(19) DANMARK

(10) **DK/EP 2914310 T3**

Patent- og
Varemærkestyrelsen

(12) Oversættelse af
europæisk patentskrift

(51) Int.Cl.: ***A 61 L 31/08 (2006.01)*** ***A 61 L 31/18 (2006.01)***

(45) Oversættelsen bekendtgjort den: **2020-07-27**

(80) Dato for Den Europæiske Patentmyndigheds
bekendtgørelse om meddelelse af patentet: **2020-06-17**

(86) Europæisk ansøgning nr.: **13795879.9**

(86) Europæisk indleveringsdag: **2013-10-31**

(87) Den europæiske ansøgnings publiceringsdag: **2015-09-09**

(86) International ansøgning nr.: **NL2013050779**

(87) Internationalt publikationsnr.: **WO2014070012**

(30) Prioritet: **2012-10-31 EP 12190924**

(84) Designerede stater: **AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR**

(73) Patenthaver: **Encapson B.V., Institutenweg 25A, 7521 PH Enschede, Holland**

(72) Opfinder: **VRIEZEMA, Dennis Manuel, Weefgewichtstraat 108, NL-6515 JM Nijmegen, Holland**
AYRES, Lee, c/o Hengelosestraat 705, 7521 PA Enschede, Holland
ASRIAN, David, Ceres 42, NL-6681 PS Bemmel, Holland
OPSTEEN, Johannes Antonius, c/o Hengelosestraat 705, 7521 PA Enschede, Holland

(74) Fuldmægtig i Danmark: **HØIBERG P/S, Adelgade 12, 1304 København K, Danmark**

(54) Benævnelse: **Medicinske indretninger med coatings til forbedret ekkogenicitet**

(56) Fremdragne publikationer:
EP-A1- 0 552 924
EP-A2- 1 118 337
WO-A1-2012/148265
US-A- 5 081 997
US-A- 5 289 831
US-A1- 2009 318 746
OLIVIER COUTURE: "A model for reflectivity enhancement due to surface bound submicrometer particles", ULTRASOUND IN MEDICINE AND BIOLOGY, vol. 32, no. 8, 2006, pages 1247-1255, XP002713682, cited in the application

DESCRIPTION

[0001] The invention relates to the fields of medicine, physics and biotechnology.

[0002] In order to precisely locate a medical device such as for instance a needle or catheter inside a patient, ultrasound imaging is commonly used. Ultrasound imaging relies on the different ways in which sound waves are reflected from interfaces between substances. Ultrasound waves, with frequencies above the audible range of normal human hearing, typically from 20 kHz up to several gigahertz, are reflected in areas of density differences. In practice, a transducer is used that emits ultrasound waves, where after some of the reflected sound waves are detected by the transducer which turns the vibrations into electrical pulses. These electrical pulses are processed and transformed into digital images.

[0003] The use of ultrasound imaging for medical devices is well known in the art. In order to enhance the quality of ultrasound images of medical devices, the surface of such a device is typically grooved or otherwise roughened, or an ultrasound coating is applied to at least part of the surface of the device. For instance, US patents 5,289,831 and 5,081,997 describe echogenic medical devices having a surface with partially spherical indentations, or having a surface that is coated with spherically-shaped particles, which scatter an ultrasound signal. International patent application WO 00/51136 describes the use of gas bubbles or metal particles for enhancing an ultrasound signal. The use of an echogenic material containing cavities or gas bubbles is also described in European patent application EP 0624342, whereas international patent applications WO 98/18387 and WO 00/66004 describe medical instruments with bubble generating means, which produce bubbles that are visible with ultrasound. Additionally, US patent application 2004/0077948 discloses an echogenic surface having structures entrapping gas, the entrapped gas causing the device to be ultrasonically visible.

[0004] US patent application 2005/0074406 describes an ultrasound coating containing membranes encapsulating a gas-filled core.

[0005] European patent application EP 1118337 and US patent 6,506,156 use an echogenic layer including a polymeric matrix with a plurality of void spaces, or glass microsphere particles, or both. US patent application 2009/0318746 describes lubricious echogenic coatings containing polymeric gas/liquid containing microparticles.

[0006] The use of roughened surfaces in order to enhance ultrasound visibility, however, involves an increased risk of discomfort for the patient since a roughened surface typically requires more force to move the device inside the patient's body and gives only a limited ultrasound visability enhancement. The use of gas bubbles for improving ultrasound visibility has the disadvantage that it is difficult to control the concentration and size of the formed bubbles, leading to variations between coatings so that it is more difficult to obtain an optimized ultrasound imaging coating.

[0007] The use of echogenic particles is, therefore, preferred.

[0008] WO 2012/148265 discloses a coating for improving the ultrasound visibility of a device, said coating is made of a matrix material and of a plurality of gas-filled microparticles having a diameter in the range of 0.5 to 100 microns, e.g. 20 microns. The microparticles are in the form of a hollow centre surrounded by a wall, wherein a gas is present within the hollow centre. The density of the microparticles on the substrate is between 10^6 and 1 particles/mm^2, preferably between 10^4 and 400 particles/mm^2.

[0009] Although various alternatives for ultrasound imaging with microparticles are available, it is advantageous to optimize the visibility (i.e. the accuracy) of the obtained ultrasound images. It is an object of the present invention to provide such optimized coatings for ultrasound detection.

[0010] The present invention provides the insight that an ultrasound image is optimized if at least 60% of the echogenic microparticles on a medical device have a diameter of between 10 and 45 µm and the density of the echogenic microparticles on the surface of the device is between 45 and 450 particles/mm^2. This is for instance apparent from the Examples: when particles with a diameter of between 10 and 45 µm are used, densities of between 45 and 450 particles/mm^2 provide a good visibility of the coated object, whereas lower or higher densities typically result in an image with an undesired deviation of the object size. Hence, the visibility of the object is best when densities of between 45 and 450 particles/mm^2 are used. In one preferred embodiment, a medical device is coated with echogenic particles wherein at least 60% of the echogenic microparticles on a medical device have a diameter of between 22 and 45 µm and the density of the echogenic microparticles on the surface of the device is between 45 and 450 particles/mm^2 or, preferably, between 60 and 450 particles/mm^2.

[0011] As used herein, the visibility of an object as measured with ultrasound waves (also called the ultrasound visibility of an object) is defined as the accuracy with which the exact location of said object can be determined. Hence, visibility is proportional to the detail, or sharpness, of the obtained ultrasound image; the more detailed (sharper) the image, the better the user can locate the object, hence the better the visibility of the object is. Interestingly, within the tested density ranges of between 0-1800 microspheres/mm^2, roughly corresponding to a surface packing of between 0.1 and 100% (a surface packing of 100% meaning that the highest possible hexagonal packing of spherical particles in a plane is achieved), it appears that objects with a surface density, and hence a reflectivity, above an optimal value lead to an overestimation of the object size under ultrasound. Hence, a higher reflectivity of ultrasound waves does not always result in a better visibility of a medical object. Contrary, the inventors have found that there is an optimal particle density, depending on the particle size. If the density becomes too high, the reflectivity will increase but the ability of a user to determine the exact location of a device will decrease because the ultrasound image will provide an overestimation of the object's size. The boundaries between the object and the environment

become more vague, thereby decreasing the visibility of the object.

[0012] Without wishing to be bound by any theory, it is believed that as the number of particles on the surface increases, more ultrasound waves are scattered and returned to the transducer resulting in an increase of reflectivity. At low particle densities, this increase in reflectivity increases the contrast-to-noise ratio of the signal of the coated device on the ultrasound machines screen, when compared to the signal of the surrounding medium, and it also increases the sharpness of the image, resulting in an improved ultrasound image on a screen. However, when the number of particles increases beyond an optimum point, the scattering is further increased but the ultrasound image of the device becomes larger and less defined, leading to a less defined or less sharp image on the screen. This results in an overestimation of the size of the device, the appearance of ultrasound artefacts and a less defined ultrasound image for a user. The result of this is a suboptimal image of the device and, hence, a decreased visibility.

[0013] This insight of the present invention is in contrast with the general teaching in the art. For instance, Couture et al (Ultrasound in Medicine and Biology, Vol. 32, No. 8, pp. 1247-1255, 2006) describes two mathematical models to predict the signal enhancement, or reflectivity, of microparticles on a surface. In the so-called layer model, the ultrasound particles are viewed as a continuous film covering the surface, with thickness corresponding to the particle diameter. According to this model, the reflectivity depends only on the film thickness (particle size) and not the particle density. In the second mathematical model proposed in Couture et al, at low surface concentration the response to ultrasound radiation is modelled as the sum of the individual impulse response of all the particles, with all phases accounted for. From equation (5) on page 1249 of Couture et al it is clear that according to this model the reflectivity is proportional to the surface density of the ultrasound particles. Experimental data subsequently demonstrate that this is indeed the case for confluence fractions (surface packing) of up to 200% (which would roughly involve a particle density of up to 70.000 particles/mm^2 when the 5 µm particles of Couture et al are used). For practical reasons, such high particle densities are normally not used on medical devices because it would become problematic to bind such high amounts of particles to a surface. Hence, Couture et al only investigates the ultrasound reflectivity of echogenic particles and teaches a linear relationship between reflectivity and particle density up to 70.000 particles/mm^2. What is not realized in Couture et al, however, is the insight of the present invention that the amount of reflectivity of the ultrasound particles does not always correlate to the visibility of the device in a patient. The present invention provides the insight that too much reflectivity actually decreases the visibility. According to the invention, if the reflectivity is too high, then signal broadening and artefacts begin to appear and the ultrasound image seen by the user becomes less detailed (less sharp). In this case the user will overestimate the size of the device and loose accuracy. The present invention therefore provides coated medical devices with an improved ultrasound visibility. The diameters and the densities of the echogenic particles are adjusted in order to obtain an ultrasound image with improved visibility, meaning that the user is capable of accurately determining the position of the device inside a body.

[0014] Accordingly, the invention provides a medical device comprising a coating for ultrasound detection, said coating comprising microparticles that are visible with ultrasound, wherein the microparticles are solid, and wherein the diameter of at least 60% of said microparticles on said medical device is between 10 and 45 µm and wherein the density of said microparticles on the surface of said medical device is between 45 and 450 particles/mm^2. Preferably, at least 65% of said microparticles on said medical device have a diameter of between 10 and 45 µm. More preferably, at least 70%, or at least 75%, of said microparticles on said medical device have a diameter of between 10 and 45 µm. More preferably, at least 80%, or at least 85%, or at least 90% of said microparticles on said medical device have a diameter of between 10 and 45 µm. Most preferably, at least 95% of said microparticles on said medical device have a diameter of between 10 and 45 µm. By using a high proportion of particles with a diameter between 10 and 45 µm, and a surface density of between 45 and 450 particles/mm^2, an optimal visibility of the medical device is obtained. In one particularly preferred embodiment, a medical device is provided that comprises a coating for ultrasound detection, wherein said coating comprises microparticles that are visible with ultrasound and wherein the diameter of at least 60% (preferably of at least 65%, 70%, 75%, 80%, 85%, 90% or 95%) of said microparticles on said medical device is between 22 and 45 µm and wherein the density of said microparticles on the surface of said medical device is between 45 and 450 particles/mm^2. In another preferred embodiment, said density is between 60 and 450 particles/mm^2.

[0015] In one embodiment, the diameter size of at least 60% of the individual particles is randomly distributed between 10 and 45 µm. In another embodiment, the diameter size of at least 60% of the individual particles is randomly distributed between 22 and 45 µm. It is also possible to use a mixture of particles with a higher proportion of particles with a diameter size between a more narrow sub-range. For instance, one preferred embodiment provides a medical device according to the present invention, wherein the diameter of at least 60% of said microparticles on said medical device is between 22 and 27 µm. In such case, a particle density of between 150 and 450 particles/mm^2 provides an optimal visibility of the medical device and is, therefore, preferred. Even more preferably, said particle density is between 150 and 300 particles/mm^2 for optimal visibility.

[0016] One embodiment therefore provides a medical device comprising a coating for ultrasound detection, said coating comprising microparticles that are visible with ultrasound, wherein the diameter of at least 60% of said microparticles on said medical device is between 22 and 27 µm and wherein the density of said microparticles on the surface of said medical device is between 150 and 450 particles/mm^2, preferably between 150 and 300 particles/mm^2. Preferably, at least 65%, more preferably at least 70%, more preferably at least 75%, more preferably at least 80%, more preferably at least 85%, more preferably at least 90%, more preferably at least 95% of said microparticles on said medical device have a diameter between 22 and 27 µm.

[0017] In yet another embodiment, a medical device is coated with ultrasound particles wherein the diameter of at least 60% of said microparticles on said medical device is between 27 and 32 µm. In this case, a particle density of between 70 and 450 particles/mm^2 is particularly preferred because a combination of a particle size of between 27 and 32 µm and a density of between 70 and 450 particles/mm^2 improves the visibility of a medical device inside a body. Even more preferably, said particle density is between 80 and 300 particles/mm^2 for optimal visibility.

[0018] Further provided is therefore a medical device comprising a coating for ultrasound detection, said coating comprising microparticles that are visible with ultrasound, wherein the diameter of at least 60% of said microparticles on said medical device is between 27 and 32 µm and wherein the density of said microparticles on the surface of said medical device is between 70 and 450 particles/mm^2, preferably between 80 and 300 particles/mm^2. Preferably, at least 65%, more preferably at least 70%, more preferably at least 75%, more preferably at least 80%, more preferably at least 85%, more preferably at least 90%, more preferably at least 95% of said microparticles on said medical device have a diameter between 27 and 32 µm.

[0019] In yet another embodiment, a medical device is coated with ultrasound particles wherein the diameter of at least 60% of said microparticles on said medical device is between 32 and 38 µm. In this case, a particle density of between 45 and 225 particles/mm^2 is particularly preferred because a combination of a particle size of between 32 and 38 µm and a density of between 45 and 225 particles/mm^2 improves the visibility of a medical device inside a body. Further provided is therefore a medical device comprising a coating for ultrasound detection, said coating comprising microparticles that are visible with ultrasound, wherein the diameter of at least 60% of said microparticles on said medical device is between 32 and 38 µm and wherein the density of said microparticles on the surface of said medical device is between 45 and 225 particles/mm^2. Again, it is preferred that at least 65%, more preferably at least 70%, more preferably at least 75%, more preferably at least 80%, more preferably at least 85%, more preferably at least 90%, more preferably at least 95% of said microparticles on said medical device have a diameter between 27 and 32 µm. By using a high proportion of particles with the recited diameters and the recited surface densities, an optimal visibility of the medical device is obtained.

[0020] In yet another embodiment, a medical device is coated with ultrasound particles wherein the diameter of at least 60% of said microparticles on said medical device is between 38 and 45 µm. In this case, a particle density of between 45 and 150 particles/mm^2 is particularly preferred because a combination of a particle size of between 38 and 45 µm and a density of between 45 and 150 particles/mm^2 improves the visibility of the device.

[0021] Further provided is therefore a medical device comprising a coating for ultrasound detection, said coating comprising microparticles that are visible with ultrasound, wherein the

diameter of at least 60% of said microparticles on said medical device is between 38 and 45 µm and wherein the density of said microparticles on the surface of said medical device is between 45 and 150 particles/mm^2. Preferably, at least 65%, more preferably at least 70%, more preferably at least 75%, more preferably at least 80%, more preferably at least 85%, more preferably at least 90%, more preferably at least 95% of said microparticles on said medical device have a diameter between 38 and 45 µm.

[0022] The insight of the present invention is in contrast with prior art teachings such as US patents 5,289,831 and 5,081,997, which suggest that any amount of particles will provide a good image. US patents 5,081,997 (column 6) and 5,289,831 (column 7) teach that glass microspheres with an outer diameter of about 5 microns is one acceptable option. Further, a general size range of 1-50 microns is given. US patent application 2009/0318746 discloses a preferred size range for echogenic particles of 0.1-30 µm. Furthermore, European patent application EP 1118337 and US patent 6,506,156 describe general size ranges of 20-200 µm and 50-150 µm. Hence, according to the prior art, the size of the echogenic particles is not very critical. Furthermore, no correlation is made between the sizes of the particles and optimal particle densities, as provided by the present invention. It is this insight about the specific combinations of particle sizes and particle densities that improves the visibility of ultrasound images of medical devices in a body. The optimal density ranges and particle sizes as provided by the present invention are not disclosed nor suggested in the prior art.

[0023] A medical device according to the present invention can be coated with various kinds of microparticles that are visible with ultrasound. Such microparticles are known in the art. Suitable microparticles are for instance made from a material selected from the group consisting of polymers, ceramics, glasses, silicates, organic materials, metals and any combination thereof. Solid microparticles are used.

[0024] In one preferred embodiment, said echogenic microparticles are echogenic microspheres. In one embodiment, said microparticles are present on the surface of a medical device as a monolayer because this reduces the thickness and roughness of the surface, as compared to double layers and multilayers. A less roughened surface typically requires less force to move the device inside a patient's body. A thinner coating affects the properties of the medical device less.

[0025] The echogenic microparticles with a diameter between 10 and 45 µm or between 22 and 45 µm are used. This means that at least 60%, preferably at least 65%, preferably at least 70%, preferably at least 75%, preferably at least 80%, preferably at least 85%, preferably at least 90% and most preferably at least 95% of the particles have a diameter between 10 and 45 µm or between 22 and 45 µm. Hence, some variations are tolerated, as long as the majority of the particles have a diameter within the recited diameter range. Echogenic microparticles with a diameter between 10 and 45 µm are used for coating medical devices, because significantly smaller particles have a lower ultrasound scattering capacity so that echogenicity is often not sufficiently enhanced and the contrast-to-noise ratio is often too low, whereas significantly larger particles often result in a highly increased scattering effect and therefore an

overestimation of the size of the medical device. Furthermore, with particles with a diameter of 45 or less, a coated medical device is typically sufficiently smooth to avoid discomfort for a subject, which would be due to resistance that is experienced when moving a device with a rough surface inside a subject's body.

[0026] A medical device is defined herein as any kind of device that can be used in an animal or human body. Said medical device can preferably be inserted or implanted in said body. Preferably such medical device is an instrument used in surgery, treatment and/or diagnosis. Surgical instruments are well known in the art. Non-limiting examples of medical devices include cathethers, needles, stents, cannulas, tracheotomes, endoscopes, dilators, tubes, introducers, markers, stylets, snares, angioplasty devices, trocars and forcepses. A medical device according to the present invention is, therefore, preferably selected from the group consisting of cathethers, needles, stents, cannulas, tracheotomes, endoscopes, dilators, tubes, introducers, markers, stylets, snares, angioplasty devices, fiducials, trocars and forcepses.

[0027] As used herein, a coating for ultrasound detection comprises any coating that is tolerated by a human or animal body and that comprises microparticles that can be visualized, due to scattering of ultrasound waves. Typically, such coating comprises biocompatible materials that are non-toxic, hypoallergenic and stable.

[0028] An ultrasound wave (also called "an ultrasound signal" or "ultrasound") is defined as a sound pressure wave with a frequency above the audible range of normal human hearing. Typically, ultrasound waves have a frequency above 20 kHz. For imaging of medical devices, ultrasound waves with a frequency between 2 MHz and 50MHz are preferably used.

[0029] As used herein, the term "ultrasound image" means any kind of visualization of an object using ultrasound waves. Typically, reflected ultrasound waves are converted into electrical pulses which are processed and transformed into digital images. Such images are embraced by the term ultrasound image.

[0030] A microparticle is defined herein as a particle with a size below 1000 µm (preferably equal to or higher than 1 µm and lower than 1000 µm). Microparticles can have any shape, such as a regular shape (for instance spherical, oval or cubical) or an irregular shape.

[0031] A microsphere is defined herein as an essentially spherical particle with a diameter lower than 1000 µm, preferably lower than 500 µm. The term "essentially spherical" reflects the fact that the particles need not be perfectly spherical as long as the distances between the centre and any point at the surface do not differ more than 50%, more preferably no more than 30%, from each other in at least 70%, preferably at least 80%, most preferably at least 90% of the particles.

[0032] A monolayer, also called a single layer, is defined herein as a one-particle thick layer of particles on the surface of a device, meaning that there is on average no more than one particle on an axis perpendicular to the surface of the device. Some variations in thickness of

the layer are tolerated, as long as at least 70%, preferably at least 80%, most preferably at least 90% of the surface of a device is coated with a single layer of particles.

[0033] A double layer is defined herein as a two-particle thick layer of particles on the surface of a device, meaning that there is on average no more than two particles on an axis perpendicular to the surface of the device. Again, some variations in thickness of the layer are tolerated, as long as at least 70%, preferably at least 80%, most preferably at least 90% of the surface of a device is coated with a double layer of particles.

[0034] Echogenic microparticles are defined herein as microparticles that are able to reflect an ultrasound wave.

[0035] A diameter of a microparticle according to the invention is defined herein as the maximal size of said particle. Said particle does not need to be exactly spherical although, in practice, essentially spherical particles are preferred.

[0036] A microparticle with a diameter between a given range is defined herein as a microparticle which has a diameter which lies within the recited range, including the lower and upper value of said range. For instance, a microparticle with a diameter between 10 and 45 µm may have a diameter of 10 µm, a diameter of 45 µm, or a diameter with a value anywhere within this range.

[0037] A silicate is defined herein as any compound comprising SiO_2 and/or SiO_4 groupings, or any salt derived from the silicic acids or from silica.

[0038] As used herein, the term "glass" refers to a solid material that exhibits a glass transition when heated towards the liquid state. Preferably, silica glass is used, which is a SiO_2 containing glass. Typically, soda-lime-silica glass is used, which is the most prevalent type of glass. It comprises SiO_2, sodium carbonate, calcium oxide, magnesium oxide and/or aluminium oxide. Other types of glasses can be used, such as for instance quartz, sodium borosilicate or other borosilicate glasses, lead oxide, and/or aluminosilicate.

[0039] The term "plastic" refers to organic polymers of high molecular mass. Non-limiting examples of plastics include poly(ether sulfone)s, polyisocyanates, polyurethanes, polytetrafluoroethylene, polymers or copolymers of N-vinyl-pyrrolidone (e.g. copolymers with butylacrylate), poly-(4-vinyl pyridine), polyacrylamide (e.g. poly(N-isopropylacrylamide)s), poly(amido-amine)s, poly(ethylene imine)s, block copolymers of ethylene oxide and propylene oxide (e.g. a poly(ethylene oxide-block-propylene oxide) or poly(ethylene oxide-block-propylene oxide-block-ethylene oxide)), block copolymers of styrene (e.g. a poly(styrene-block-isobutylene-block-styrene) or poly(hydroxystyrene-block-isobutylene-block-hydroxystyrene)), polydialkylsiloxanes, polysaccharides, polystyrenes, polyacrylates, polyalkylacrylates (e.g. a polymethylmethacrylate or a poly(2-hydroxyethylmethacrylate)), polyalkanes (e.g. polyethylene, polypropylene and polybutadiene), poly(ether ketone)s (e.g. poly(ether ketone) or poly(ether ether ketone)), polyesters (e.g. poly(ethylene terephthalate), polyglycolides,

poly(trimethylene terephthalate) or poly(ethylene naphthalate), poly(lactic acid), polycapralatone, poly(butylene terephthalate), polyamides (e.g. nylon-6,6, nylon-6, a polyphthalamide or a polyaramide), and one or more combinations of the above.

[0040] As used herein, the term "surface coverage" refers to the percentage of a surface that is covered by echogenic microparticles. The surface coverage is typically determined by dividing the added-up dimensions of microparticle-covered surface parts by the total dimension of the surface as a whole.

[0041] The term "surface density" is defined herein as the amount of particles per square millimeter of the surface of a device. In common practice, some non-significant variation between the actual density of a coated object and an indicated density value is typically allowed. For instance, a 5-10% difference is typically considered non-significant.

[0042] The term "reflectivity" as used herein typically refers to the fraction or amount of ultrasound waves returned from a surface or interface, e.g. to be received by an ultrasound transducer.

[0043] The term "contrast-to-noise ratio" (CNR) is defined herein as the difference between the reflection of a (the) echogenic particle(s) as described herein and the reflection of the surrounding tissue (background reflection). Methods for calculating CNRs are for instance disclosed in Song et al (Applied Optics, Vol. 43, No. 5 (2004); 1053-1062) and in Baldelli et al (Eur. Radiol. 19 (2009); 2275-2285)

[0044] In one preferred aspect a medical device is provided that comprises a coating for ultrasound detection, said coating comprising solid microparticles that are visible with ultrasound, wherein the diameter of at least 60% of the microparticles on said medical device is between 38 and 45 µm and wherein the density of said microparticles on the surface of said medical device is lower than 150 particles/mm^2. The present inventors have found that ultrasound images obtained with medical devices that are coated with echogenic particles with a density that is higher than 150 particles/mm^2, wherein the diameter of at least 60% of the microparticles on said medical device is between 38 and 45 µm, are less accurate, because of the overestimation of the size of the device and the appearance of artefacts. This is for instance shown in Example 5 and Figure 9: the right image is obtained with a coated device whereby the diameter of at least 60% of the microparticles on said medical device is between 38 and 45 µm and the density of echogenic microparticles on the surface of said device is about 250 particles/mm^2, the middle image is obtained with a coated device with the same kind and size of particles whereby the density of echogenic microparticles on the surface of said device is about 180 particles/mm^2 and the left image is obtained with a coated device with the same kind and size of particles whereby the density of echogenic microparticles on the surface of said device is about 130 particles/mm^2. It is clear that the right image of Figure 9 has a lower detail (sharpness), so that it is for instance more difficult for a surgeon to exactly locate the end or tip of such device. Moreover, a cloud can be seen at the left end of the device,

which lowers the quality and accuracy of the obtained image even more. Furthermore, a comparison between the left image of Figure 9 (coating with a density of echogenic particles of about 130 particles/mm^2) and the middle image of Figure 9 (coating with a density of echogenic particles of about 180 particles/mm^2) shows that the detail (sharpness) and, hence, the visibility of the left image of Figure 9 is better than the detail (sharpness) of the middle image of Figure 9.

[0045] Again, contrary to expectations, the present invention provides the insight that the presence of more echogenic microparticles, resulting in more reflectivity, does not always increase the visibility of a device. On the contrary, visibility is decreased if densities above an optimum value are used.

[0046] In one embodiment, a medical device according to the present invention comprises a plastic surface. Non-limiting examples are plastics selected from the group consisting of polyurethane, polyvinyl chloride and silicones, and PEBAX. Alternatively, a medical device according to the present invention comprises a metal surface, such as for instance stainless steel, Nitinol, chromium, gold, or Platinum.

[0047] As stated before, suitable microparticles for a medical device according to the invention are for instance made from a material selected from the group consisting of polymers, ceramics, glasses, silicates, organic materials, metals and any combination thereof. Preferably, glass or silicate microparticles are used. In one particularly preferred embodiment, said microparticles are echogenic microspheres. Said microparticles are solid microparticles.

[0048] In principle, any coating capable of applying microparticles to a medical device and that is suitable for *in vivo* use is suitable for a medical device according to the present invention. Such coating is preferably non-toxic, hypo-allergenic and stable. A medical device according to the invention preferably comprises a coating which comprises a matrix material selected from the group of polymers, preferably wherein the polymer is selected from the group consisting of a poly(ether sulfone); a polyisocyanate; a polyurethane; a polytetrafluoroethylene; a polymer or copolymer of N-vinyl-pyrrolidone such as a copolymer with butylacrylate; a poly(4-vinyl pyridine); a polyacrylamide such as poly(N-isopropylacrylamide); a poly(amido-amine); a poly(ethylene imine); a block copolymer of ethylene oxide and propylene oxide such as a poly(ethylene oxide-block-propylene oxide) or a poly(ethylene oxide-block-propylene oxide-block-ethylene oxide); a block copolymer or styrene such as poly(styrene-block-isobutylene-block-styrene) or poly(hydroxystyrene-block-isobutylene-block-hydroxystyrene); a polydialkylsiloxane; a polysaccharide; a polystyrene, a polyacrylate, a polyalkane such as polyethylene, polypropylene or polybutadiene, a poly(ether ketone) such as poly(ether ketone), poly(ether ether ketone), polyesters such as poly(ethylene terephthalate), polyglycolide, poly(trimethylene terephthalate), poly(ethylene naphthalate), poly(lactice acid), polycapralatone, poly(butylene terephthalate), polyamides such as nylon-6,6, nylon-6, polyphthalamides or polyaramides, a polyalkylmethacrylate such as a polymethylmethacrylate, a poly(2-hydroxyethylmethacrylate), and combinations thereof, preferably selected from poly(ether sulfones), polyurethanes, polyacrylates, polymethacrylates, polyamindes,

polycarbonates, and combinations thereof.

[0049] In one embodiment a medical device according to the invention comprises a plastic tube. Such device for instance comprises a catheter.

[0050] Further provided are methods for preparing a medical device according to the present invention. Methods for preparing echogenic coatings and for applying these coatings on medical devices are well known in the art. A medical device is for instance coated with the microparticles by dip coating, spray coating, pad printing, roller coating, printing, painting or inkjet printing.

[0051] Reference is for instance made to US patents 5,289,831, 5,921,933, and 6,506,156, to international patent application WO 2007/089761 and to Ultrasound in Medicine and Biology, Vol. 32, No. 8, pp. 1247-1255, 2006, which describe methods for preparing echogenic particles and coatings. Such coating is preferably biocompatible, non-toxic, hypo-allergenic and stable. A medical device according to the invention preferably comprises a coating which comprises a matrix material listed herein before, comprising echogenic microparticles according to the present invention.

[0052] According to the invention, there is provided a method for preparing a medical device comprising a coating for ultrasound detection, said coating comprising solid microparticles that are visible with ultrasound, wherein diameter of at least 60% of said microparticles on said medical device is between 10 and 45 µm and wherein the density of said microparticles on the surface of said medical device is between 45 and 450 particles/mm^2, the method comprising:

- providing a medical device, and
- coating said device with solid microparticles that are visible with ultrasound, such that the diameter of at least 60% of said microparticles on said medical device is between 10 and 45 µm and the density of said microparticles on the surface of said medical device is between 45 and 450 particles/mm^2.

[0053] At least 60%, more preferably at least 65%, more preferably 75%, more preferably at least 80%, more preferably at least 85%, more preferably at least 90%, more preferably at least 95% of said microparticles on said medical device have a diameter between 10 and 45 µm.

[0054] Also provided is a method for preparing a medical device comprising a coating for ultrasound detection, said coating comprising solid microparticles that are visible with ultrasound, wherein diameter of at least 60% of said microparticles on said medical device is between 22 and 45 µm and wherein the density of said microparticles on the surface of said medical device is between 45 and 450 particles/mm^2, the method comprising:

- providing a medical device, and
- coating said device with solid microparticles that are visible with ultrasound, such that the diameter of at least 60% of said microparticles on said medical device is between 22 and 45 µm and the density of said microparticles on the surface of said medical device is between 45 and 450 particles/mm^2. In one preferred embodiment, said device is coated with microparticles that are visible with ultrasound, such that the diameter of at least 60% of said microparticles on said medical device is between 22 and 45 µm and the density of said microparticles on the surface of said medical device is between 60 and 450 particles/mm^2.

[0055] Preferably, at least 60%, more preferably at least 65%, more preferably 75%, more preferably at least 80%, more preferably at least 85%, more preferably at least 90%, more preferably at least 95% of said microparticles on said medical device have a diameter between 22 and 45 µm.

[0056] In one embodiment, the diameter size of at least 60% of the individual particles is randomly distributed between 10 and 45 µm. In another embodiment, the diameter size of at least 60% of the individual particles is randomly distributed between 22 and 45 µm. It is also possible to use a mixture of particles with a higher proportion of particles with a diameter size between a more narrow sub-range. For instance, one preferred embodiment provides a medical device according to the present invention, wherein the diameter of at least 60% of said microparticles on said medical device is between 22 and 27 µm. In such case, a particle density of between 150 and 450 particles/mm^2 provides a particularly good visibility of the medical device and is, therefore, preferred. Even more preferred is a particle density of between 150 and 300 particles/mm^2.

[0057] One embodiment therefore provides a method for preparing a medical device comprising a coating for ultrasound detection, said coating comprising solid microparticles that are visible with ultrasound, wherein the diameter of at least 60% of said microparticles on said medical device is between 22 and 27 µm and wherein the density of said microparticles on the surface of said medical device is between 150 and 450 particles/mm^2, preferably between 150 and 300 particles/mm^2, the method comprising:

- providing a medical device, and
- coating said device with solid microparticles that are visible with ultrasound, such that the diameter of at least 60% of said microparticles on said medical device is between 22 and 27 µm and the density of said microparticles on the surface of said medical device is between 150 and 450 particles/mm^2, preferably between 150 and 300 particles/mm^2.

[0058] Preferably, at least 65%, more preferably at least 70%, more preferably at least 75%, more preferably at least 80%, more preferably at least 85%, more preferably at least 90%, more preferably at least 95% of said microparticles on said medical device have a diameter between 22 and 27 µm.

[0059] In yet another embodiment, a medical device is coated with solid ultrasound particles wherein the diameter of at least 60% of said microparticles on said medical device is between 27 and 32 µm. In this case, a particle density of between 70 and 450 particles/mm^2 is particularly preferred because a combination of a particle size of between 27 and 32 µm and a density of between 70 and 450 particles/mm^2 improves the visibility of a device inside a body. Even more preferably, said particle density is between 80 and 300 particles/mm^2 for optimal visibility.

[0060] Further provided is therefore a method for preparing a medical device comprising a coating for ultrasound detection, said coating comprising solid microparticles that are visible with ultrasound, wherein the diameter of at least 60% of said microparticles on said medical device is between 27 and 32 µm and wherein the density of said microparticles on the surface of said medical device is between 70 and 450 particles/mm^2, preferably between 80 and 300 particles/mm^2, the method comprising:

- providing a medical device, and
- coating said device with solid microparticles that are visible with ultrasound, such that the diameter of at least 60% of said microparticles on said medical device is between 27 and 32 µm and the density of said microparticles on the surface of said medical device is between 70 and 450 particles/mm^2, preferably between 80 and 300 particles/mm^2. Preferably, at least 65%, more preferably at least 70%, more preferably at least 75%, more preferably at least 80%, more preferably at least 85%, more preferably at least 90%, more preferably at least 95% of said microparticles on said medical device have a diameter between 27 and 32 µm.

[0061] In yet another embodiment, a medical device is coated with solid ultrasound particles wherein the diameter of at least 60% of said microparticles on said medical device is between 32 and 38 µm. In this case, a particle density of between 45 and 225 particles/mm^2 is particularly preferred because a combination of a particle size of between 32 and 38 µm and a density of between 45 and 225 particles/mm^2 improves the visibility of a medical device inside a body. Further provided is therefore a method for preparing a medical device comprising a coating for ultrasound detection, said coating comprising solid microparticles that are visible with ultrasound, wherein the diameter of at least 60% of said microparticles on said medical device is between 32 and 38 µm and wherein the density of said microparticles on the surface of said medical device is between 45 and 225 particles/mm^2, the method comprising:

- providing a medical device, and
- coating said device with solid microparticles that are visible with ultrasound, such that the diameter of at least 60% of said microparticles on said medical device is between 32 and 38 µm and the density of said microparticles on the surface of said medical device is between 45 and 225 particles/mm^2. Preferably, at least 65%, more preferably at least 70%, more preferably at least 75%, more preferably at least 80%, more preferably at least 85%, more preferably at least 90%, more preferably at least 95% of said microparticles on said medical device have a diameter between 32 and 38 µm.

[0062] In yet another embodiment, a medical device is coated with solid ultrasound particles wherein the diameter of at least 60% of said microparticles on said medical device is between 38 and 45 µm. In this case, a particle density of between 45 and 150 particles/mm^2 is particularly preferred because a combination of a particle size of between 38 and 45 µm and a density of between 45 and 150 particles/mm^2 improves the visibility of the device even more.

[0063] Further provided is therefore a method for preparing a medical device comprising a coating for ultrasound detection, said coating comprising solid microparticles that are visible with ultrasound, wherein the diameter of at least 60% of said microparticles on said medical device is between 38 and 45 µm and wherein the density of said microparticles on the surface of said medical device is between 45 and 150 particles/mm^2, the method comprising:

- providing a medical device, and
- coating said device with solid microparticles that are visible with ultrasound, such that the diameter of at least 60% of said microparticles on said medical device is between 38 and 45 µm and the density of said microparticles on the surface of said medical device is between 45 and 150 particles/mm^2.

[0064] Preferably, at least 65%, more preferably at least 70%, more preferably at least 75%, more preferably at least 80%, more preferably at least 85%, more preferably at least 90%, more preferably at least 95% of said microparticles on said medical device have a diameter between 38 and 45 µm.

[0065] The invention is further illustrated by the following examples. These examples are not limiting the invention in any way, but merely serve to clarify the invention.

Brief description of the drawings

[0066]

Figure 1: Plot of the CNR against the microsphere density on the surface for different microsphere sizes.

Figure 2: for microspheres with a diameter between 22 and 27 µm, the CNR is plotted against the microsphere density, along with the US estimation error on the secondary y-axis.

Figure 3: for microspheres with a diameter between 27 and 32 µm, the CNR is plotted against the microsphere density, along with the US estimation error on the secondary y-axis.

Figure 4: for microspheres with a diameter between 32 and 38 µm, the CNR is plotted against the microsphere density, along with the US estimation error on the secondary y-axis.

Figure 5: for microspheres with a diameter between 38 and 45 µm, the CNR is plotted against the microsphere density, along with the US estimation error on the secondary y-axis.

Figure 6: for microspheres with a diameter between 45 and 53 µm, the CNR is plotted against the microsphere density, along with the US estimation error on the secondary y-axis.

Figure 7: CNR values for glass and plastic surfaces coated with solid glass microspheres with a diameter ranging from 38 to 45 µm.

Figure 8: CNR values for glass slides coated with solid glass microparticles and hollow glass microparticles.

Figure 9: Influence of the microsphere density on the surface. A microparticle density of lower than 250 particles/mm^2 on the surface of a medical device provides better ultrasound images than higher densities.

Left image: hollow glass microspheres, surface density = about 130 particles/mm^2

Left image: hollow glass microspheres, surface density = about 180 particles/mm^2

Left image: hollow glass microspheres, surface density = about 250 particles/mm^2 Of note, the left part of each image shows a blank consisting of a chicken breast without tube; the right part of each image shows the results with a chicken breast with a coated tube.

Figure 10: Ultrasound images taken in a phantom gel of glass slides on which marker bands (width 1 cm) were applied of Sono-Coat comprising different concentrations of microspheres (size range 38-45 µm).

Figure 11: US estimation error plotted against the microsphere density on glass and plastic surfaces coated with microspheres with a diameter between 27-32 µm.

Examples

Example 1

[0067] Commercially available solid glass microspheres (from Cospheric) with diameters ranging from 10 to 22 µm, 22 to 27 µm, 27 to 32 µm, 32 to 38 µm, 38 to 45 µm and 45 to 53 µm, all with a density of 2.5 g/mL, were mixed through a polyurethane coating matrix. The microspheres were added in different amounts in order to prepare mixtures containing 0.5 to 75.0 vol. % microspheres in the coating matrix. Subsequently, either 30 or 60 µm thick coating films were drawn on both glass and PEBAX 6233 slides as substrates using a film applicator. The density of microspheres was determined to vary from 2 to 1831 particles/mm^2.

[0068] The coated substrates were measured by ultrasound using a 33 mm linear array probe operating in brightness-mode (B-mode) at 6 MHz. The substrates were placed under an approximate angle of 45 degrees inside a commercially available ultrasound phantom which acted as the medium.

[0069] From the recorded images the contrast-to-noise ratio (CNR) was determined by comparing the average pixel intensity and standard deviation of the coated objects to the values obtained for the surrounding medium, according to:

$$CNR = \frac{P_{ROI} - P_{medium}}{\sqrt{\frac{\sigma_{ROI}^2 - \sigma_{medium}^2}{2}}}$$

where

P_{ROI}=*average pixel intensity of region of interest*

P_{medium}=*average pixel intesity of medium*

σ_{ROI}=*standard deviation in region of interest*

σ_{medium}=*standard deviation in medium*

[0070] The determined CNRs were plotted against the microsphere density in particles/mm^2 (Figure 1).

[0071] As can be seen in Figure 1, the CNR approaches a value of approximately 3.5 with an increasing amount of microspheres on the surface. For the microspheres ranging from 10 to 22 µm, the maximum attainable CNR was approximately 2.5. Higher CNR values could not be obtained due to the fact that the complete surface is covered with glass microspheres. Adding a second layer of microspheres on top did not result in an increase of the CNR. Therefore, particles with a diameter between 22 and 45 µm are more preferred.

Example 2

[0072] Commercially available solid glass microspheres with diameters ranging from 10 to 22 µm, 22 to 27 µm, 27 to 32 µm, 32 to 38 µm, 38 to 45 µm and 45 to 53 µm, all with a density of 2.5 g/mL, were mixed through a polyurethane coating matrix. The microspheres were added in different amounts in order to prepare mixtures containing 1.0 to 75.0 vol. % microspheres in the coating matrix. Subsequently, either 30 or 60 µm thick marker bands of coating were drawn on glass slides using a film applicator. These marker bands were applied by masking the area which was required to be uncoated. The width of the marker bands was measured.

[0073] The coated substrates were measured by ultrasound using a 33 mm linear array probe operating in brightness-mode (B-mode) at 6 MHz. The substrates were placed under an approximate angle of 45 degrees inside a commercially available ultrasound phantom which acted as the medium.

[0074] From the recorded images, the width of the marker bands as visible under ultrasound was determined. The under or overestimation of the width of the marker band under ultrasound is expressed as:

$$\text{US estimation error} = \frac{L_{US} - L_{actual}}{L_{actual}} \times 100\%$$

where

Lus=the width of the ultrasound signal stemming from the marker band

L_{actual}*=the actual width of the marker band*

[0075] In principle, a US estimation error of below 10% is considered acceptable. Preferably, said US estimation error is between 0 and about 5%.

[0076] In Figure 2, for microspheres with a diameter between 22 and 27 µm, the CNR is plotted against the microsphere density, along with the US estimation error on the secondary y-axis. As can be seen in Figure 2, the optimum range for these microspheres is lying between 150 and 450 particles/mm^2. Less microspheres on the surface leads to an underestimation of the width of the marker band, whereas above the upper limit overestimation of the width occurs. The most optimal range for these microspheres is lying between 150 and 300 particles/mm^2.

[0077] In this fashion the optimum microsphere density for each size range was established.

[0078] In Figure 3, for microspheres with a diameter between 27 and 32 µm, the CNR is plotted against the microsphere density, along with the US estimation error on the secondary y-axis. As can be seen in Figure 3, the optimum range for these microspheres is lying between 70 and 450 particles/mm^2. Less microspheres on the surface leads to an underestimation of the width of the marker band, whereas above the upper limit overestimation of the width

occurs. A particular optimal range for these microspheres is lying between 80 and 300 particles/mm^2.

[0079] In Figure 4, for microspheres with a diameter between 32 and 38 µm, the CNR is plotted against the microsphere density, along with the US estimation error on the secondary y-axis. As can be seen in Figure 4, the optimum range for these microspheres is lying between 45 and 225 particles/mm^2. Less microspheres on the surface leads to an underestimation of the width of the marker band, whereas above the upper limit overestimation of the width occurs.

[0080] In Figure 5, for microspheres with a diameter between 38 and 45 µm, the CNR is plotted against the microsphere density, along with the US estimation error on the secondary y-axis. As can be seen in Figure 5, the optimum range for these microspheres is lying between 45 and 150 particles/mm^2. Less microspheres on the surface leads to an underestimation of the width of the marker band, whereas above the upper limit overestimation of the width occurs.

[0081] For microspheres with diameters between 45 and 53 µm, on the other hand, no optimum particle density was found because overestimation of the width of the marker band is manifested over the complete range of particle density (Figure 6).

Example 3

[0082] Solid glass microspheres with a diameter ranging from 38 to 45 µm, as described above, with a density of 2.5 g/mL, were mixed through a polyurethane coating matrix. Subsequently, glass slides and plastic (PEBAX 6233) were coated with these particles in different densities. The coated substrates were measured by ultrasound using a 33 mm linear array probe operating in brightness-mode (B-mode) at 6 MHz. The substrates were placed under an approximate angle of 45 degrees inside a commercially available ultrasound phantom which acted as the medium. From the recorded images the contrast-to-noise ratio (CNR) was determined in the same way as described in Example 1, and the determined CNRs were plotted against the microsphere concentration (Figure 7).

[0083] As can be seen in Figure 7, the CNR values for glass and plastic coated with the same amount of particles are comparable. This demonstrates that the material of the used surfaces does not significantly affect the CNRs.

Example 4

[0084] Example 1 was repeated with the solid glass microspheres with a diameter ranging from 22 to 27 µm, as described above, and with hollow glass microspheres with diameter

ranging from 25 to 27 µm and densities of 0.14 g/mL and 0.46 g/mL. Glass slides were coated with these particles in different densities. The coated substrates were measured by ultrasound using a 33 mm linear array probe operating in brightness-mode (B-mode) at 6 MHz. The substrates were placed under an approximate angle of 45 degrees inside a commercially available ultrasound phantom which acted as the medium. From the recorded images the contrast-to-noise ratio (CNR) was determined in the same way as described in Example 1, and the determined CNRs were plotted against the microsphere concentration (Figure 8).

[0085] As can be seen in Figure 8, the CNR values for the solid and hollow particles are comparable, meaning that solid particles are suitable for improving the visibility of a medical device according to the present invention.

Example 5 (not according to the invention)

[0086] Commercially available air-filled glass microspheres (from Cospheric) with diameters between 38 and 45 µm and a density of 0.46 g/mL were mixed through a coating matrix, Labo coat, which is commercially available from Labo Groep (Tilburg, The Netherlands). The microspheres were added in different amounts in order to prepare mixtures containing 2.0, 3.0 and 4.0 wt. % microspheres in the coating matrix. The coating was applied by dip coating on polyurethane tubes, resulting in coated tubes with a microsphere density of about 130 particles/mm^2 (left image of Figure 9), about 180 particles/mm^2 (middle image of Figure 9), and about 250 particles/mm^2 (right image of Figure 9), respectively.

[0087] The coated tubes were tested by ultrasound with a chicken breast as medium to record the images in.

[0088] Studying the different tubes with ultrasound showed that for higher amounts of microparticles on the surface the surface of the tube starts to appear as rough, whereas at lower amounts the surface appears to be smooth (see Figure 9). At lower amounts the visibility (sharpness of the image) improves.

Example 6

[0089] Solid glass microspheres with a diameter ranging from 38 to 45 µm, as described above in Example 1, were mixed through a polyurethane coating matrix. The microspheres were added in different amounts in order to prepare mixtures containing 1.0 to 75.0 vol. % microspheres in the coating matrix. Subsequently, either 30 or 60 µm thick marker bands of coating were drawn on glass slides using a film applicator. These marker bands were applied by masking the area which was required to be uncoated. The width of the marker bands was measured.

[0090] The coated substrates were measured by ultrasound using a 33 mm linear array probe operating in brightness-mode (B-mode) at 6 MHz. The substrates were placed under an approximate angle of 45 degrees inside a commercially available ultrasound phantom which acted as the medium.

[0091] Figure 10 shows ultrasound images taken in a phantom gel of glass slides on which marker bands (width 1 cm) were applied of Sono-Coat comprising the microspheres (size range 38-45 µm) in a concentration of 38 particles/mm^2 , 125 particles/mm^2 , and 346 particles/mm^2. It is clear that the middle image, which is within the density range of 45-150 particles/mm^2 according to the invention, provides the best visibility combined with an accurate measurement of the width of the marker band. The lower image (density of 346 particles/mm^2) is more vague and overestimation of the marker band width occurs, whereas the upper image is also more vague, appears as a dotted line and underestimates the width of the marker band.

Example 7

[0092] The same kind of experiment as Example 2 was repeated. The same kind of 27-32 µm microspheres were used. These microspheres were coated on glass slides as well as on plastic (PEBAX) surfaces. In Figure 11, the US estimation error is plotted against the microsphere density. From Figure 11 it is clear that the optimum microsphere density range is the same for both the coated glass and the coated plastic surfaces. Like in Figure 3, the optimum range for these microspheres is between 70 and 450 particles/mm^2. Hence, the visibility is dependent upon the scattering effect of the coating, not the surface itself.

References

[0093]

Baldelli et al (Eur. Radiol. 19 (2009); 2275-2285)

Couture et al., Ultrasound in Medicine and Biology, Vol. 32, No. 8, pp. 1247-1255, 2006

Song et al (Applied Optics, Vol. 43, No. 5 (2004); 1053-1062)

EP 0624342

EP 1118337

US 5,081,997

US 5,289,831

US 5,921,933

US 6,506,156

US 2004/0077948

US 2005/0074406

US 2009/0318746

WO 98/18387

WO 00/51136

WO 00/66004

WO 2007/089761

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- US5289831A [0003] [0022] [0022] [0051] [0093]
- US5081997A [0003] [0022] [0022] [0093]
- WO0051136A [0003] [0093]
- EP0624342A [0003] [0093]
- WO9818387A [0003] [0093]
- WO0066004A [0003] [0093]
- US20040077948A [0003] [0093]
- US20050074406A [0004] [0093]
- EP1118337A [0005] [0022] [0093]
- US6506156B [0005] [0022] [0051] [0093]
- US20090318746A [0005] [0022] [0093]
- WO2012148265A [0008]
- US5921933A [0051] [0093]
- WO2007089761A [0051] [0093]

Non-patent literature cited in the description

- **COUTURE et al.**Ultrasound in Medicine and Biology, 2006, vol. 32, 81247-1255 [0013] [0093]
- **SONG et al.**Applied Optics, 2004, vol. 43, 51053-1062 [0043] [0093]
- **BALDELLI et al.**Eur. Radiol., 2009, vol. 19, 2275-2285 [0043] [0093]
- Medicine and Biology, 2006, vol. 32, 81247-1255 [0051]

PATENTKRAV

1. Medicinsk indretning omfattende en coating til ultralyddetektion, hvilken coating omfatter mikropartikler, der er synlige med ultralyd, hvor mikropartiklerne er faste, og hvor diameteren af mindst 60% af mikropartiklerne på den medicinske indretning er mellem 10 og 45 μm, og hvor densiteten af mikropartiklerne på overfladen af den medicinske indretning er mellem 45 og 450 partikler/mm^2.

2. Medicinsk indretning ifølge krav 1, hvor diameteren af mindst 60% af mikropartiklerne på den medicinske indretning er mellem 22 og 45 μm, og hvor densiteten af mikropartiklerne på overfladen af den medicinske indretning er mellem 45 og 450 partikler/mm^2.

3. Medicinsk indretning ifølge krav 1 eller 2, hvor diameteren af mindst 60% af mikropartiklerne på den medicinske indretning er mellem 22 og 27 μm, og hvor densiteten af mikropartiklerne på overfladen af den medicinske indretning er mellem 150 og 450 partikler/mm^2.

4. Medicinsk indretning ifølge krav 1 eller 2, hvor diameteren af mindst 60% af mikropartiklerne på den medicinske indretning er mellem 27 og 32 μm, og hvor densiteten af mikropartiklerne på overfladen af den medicinske indretning er mellem 70 og 450 partikler/mm^2.

5. Medicinsk indretning ifølge krav 1 eller 2, hvor diameteren af mindst 60% af mikropartiklerne på den medicinske indretning er mellem 32 og 38 μm, og hvor densiteten af mikropartiklerne på overfladen af den medicinske indretning er mellem 45 og 225 partikler/mm^2.

6. Medicinsk indretning ifølge krav 1 eller 2, hvor diameteren af mindst 60% af mikropartiklerne på den medicinske indretning er mellem 38 og 45 μm, og hvor densiteten af mikropartiklerne på overfladen af den medicinske indretning er mellem 45 og 150 partikler/mm^2.

7. Medicinsk indretning ifølge et hvilket som helst af kravene 1-6, hvor mikropartiklerne er fremstillet af et materiale valgt fra gruppen bestående af polymerer, keramik, glas,

silikater, organiske materialer, metaller og en hvilken som helst kombination deraf.

8. Medicinsk indretning ifølge et hvilket som helst af kravene 1-7, hvor mikropartiklerne omfatter glas eller silikat.

9. Medicinsk indretning ifølge et hvilket som helst af kravene 1-8, hvor coatingen omfatter et matrixmateriale valgt fra gruppen af polymerer, fortrinsvis hvor polymeren er valgt fra gruppen bestående af en poly(ethersulfon); et polyisocyanat; en polyurethan; en polytetrafluorethylen; en polymer eller copolymer af N-vinyl-pyrrolidon, såsom en copolymer med butylacrylat; en poly(4-vinylpyridin); et polyacrylamid, såsom poly(N-isopropylacrylamid); en poly(amido-amin); en poly(ethylenimin); en polymer eller blokcopolymer af ethylenoxid og propylenoxid, såsom et poly(ethylenoxid-blok-propylenoxid) eller et poly(ethylenoxid-blok-propylenoxid-blok-ethylenoxid); en blokcopolymer eller styren, såsom poly(styren-blok-isobutylen-blok-styren) eller poly(hydroxystyren-blok-isobutylen-blok-hydroxystyren); en polydialkylsiloxan; et polysaccharid; en polystyren, et polyacrylat; en polyalkan, såsom polyethylen, polypropylen og polybutadien; en poly(etherketon), såsom poly(etherketon) eller poly(etheretherketon); en polyester, såsom poly(ethylenterephthalat), polyglycolid, poly(trimethylenterephthalat), poly(ethylenaphthalat), poly(mælkesyre), polycapralaton, poly(butylenterephthalat); polyamider, såsom nylon-6,6, nylon-6, polyphthalamider og polyaramider; et polyalkylmethacrylat, såsom et polymethylmethacrylat og et poly(2-hydroxyethylmethacrylat); og kombinationer deraf, fortrinsvis valgt blandt poly(ethersulfoner), polyurethaner, polyacrylater, polymethacrylater, polyamider, polyisocyanater og kombinationer deraf.

10. Medicinsk indretning ifølge et hvilket som helst af kravene 1-9, hvor indretningen er valgt fra gruppen bestående af katetre, nåle, stenter, kanyler, trakeotomer, endoskoper, dilatatorer, rør, indførere, markører, styletter, snarer, angioplastiindretninger, fiducials, trokarer og tænger.

11. Fremgangsmåde til fremstilling af en medicinsk indretning ifølge et hvilket som helst af kravene 1-10, hvilken fremgangsmåde omfatter:

- tilvejebringelse af en medicinsk indretning, og

- coating af denne indretning med faste mikropartikler, der er synlige med ultralyd, således at diameteren af mindst 60% af mikropartiklerne på den medicinske indretning er mellem 10 og 45 μm, og densiteten af mikropartiklerne på overfladen af den medicinske indretning er mellem 45 og 450 partikler/mm^2.

12. Fremgangsmåde ifølge krav 11, hvor indretningen er coatet med mikropartikler, der er synlige med ultralyd, således at diameteren af mindst 60% af mikropartiklerne på den medicinske indretning er mellem 22 og 45 μm, og densiteten af mikropartiklerne på overfladen af den medicinske indretning er mellem 45 og 450 partikler/mm^2.

DRAWINGS

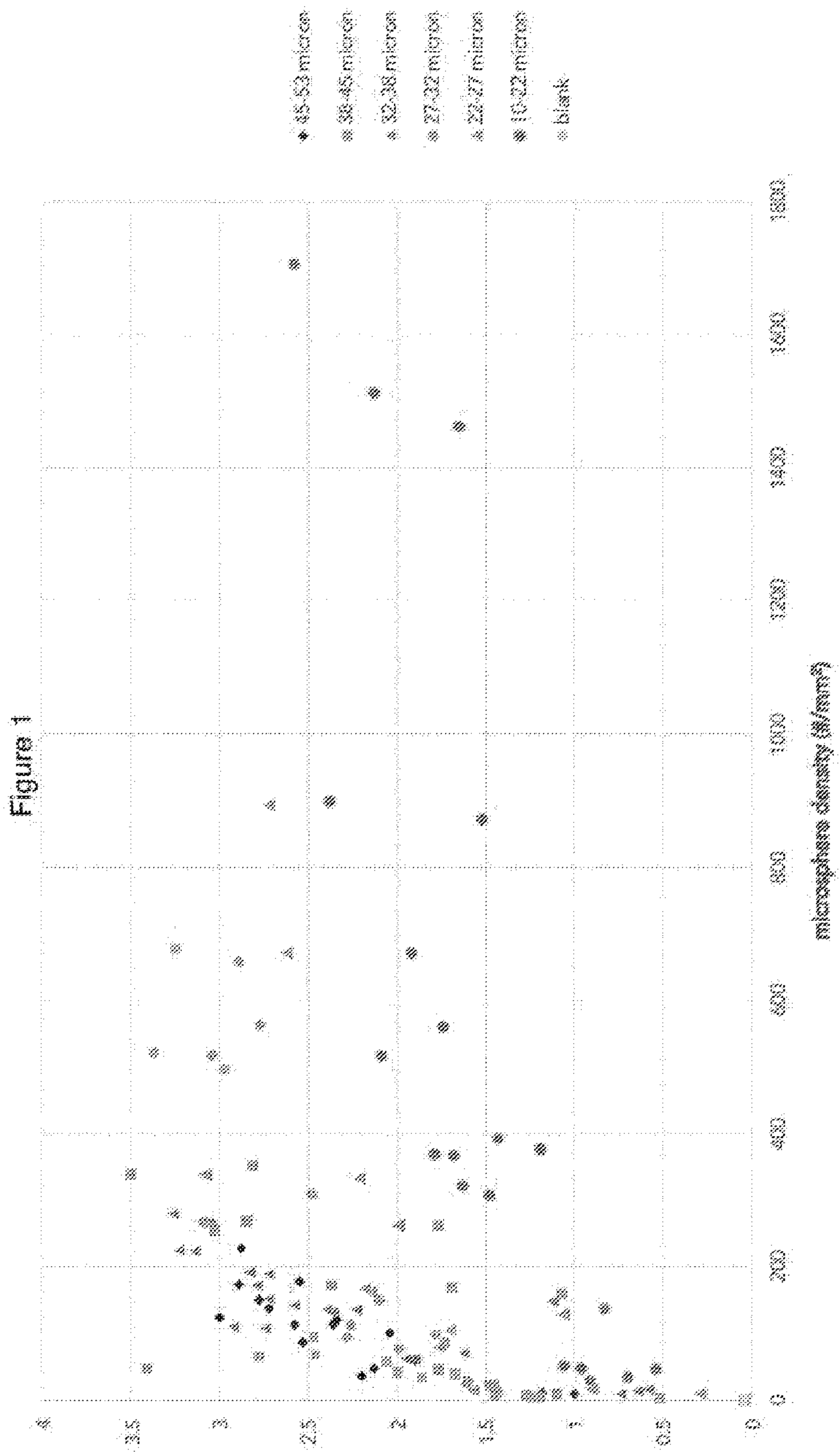
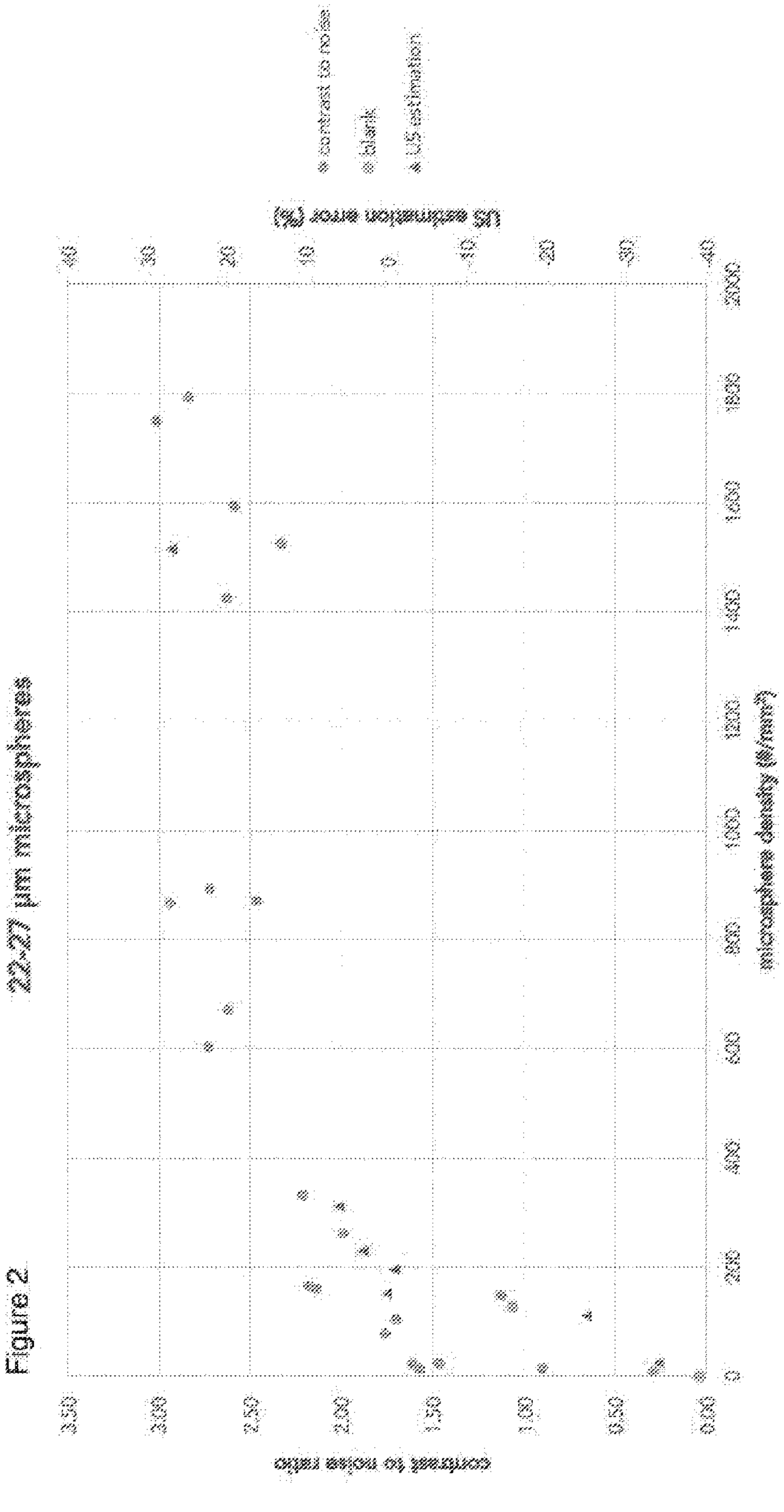


Figure 1


US estimation
blank
control to noise
US estimation error (%)
0.00
0.50
1.00
1.50
2.00
2.50
3.00
3.50
4.00
control to noise ratio
0
200
400
600
800
1000
1200
1400
1600
1800
number of samples
Figure 2

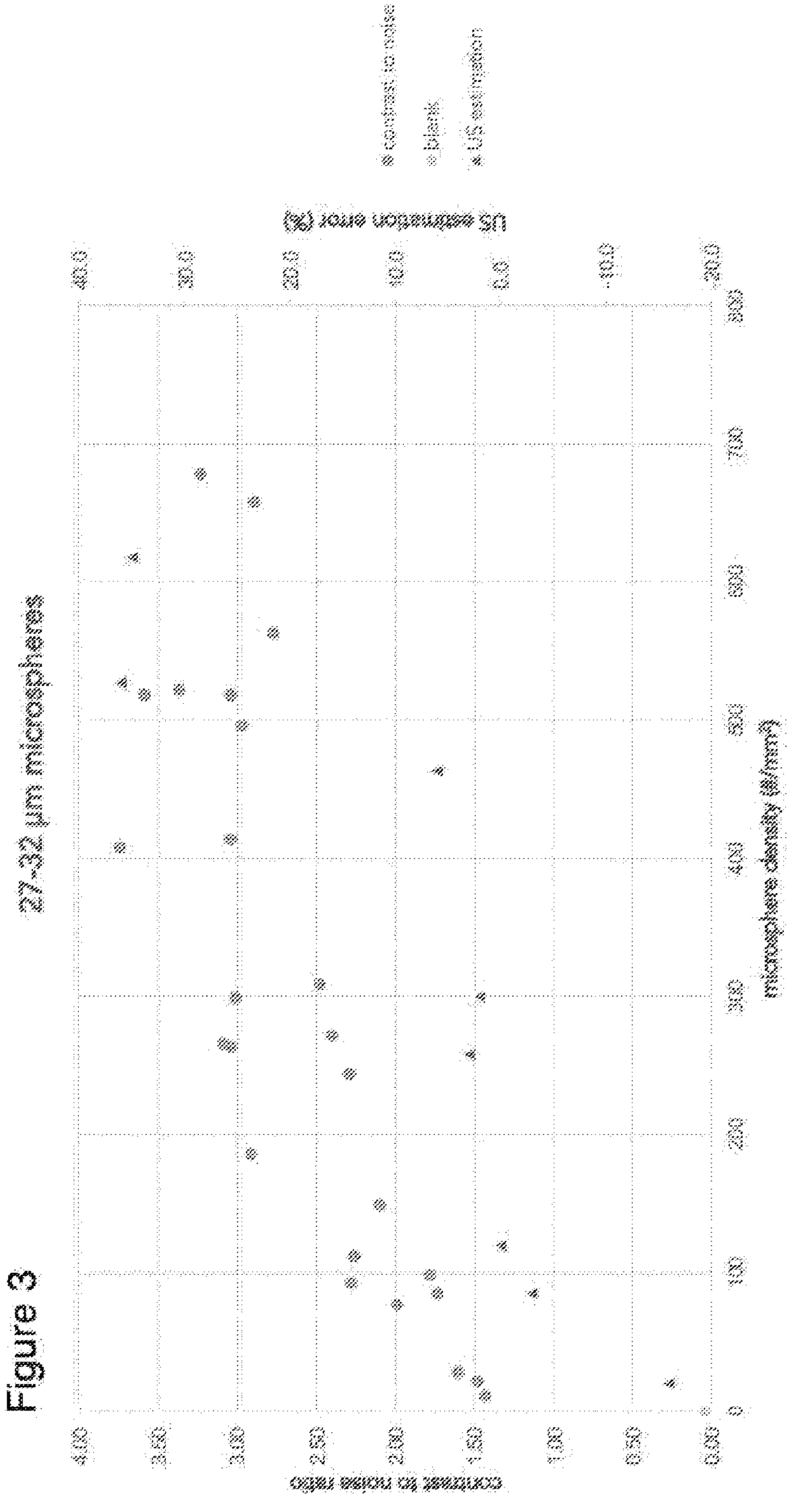

control to noise
blank
US estimation
US estimation error (%)
0.00
0.05
0.10
0.15
0.20
0.25
0.30
0.35
0.40
2-22 µm microspheres
number of microspheres
0
50
100
150
200
250
300
350
400

Figure 3

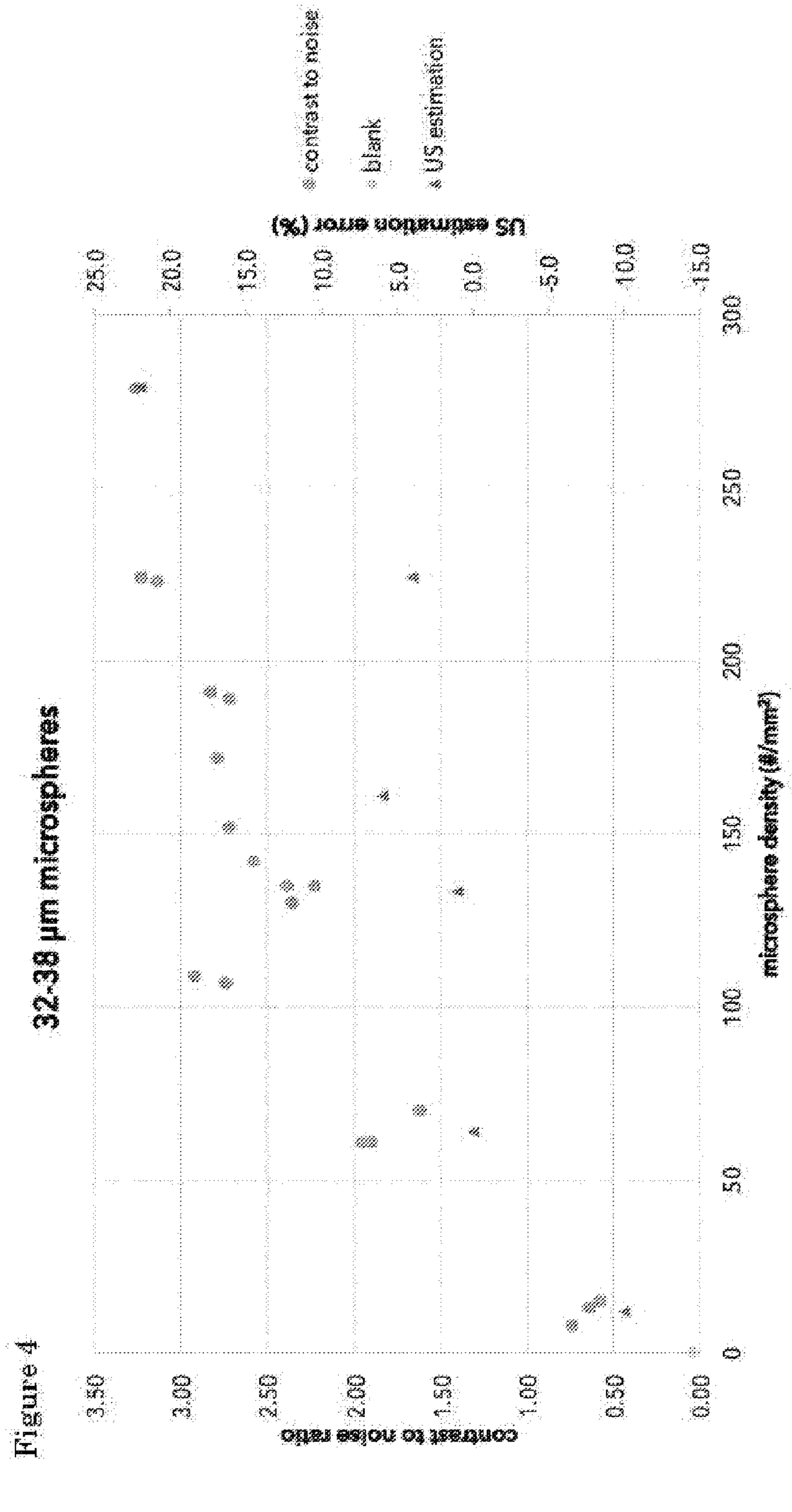

32-38 µm microspheres
contrast to noise ratio
US estimation error (%)
microsphere density (#/mm²)
contrast to noise
blank
US estimation
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00
25.0
20.0
15.0
10.0
5.0
0.0
-5.0
-10.0
-15.0
0
50
100
150
200
250
300

Figure 4

Figure 5

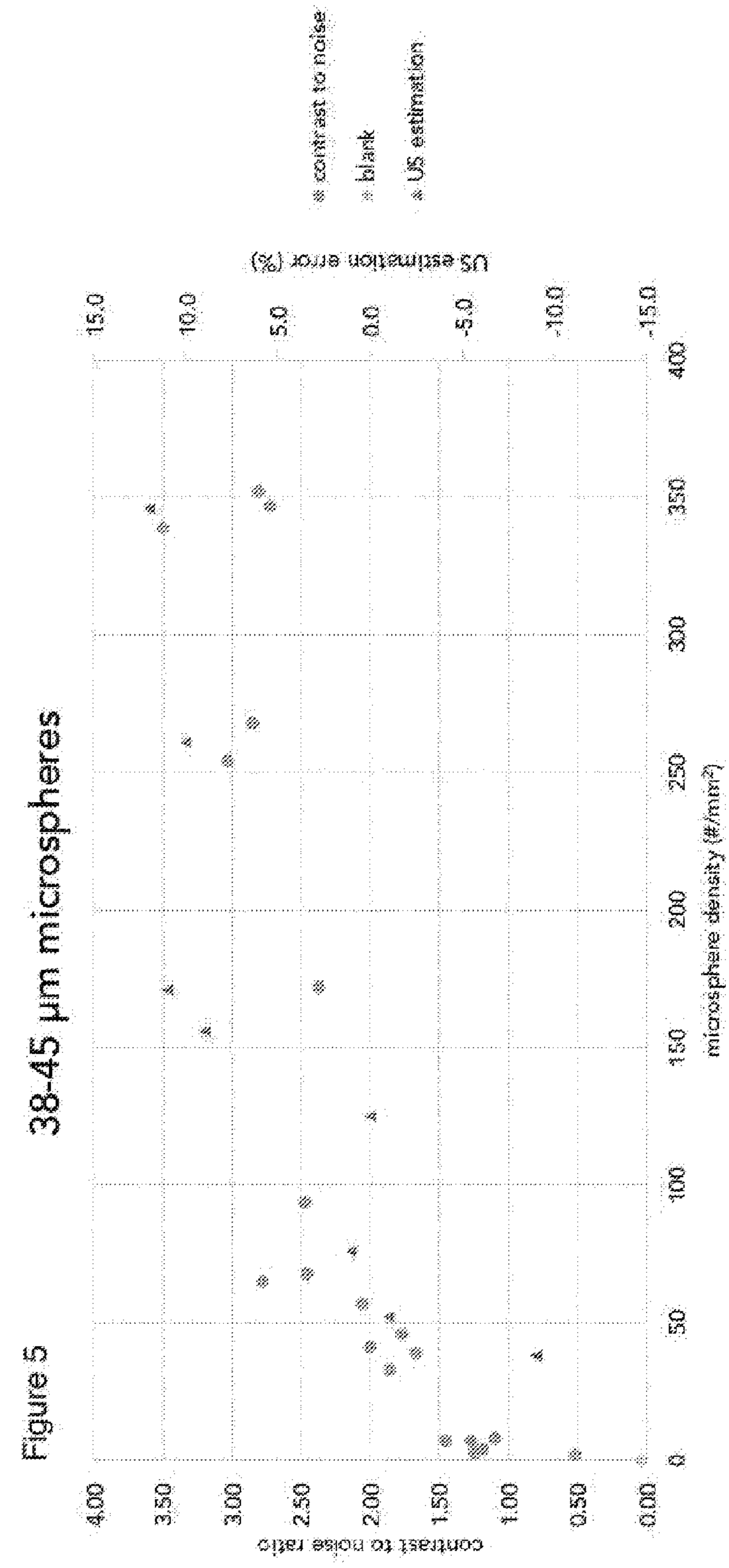
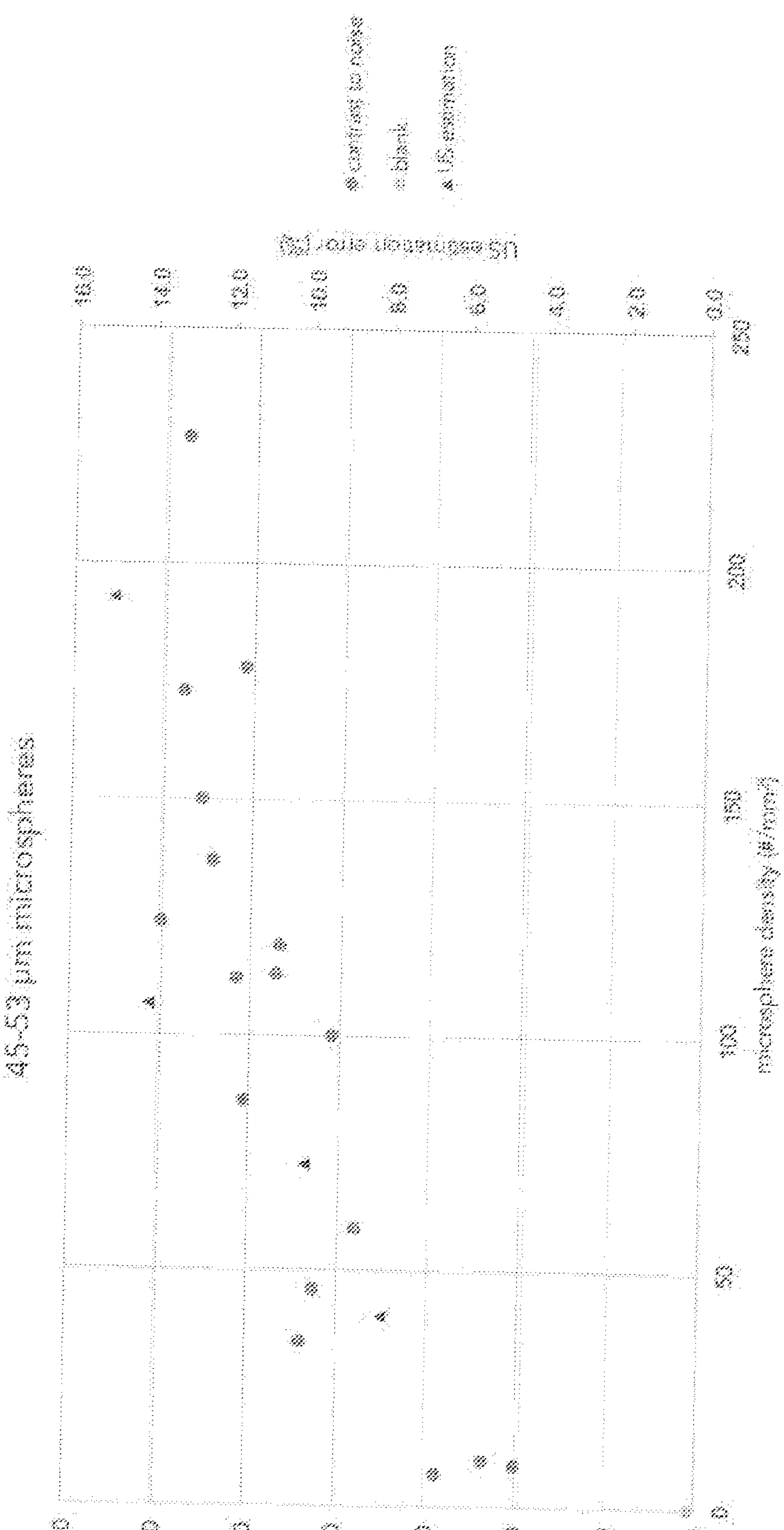

38-45 µm microspheres
US estimation error (%)
15.0
10.0
5.0
0.0
-5.0
-10.0
-15.0
400
350
300
250
200
150
100
50
0
microsphere density (#/mm²)
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00
contrast to noise ratio
blank
US estimation
contrast to noise

Figure 6


45-53 µm microspheres
contrast to noise ratio
microsphere density (#/mm²)
US estimation error (%)
contrast to noise
blank
US estimation
0.00
0.50
1.00
1.50
2.00
2.50
3.00
3.50
0
50
100
150
200
250
0.0
2.0
4.0
6.0
8.0
10.0
12.0
14.0
16.0

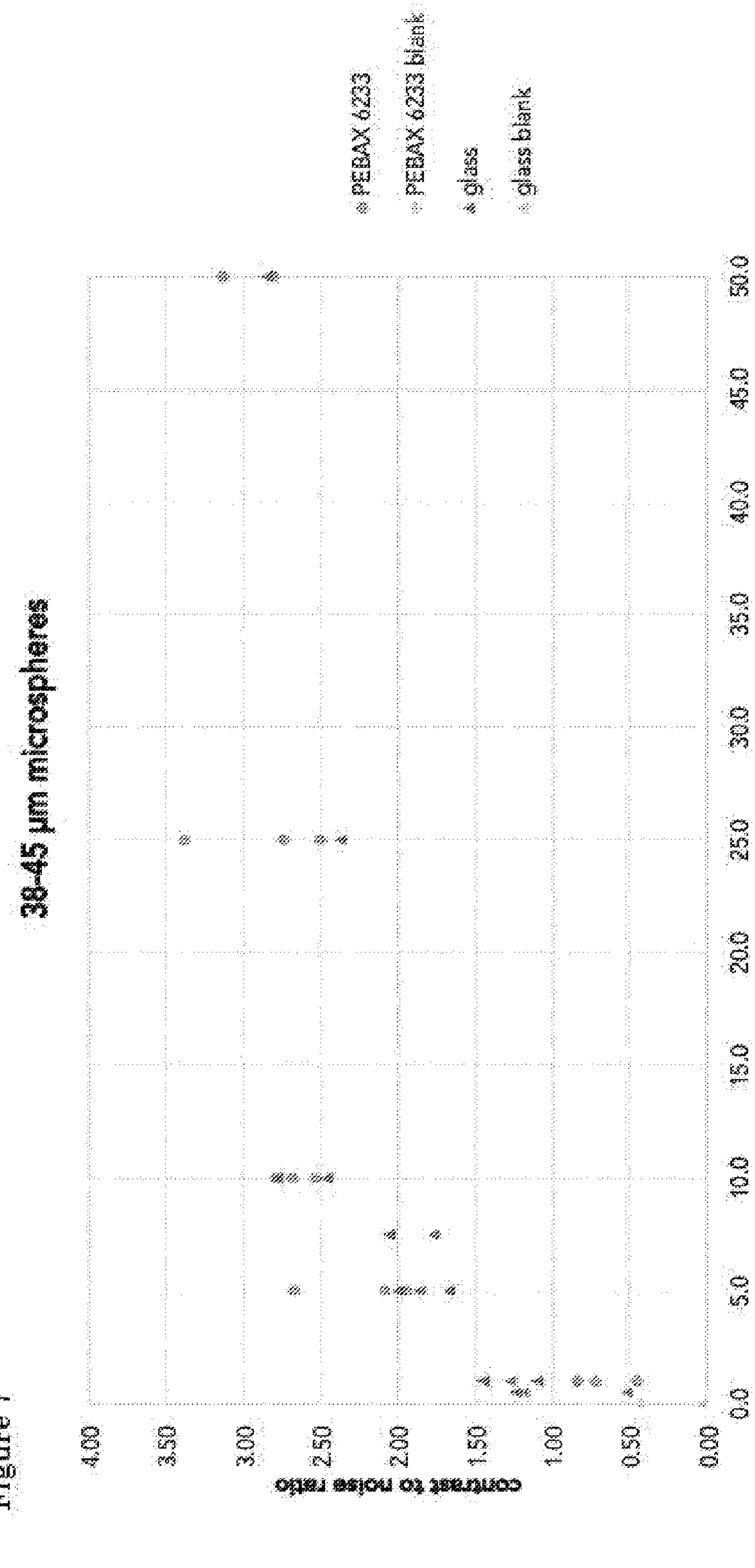

30-45 µm microspheres
PEBAX 6233
PEBAX 6233 blank
glass
glass blank
contrast to noise ratio
microsphere concentration (%(v/v))
0.00
0.50
1.00
1.50
2.00
2.50
3.00
3.50
4.00
0.0
5.0
10.0
15.0
20.0
25.0
30.0
35.0
40.0
45.0
50.0

Figure 7

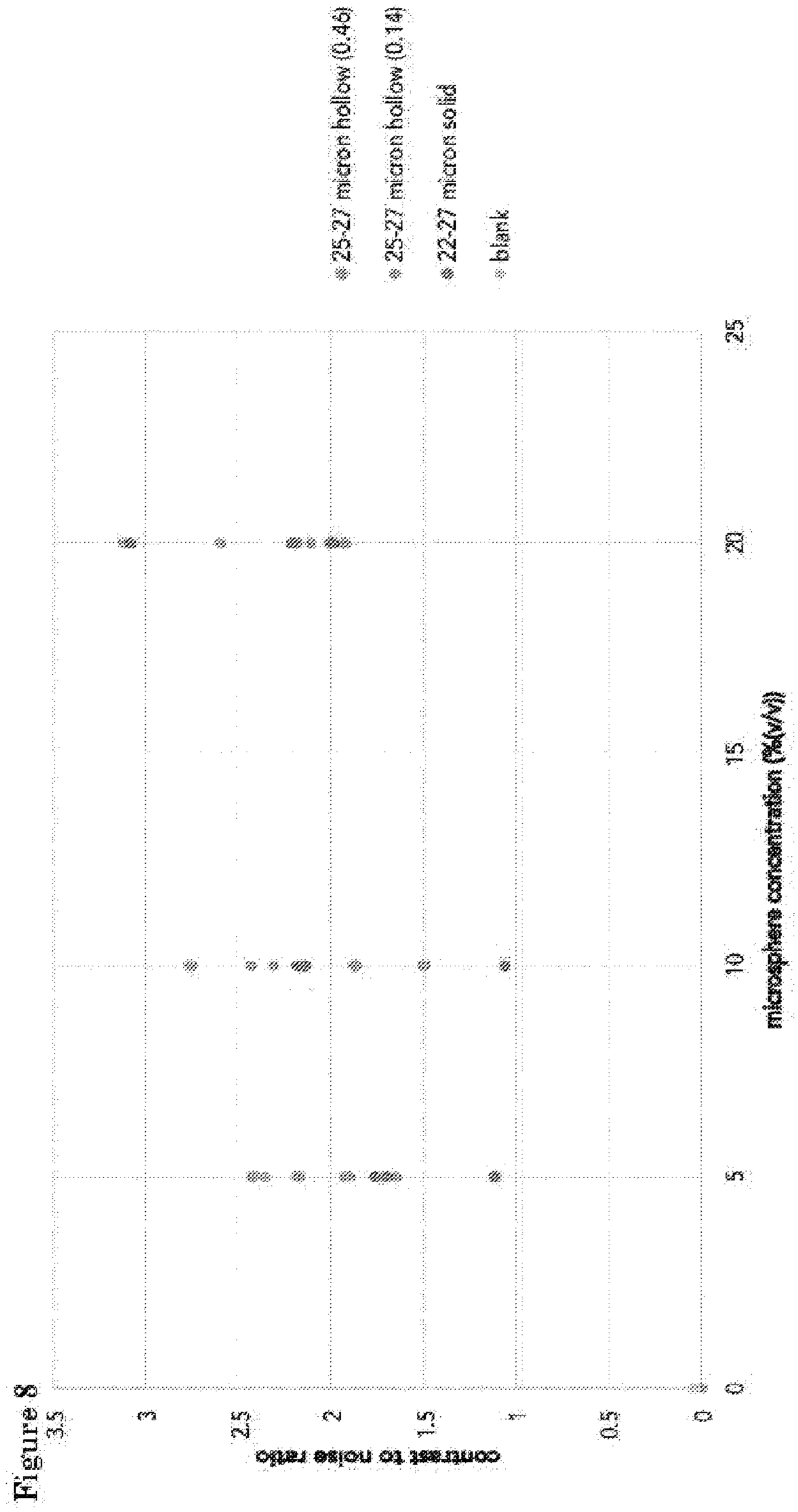

25-27 micron hollow (0.46)
25-27 micron hollow (0.14)
22-27 micron solid
blank
contrast to noise ratio
3.5
3
2.5
2
1.5
1
0.5
0
0
5
10
15
20
25
microsphere concentration (%v/v)

Figure 8

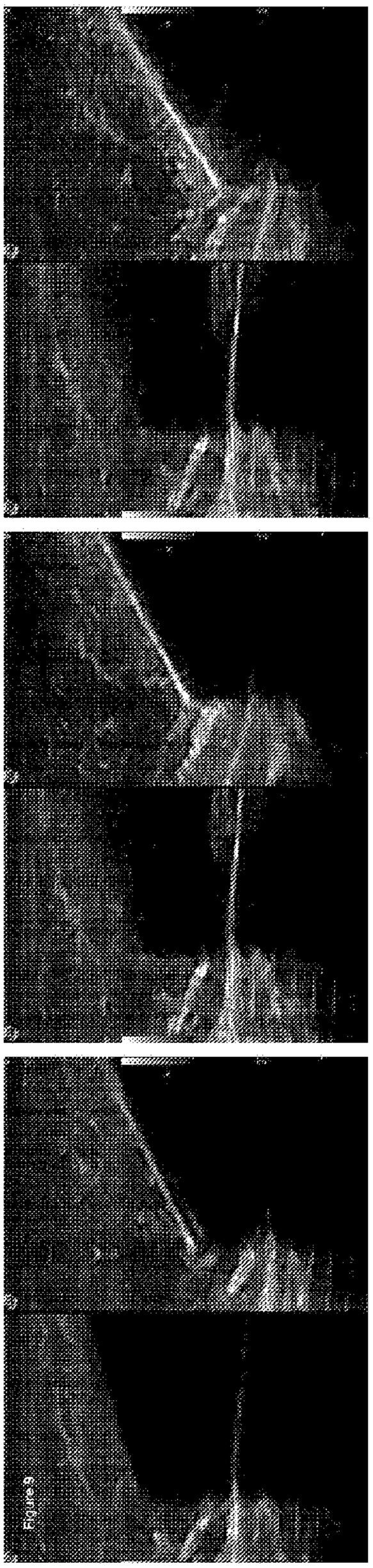


Figure 9

Figure 10

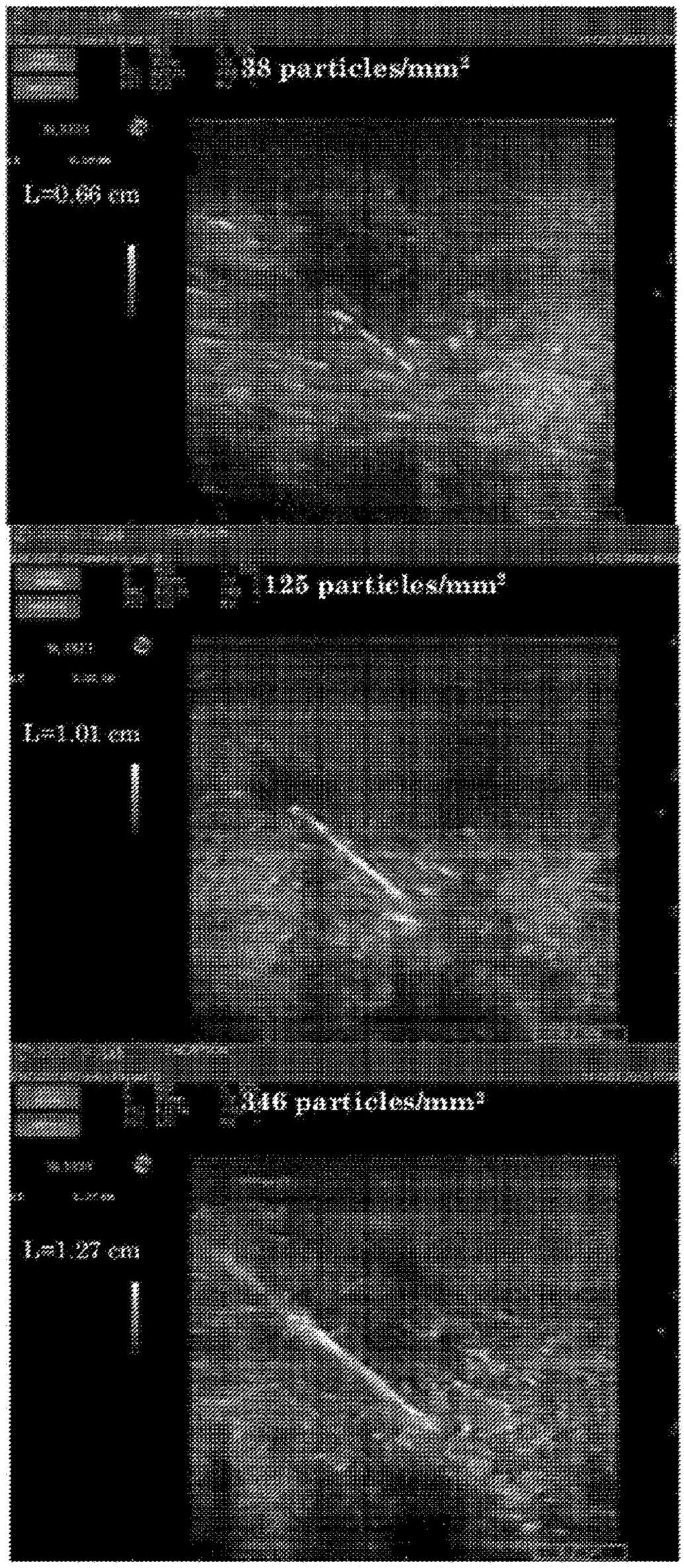

88 particles/mm²
L=0.66 cm
125 particles/mm²
L=1.01 cm
346 particles/mm²
L=1.27 cm

Figure 11

27-32 µm microspheres