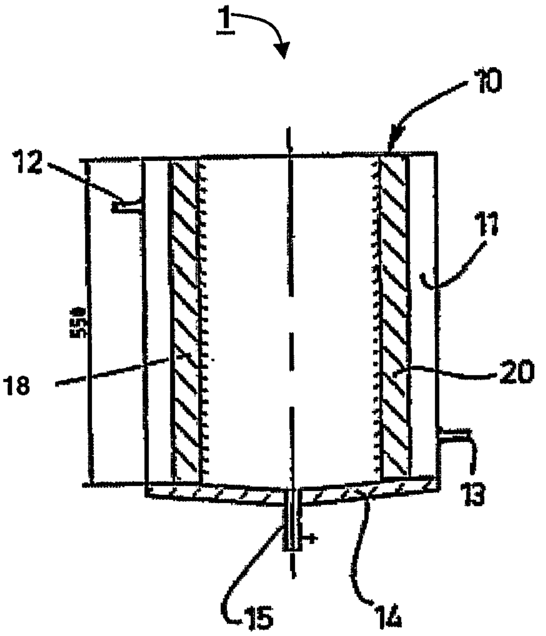


Fig. 1A (Prior Art)

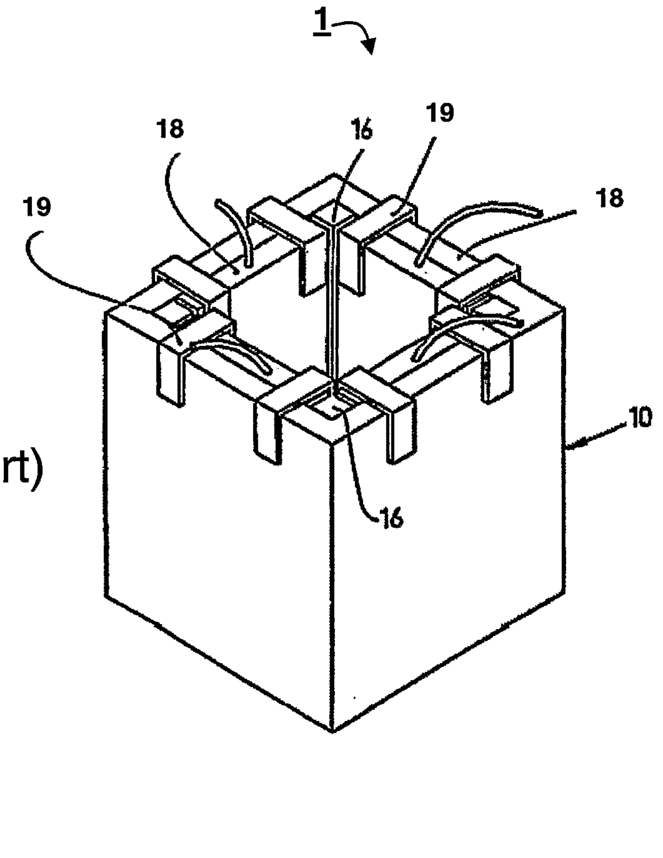


Fig. 1B (Prior Art)

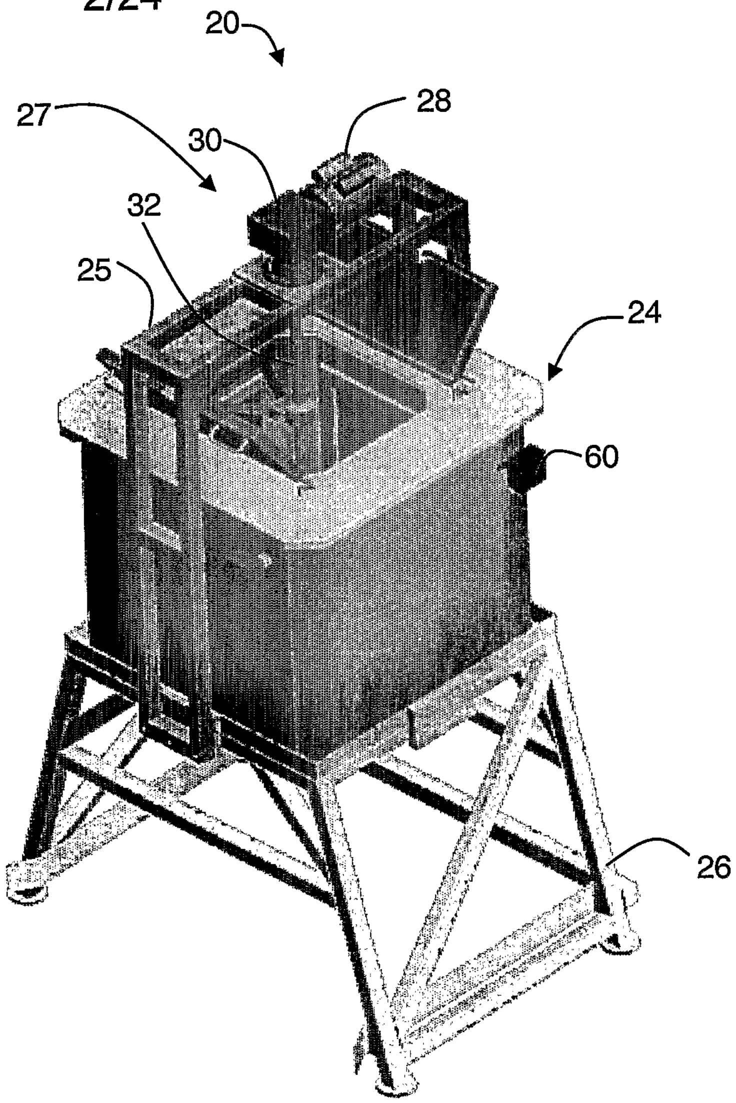
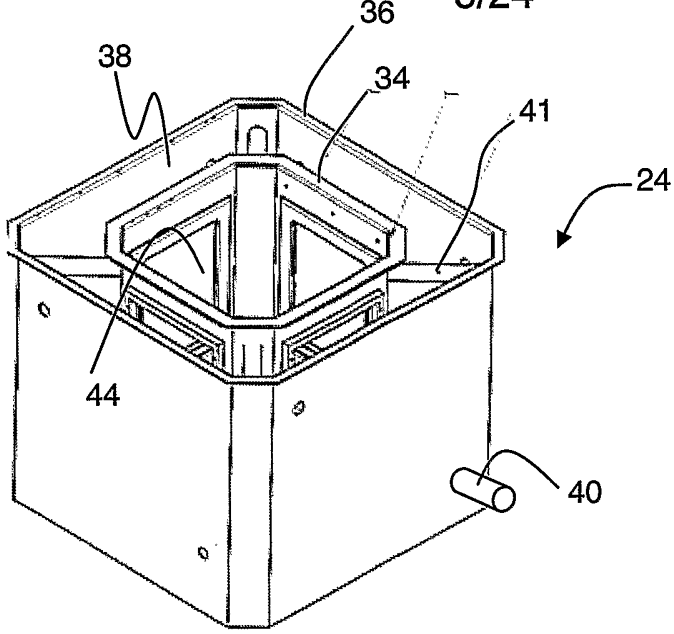


Fig. 2


36
38
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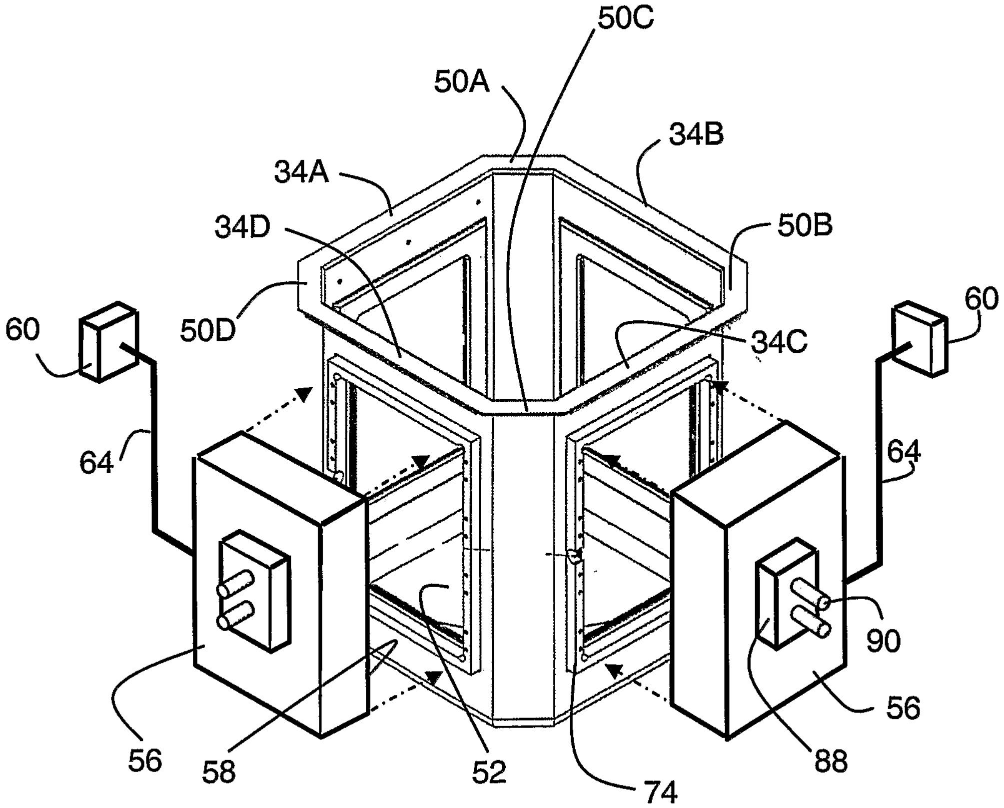
24
44
40

Fig. 3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50A
34B
34A
34D
50B
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50D
34C
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74
88

Fig. 4

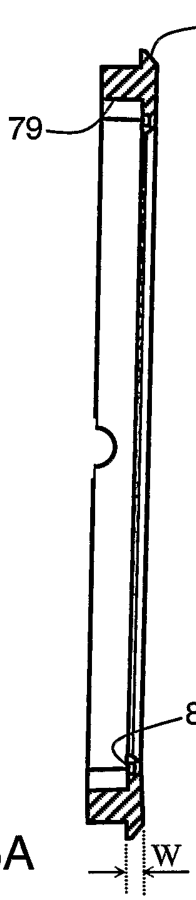

Fig. 5A

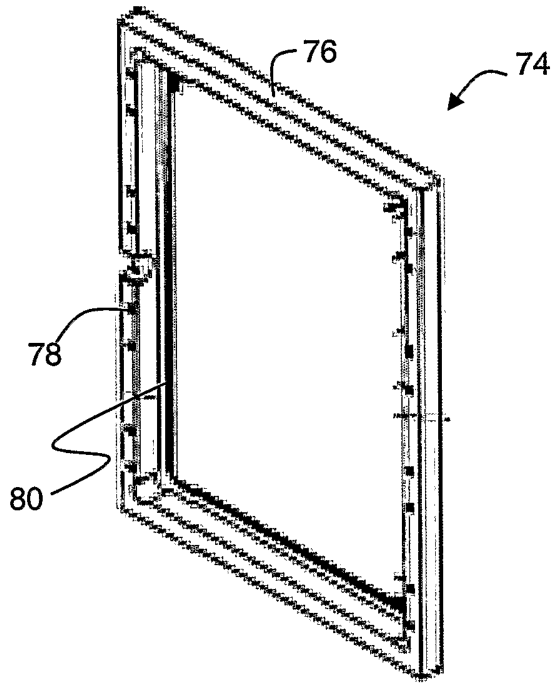

Fig. 5B

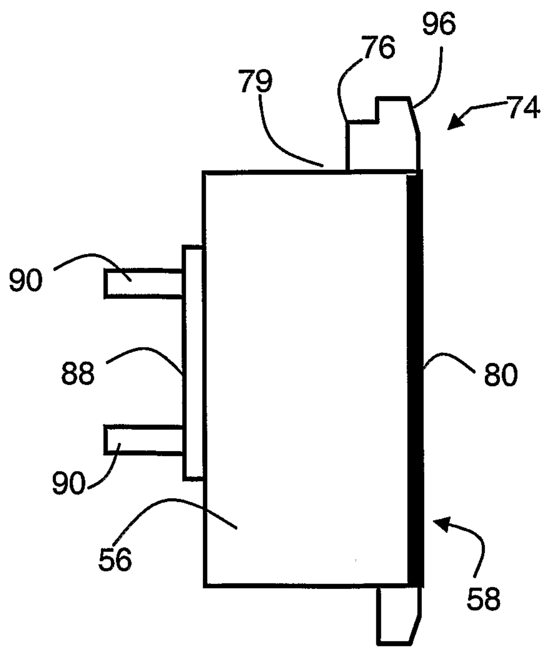

Fig. 6

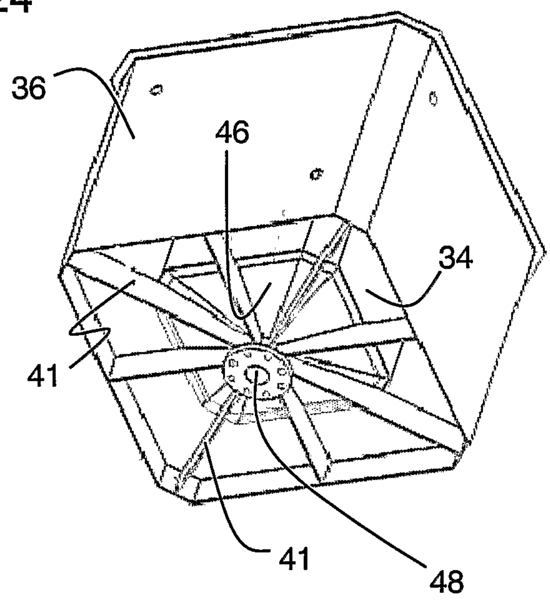

Fig. 7A

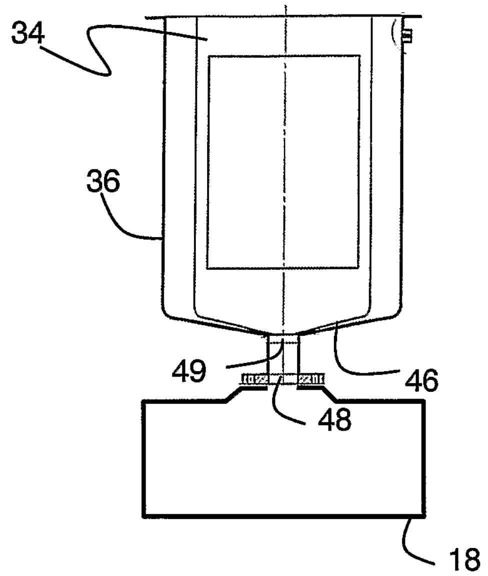

Fig. 7B

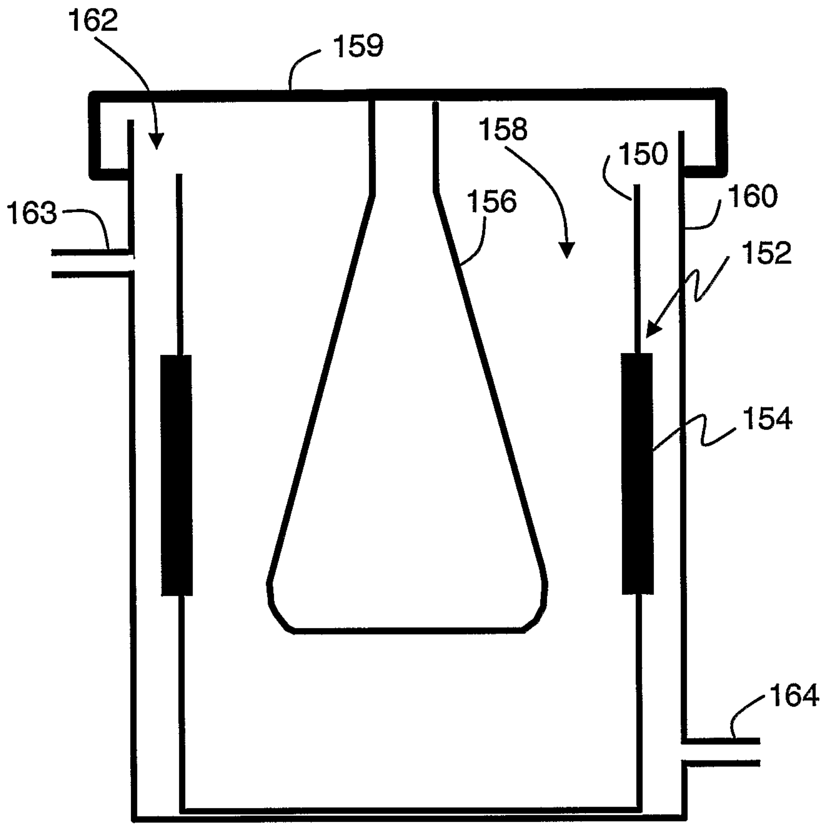

Fig. 8


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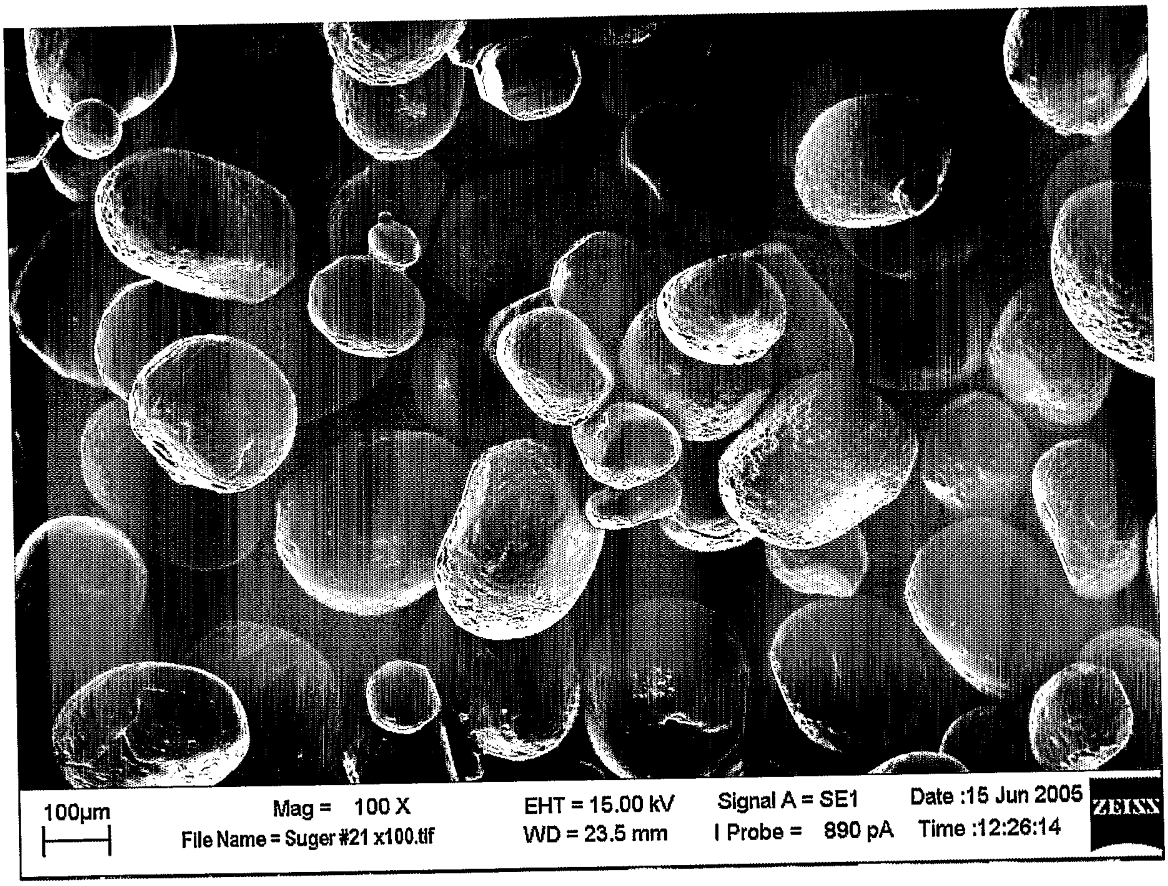
ZEISS

Fig. 9A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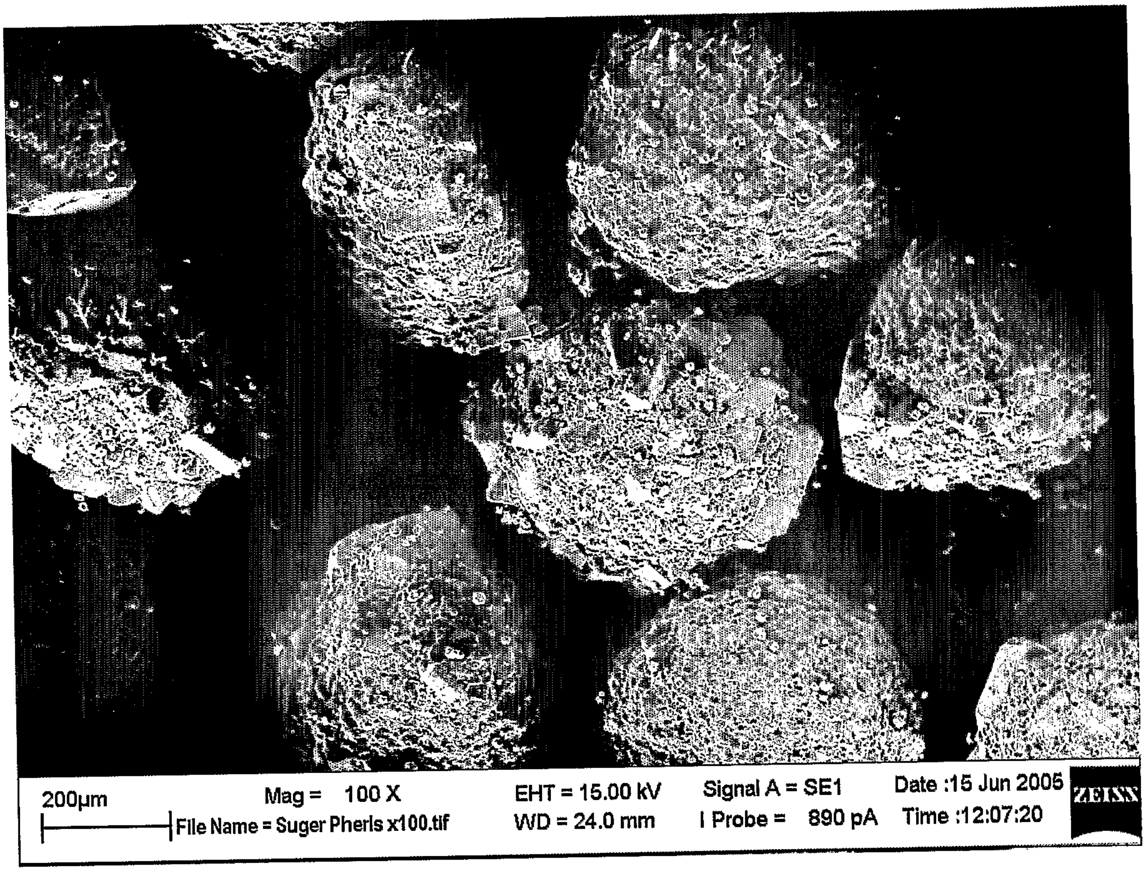
ZEISS

Fig. 9B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ZEISS

Fig. 9C

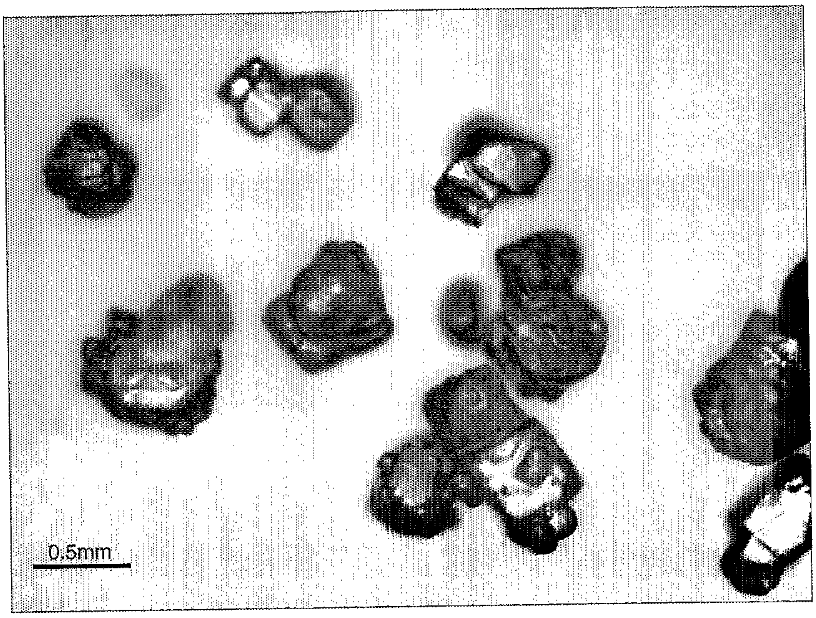


Fig. 10A

Fig. 10B

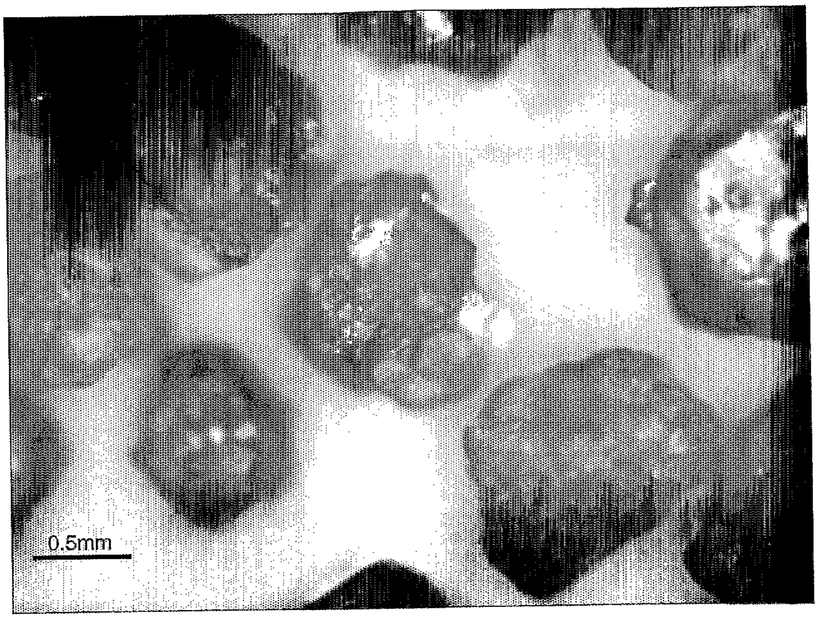


Fig. 10C

Fig. 10D

Fig. 11A

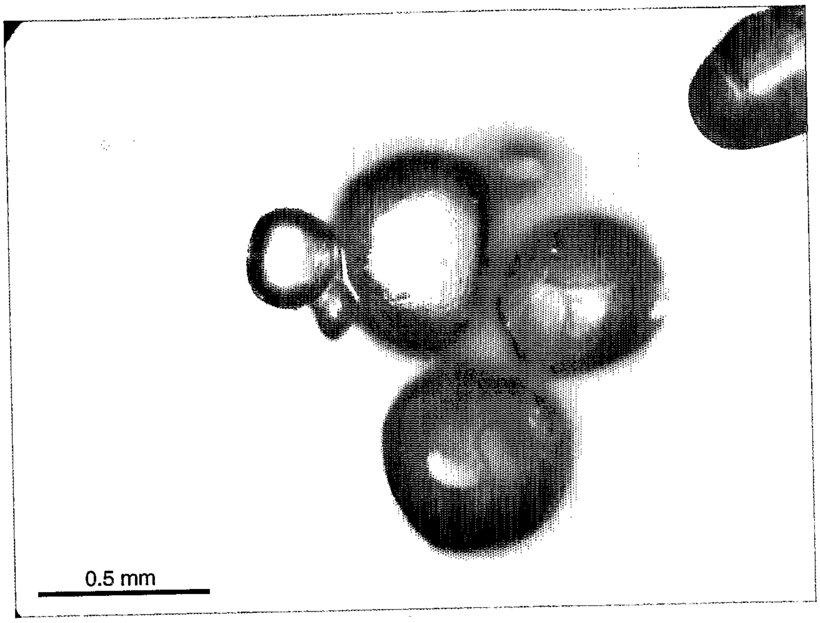


Fig. 11B

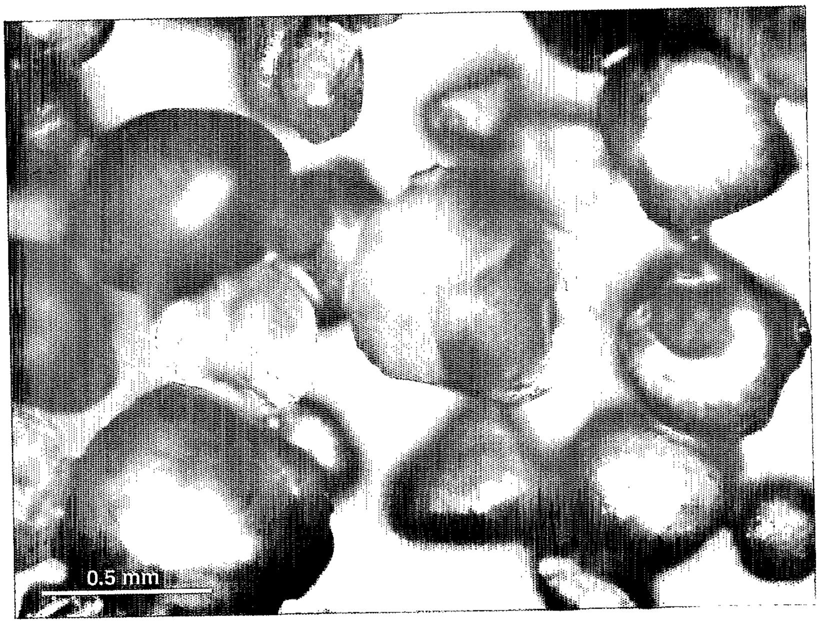


Fig. 11C

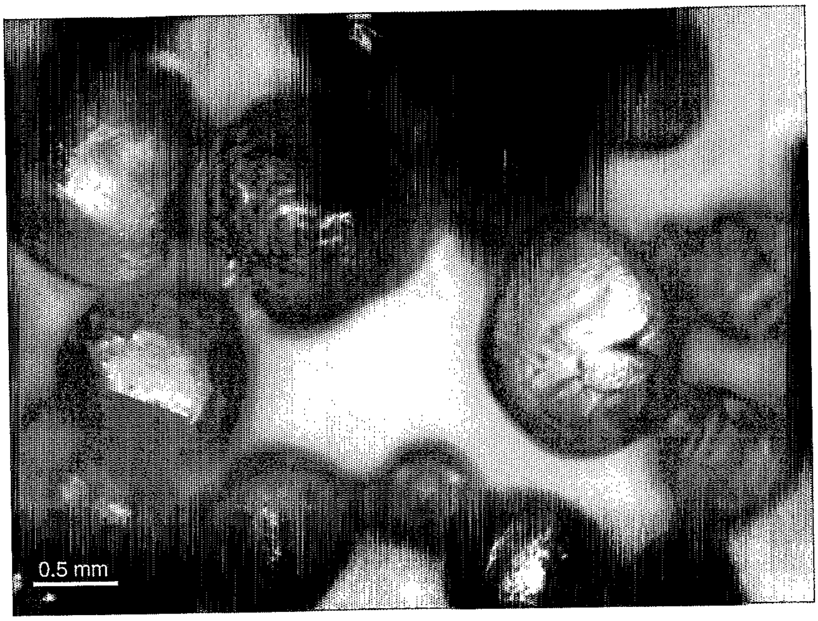
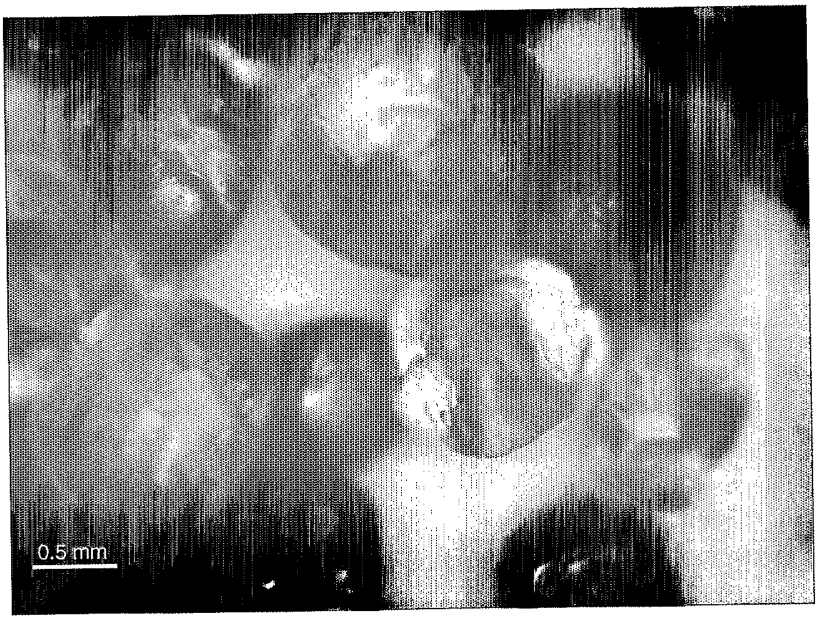


Fig. 11D



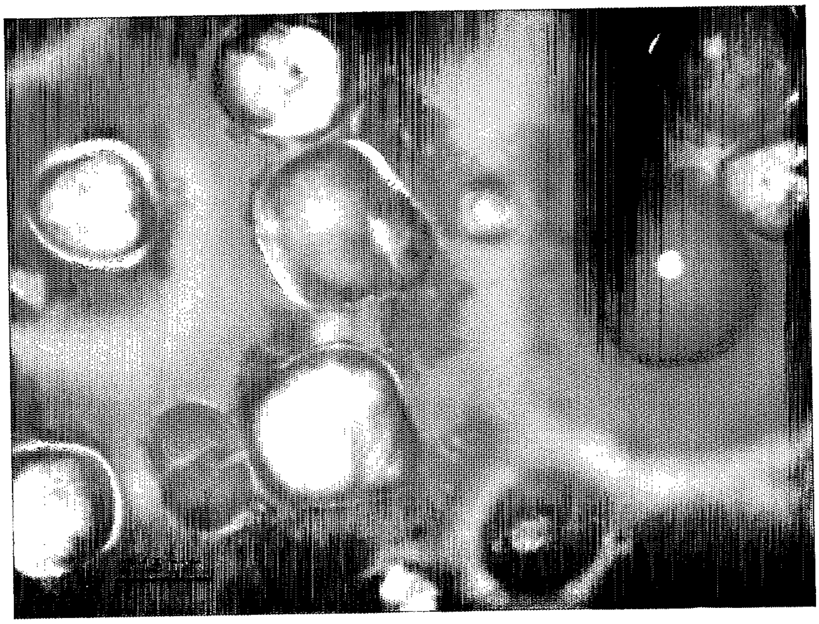


Fig. 11E

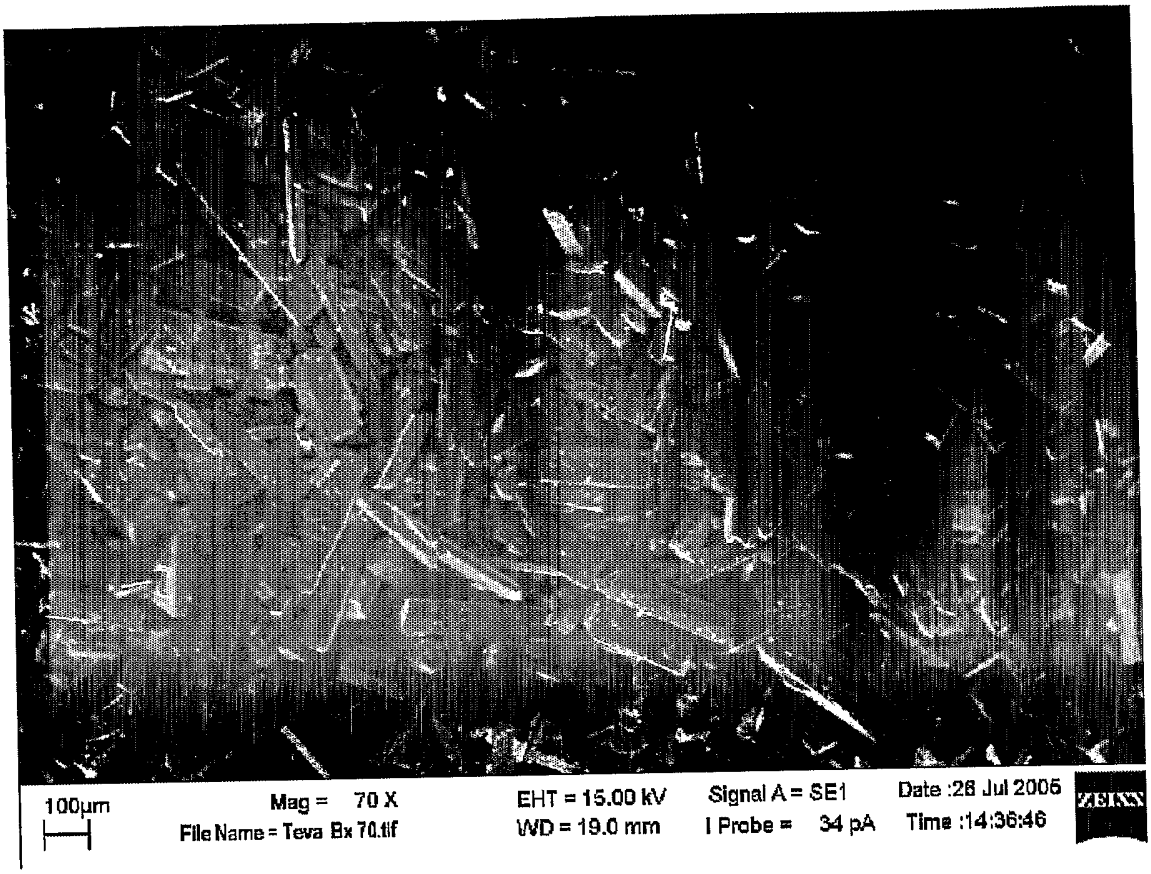

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Fig. 12

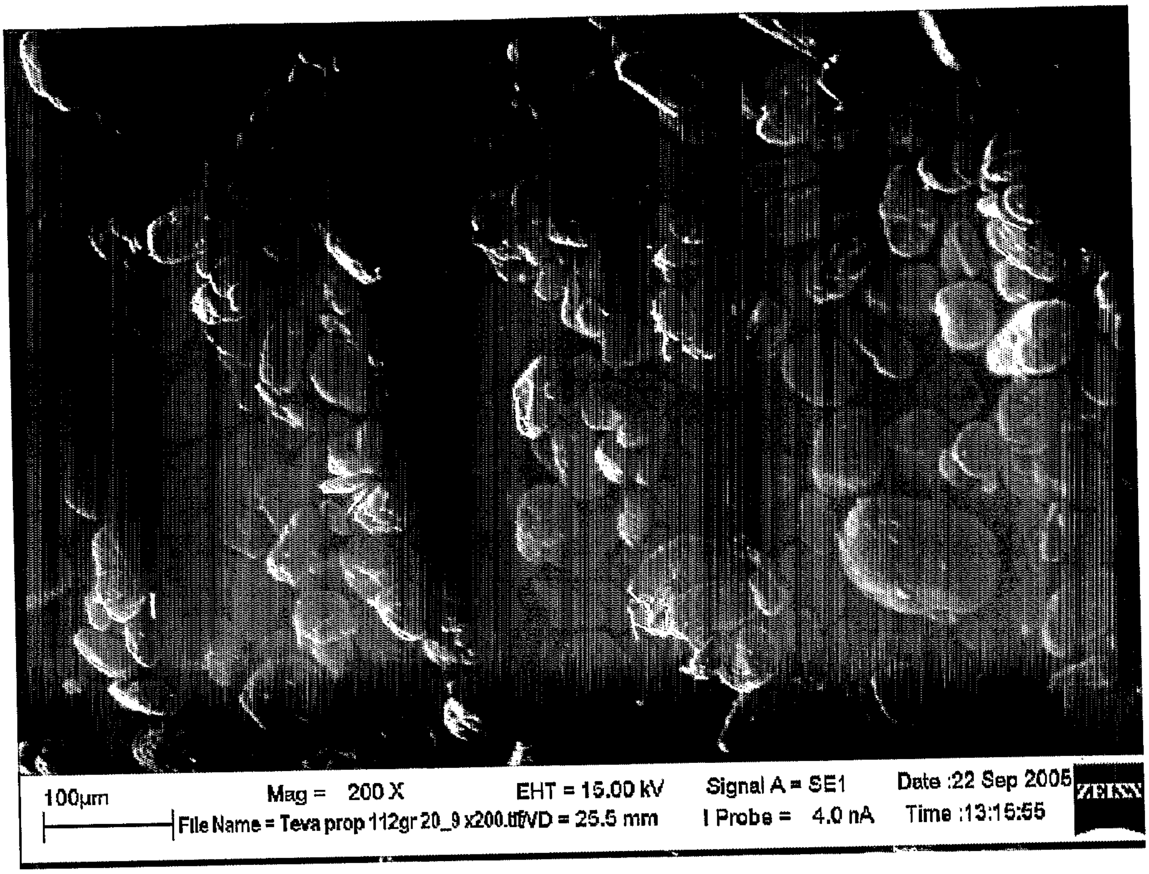
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Fig. 13

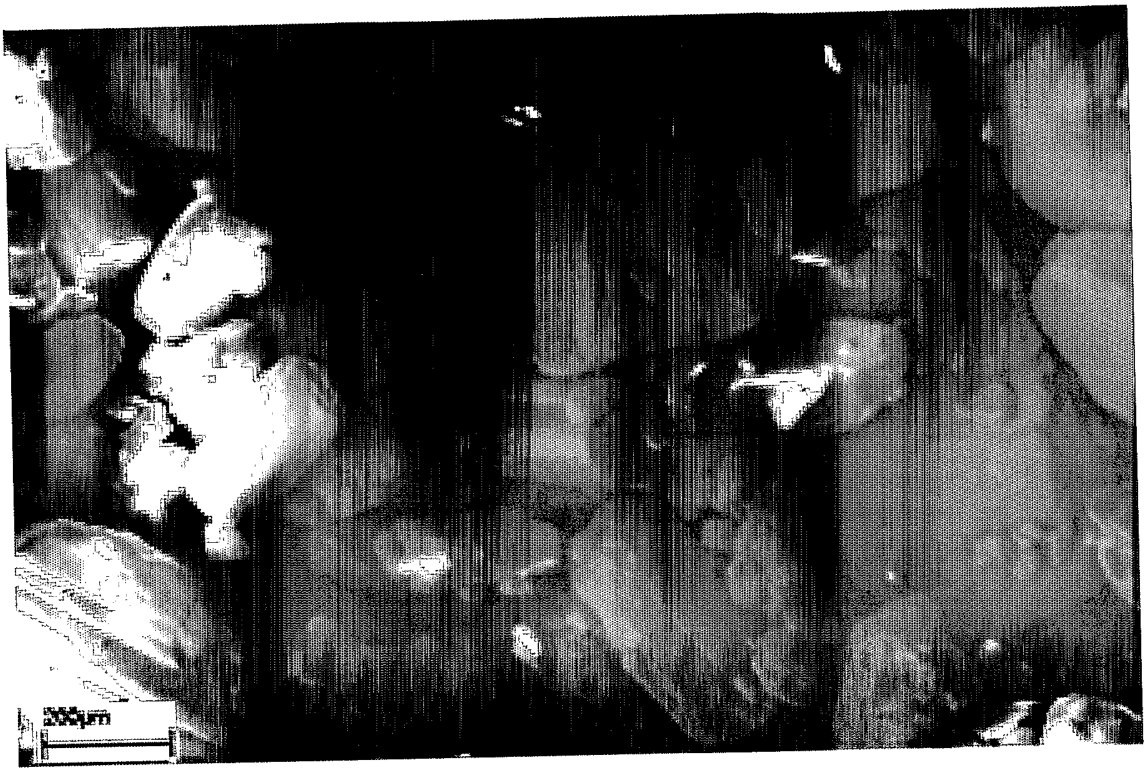


Fig. 14

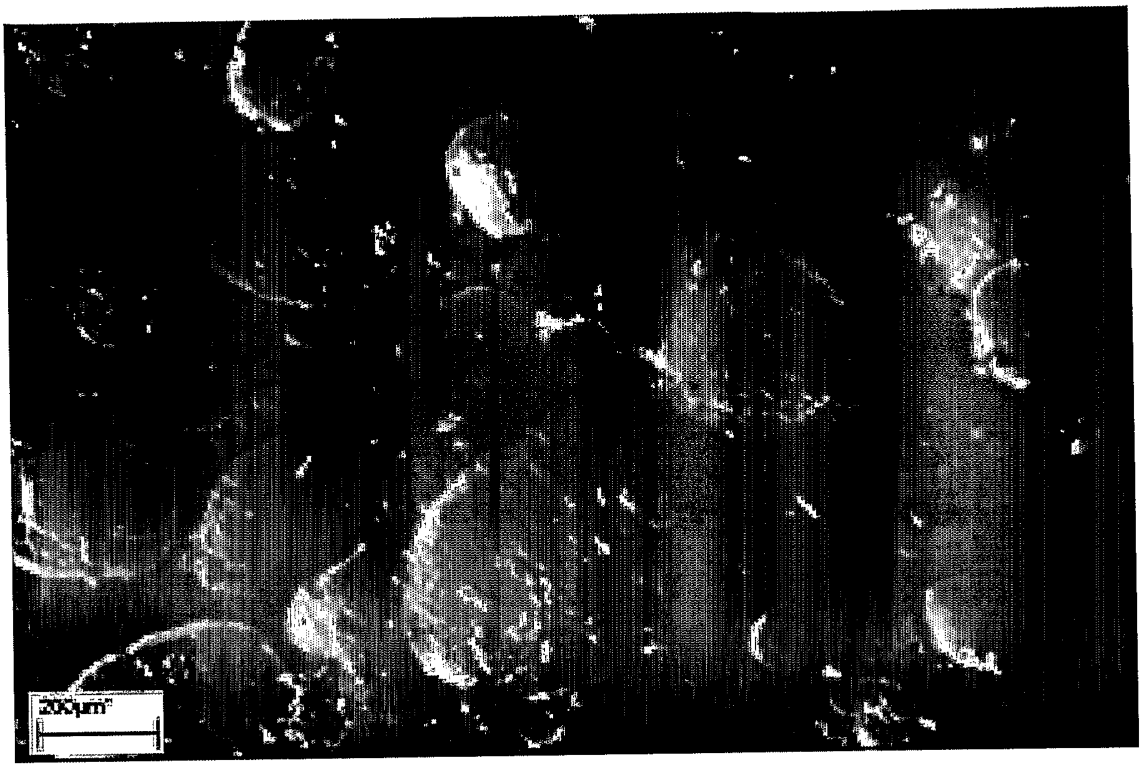


Fig. 15

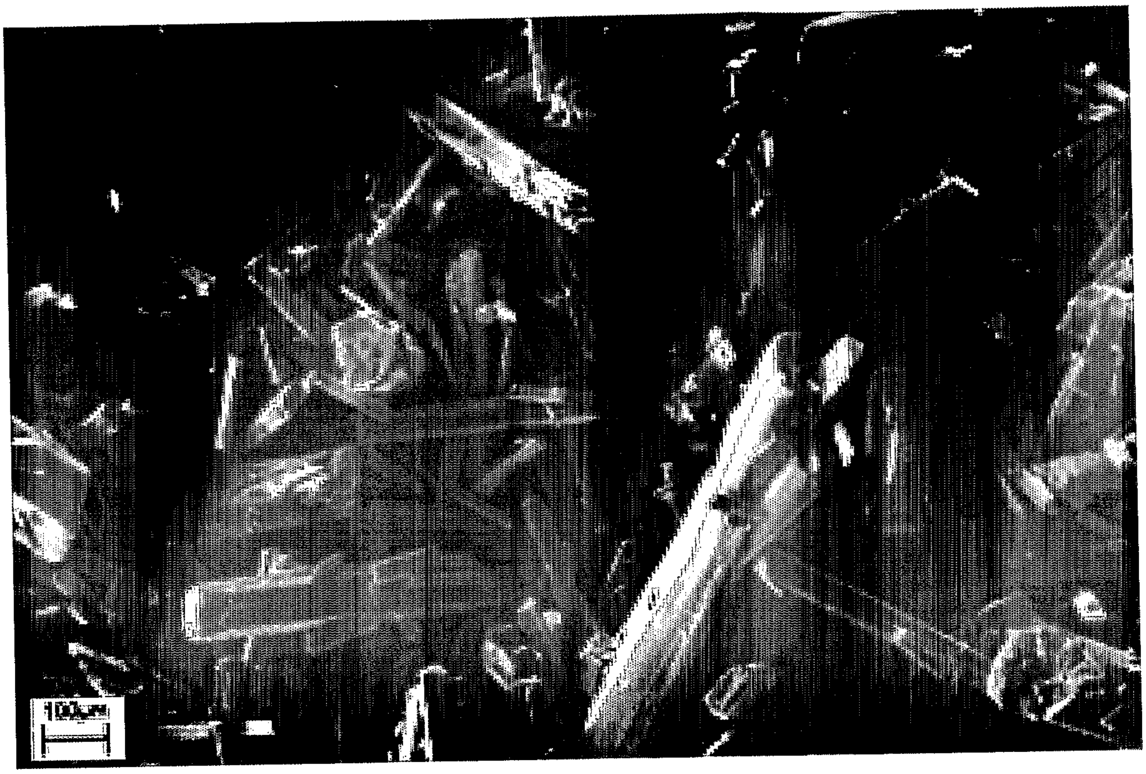


Fig. 16

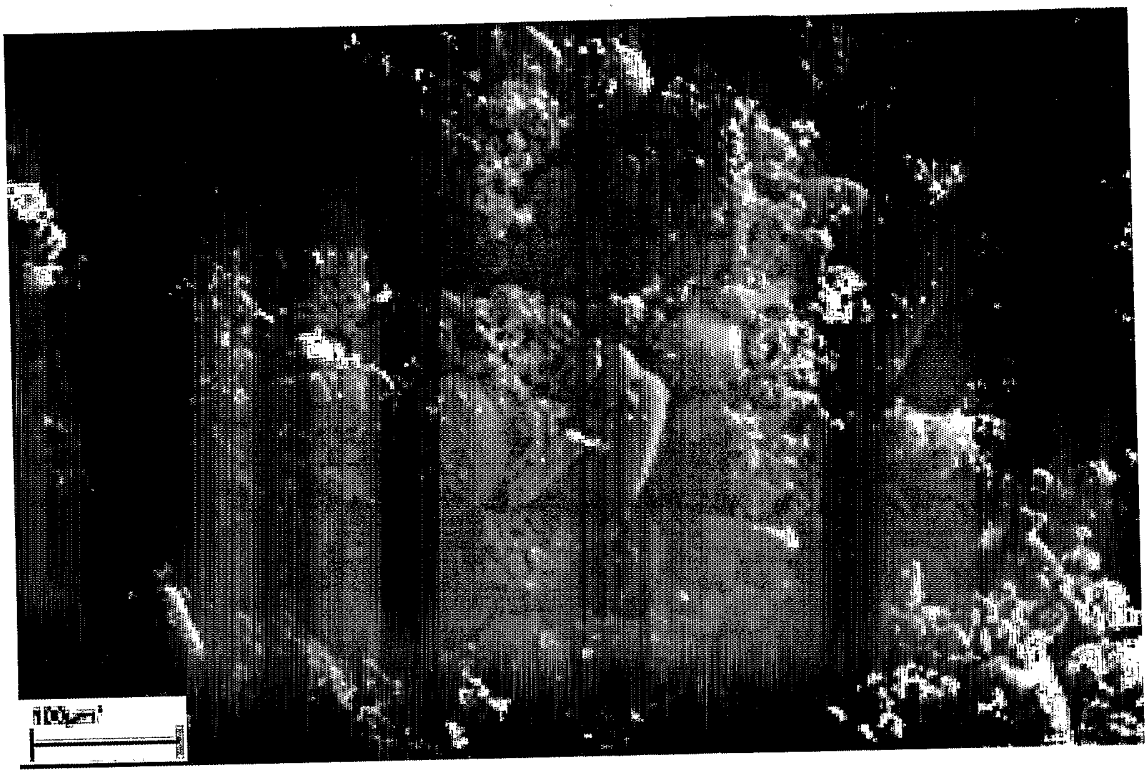


Fig. 17

Fig. 18A

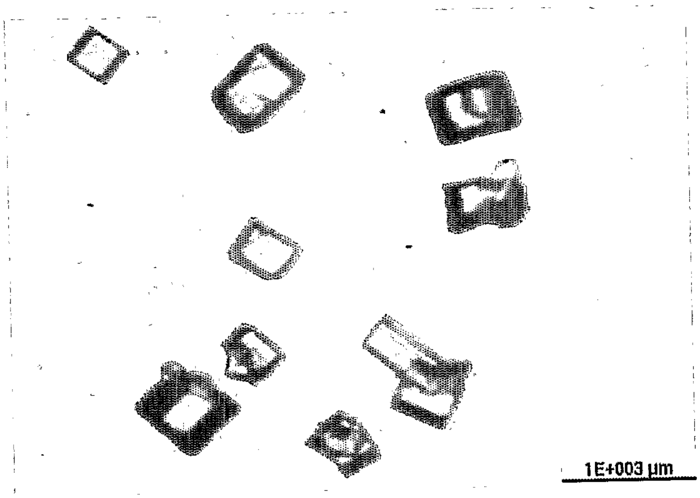


Fig. 18B

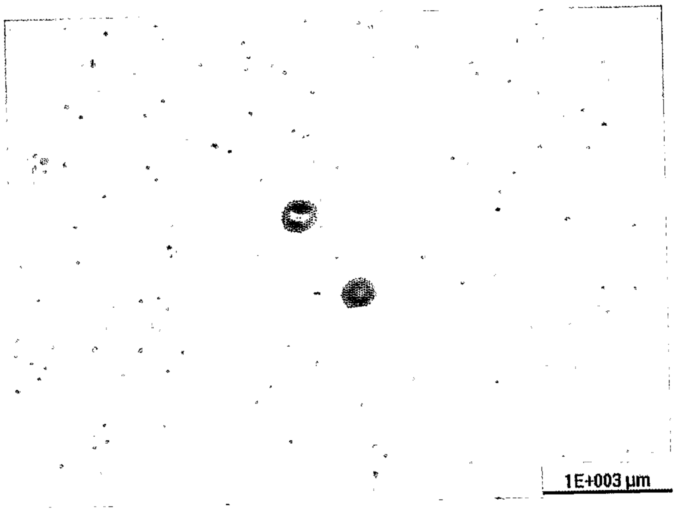


Fig. 18C

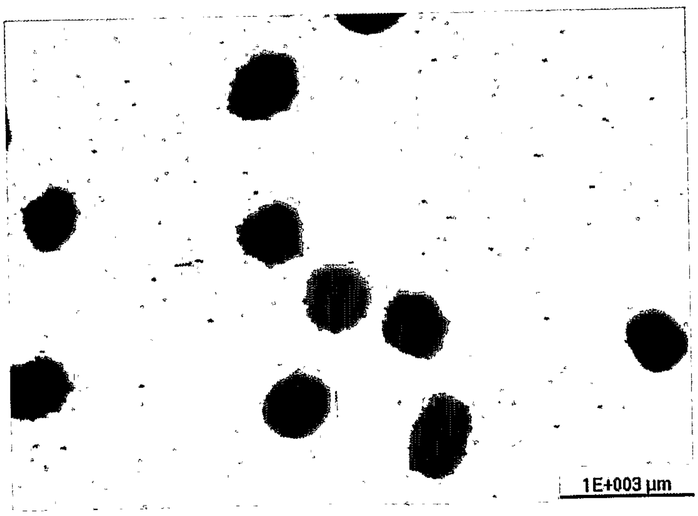


Fig. 19

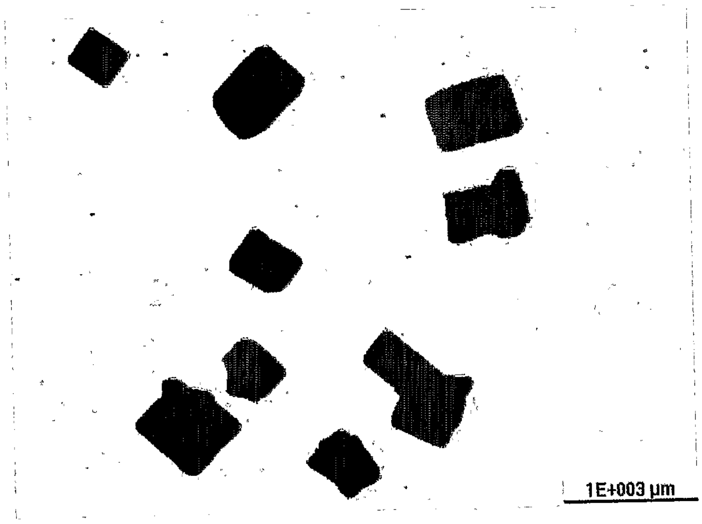


Fig. 20A

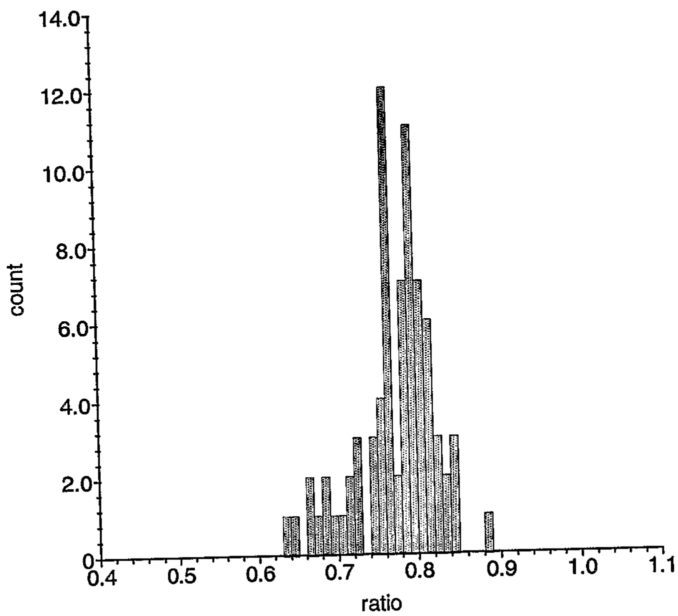


Fig. 20B

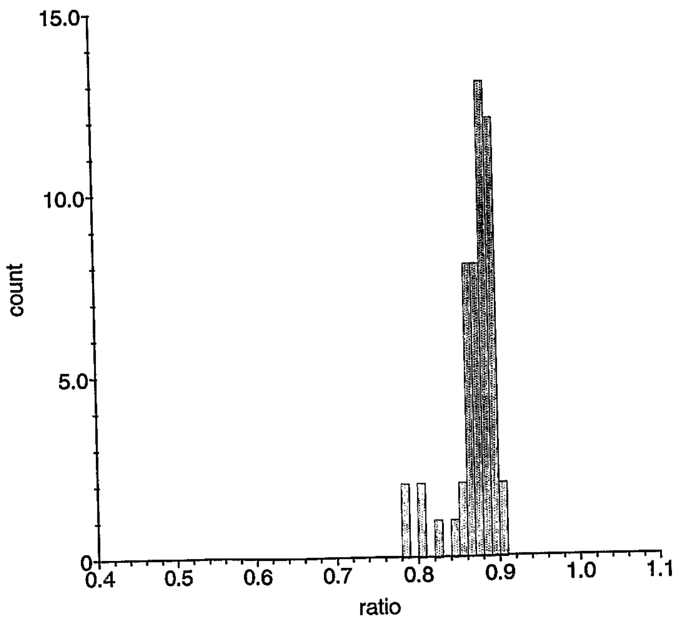
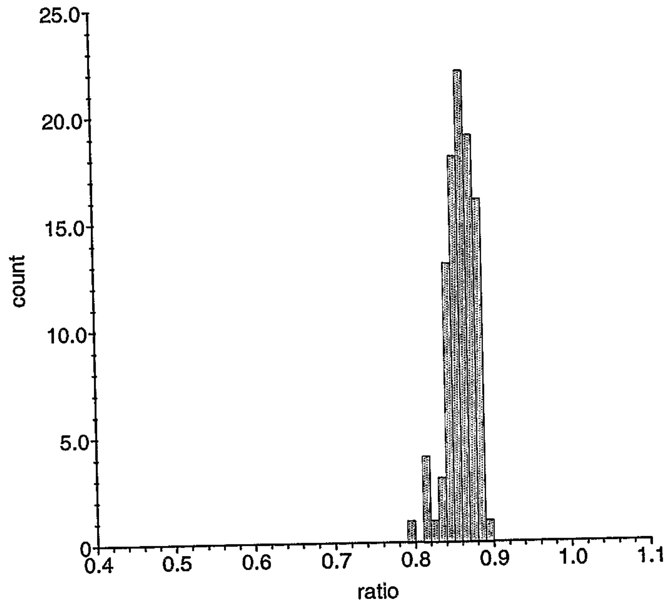


Fig. 20C



INTERNATIONAL SEARCH REPORT

International application No
PCT/IL2006/000403

A. CLASSIFICATION OF SUBJECT MATTER
INV. B01J19/10 B01J19/00 B02C19/18

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)
B01J B02C B06B

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 practical, search terms used)

EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 484 573 A (BERGER ET AL) 16 January 1996 (1996-01-16) the whole document	1,6-13, 18
X	US 2 578 505 A (CARLIN BENSON) 11 December 1951 (1951-12-11)	1,4-6,18
Y	column 3, line 17 - line 24; figure 3	14-17,19
X	US 5 711 888 A (TRAMPLER ET AL) 27 January 1998 (1998-01-27) column 15, line 60 - column 16, line 18 figures 3,10,12	1-3, 6-11,18
Y	US 4 118 649 A (SHWARTZMAN ET AL) 3 October 1978 (1978-10-03) column 2, line 31 - line 65 column 4, line 8 - line 46; figures 1-3	14-17,19

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 August 2006	17/08/2006

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, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Vlassis, M

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IL2006/000403

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