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627456

APPLICATION FOR A STANDARD PATENT

Schering Aktiengesellschaft, a company registered under the laws of the Federal Republic of Germany, of Mullerstrasse 170-178, D-1000 BERLIN 65, FEDERAL REPUBLIC OF GERMANY

hereby applies for the grant of a standard patent for an invention entitled

Ultrasonic contrast medium made up of small gas bubbles and fatty-acid-containing microparticles

which is described in the accompanying complete specification.

Details of basic application(s):

Basic Application: Country:

P 38 34 705.9

FEDERAL REPUBLIC OF GERMANY

Date:

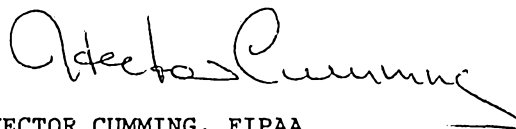
7 October 1988

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DATED this TWENTY SEVENTH day of APRIL
1989

Schering Aktiengesellschaft
By Its Patent Attorneys
ARTHUR S. CAVE & CO.



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The Commissioner of Patents
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FEE: 285.00

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NOTICE OF ENTITLEMENT

We, SCHERING AKTIENGESELLSCHAFT of Mullerstrasse 170-178, D-1000 Berlin 65, Germany, being the applicant in respect of Application No. 33900/89, state the following:-

The person nominated for the grant of the patent has entitlement from the actual inventors namely Professor Lothar Lange, Jurgen Hilmann, Dr. Thomas Fritzsche and Dr. Joachim Siegert by assignment

The person nominated for the grant of the patent is the applicant of the basic application listed on the patent request form. The basic application listed on the patent request form is the first application made in a Convention country in respect of the invention.

Dated this 11th day of June, 1992



A member of the firm of DAVIES COLLISON CAVE
for and on behalf of the applicant

(12) PATENT ABRIDGMENT (11) Document No. AU-B-33900/89
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 627456

- (54) Title
ULTRASONIC CONTRAST MEDIUM MADE UP OF SMALL GAS BUBBLES AND FATTY-ACID-CONTAINING MICROPARTICLES
- International Patent Classification(s)
(51)⁴ **A61K 049/00**
- (21) Application No. : **33900/89** (22) Application Date : **01.05.89**
- (30) Priority Data
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- (56) Prior Art Documents
DE 3637926
AU 26806/84 A61K 49/00
AU 26805/84 A61K 49/00
- (57) Claim

1. A contrast medium for ultrasonic diagnostics comprising a liquid vehicle containing (a) suspended microparticles comprising palmitic-, myristic-, stearic- or arachic- acid or mixtures thereof and at least one solid that is not a surfactant and (b) small gas bubbles.

Our Ref: 249220

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FORM 10

COMPLETE SPECIFICATION

(ORIGINAL)

Application Number:
Lodged:

Complete Specification Lodged:
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Priority:
Related Art:

Applicant(s): Schering Aktiengesellschaft
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Complete specification for the invention entitled "Ultrasonic contrast medium made up of small gas bubbles and fatty-acid-containing microparticles".

The following statement is a full description of this invention, including the best method of performing it known to me:-

ULTRASONIC CONTRAST MEDIUM MADE UP OF SMALL GAS
BUBBLES AND FATTY-ACID-CONTAINING MICROPARTICLES

Cross-Reference to Related Application

This application is a continuation-in-part of
5 Serial No. 06/917,574, filed October 10, 1986, which is
a continuation-in-part of Serial No. 06/600,691, filed
April 16, 1984, the entirety of both of which are
incorporated by reference herein.

Background of the Invention

10 The invention relates to contrast media useful for
ultrasonic diagnostics made up of small gas bubbles and
microparticles; these media ~~are characterized in that~~
they contain as the microparticles a ~~mixture of at least~~
one (C₁₆-C₂₀) fatty acid ^{or mixture of fatty acids} with at least one solid that is
15 not a surfactant, suspended in a liquid vehicle.

The ultrasonic examination of organs (sonography)
is a diagnostic method that has been popular and has
been practiced for several years. Ultrasonic waves in
the megahertz range (above 2 megahertz with wavelengths
20 of between 1 and 0.2 mm) are reflected on interfaces of
various types of tissue. The thus-produced echoes are
amplified and made visible. In this connection, the
examination of the heart with the use of this method,
called echocardiography, is of special significance
25 (Haft, J.I. et al.: "Clinical Echocardiography", Futura,
Mount Kisco, New York 1978; Köhler, E., "Klinische
Echokardiographie" [Clinical Echocardiography], Enke,
Stuttgart 1979; Stefan, G., et al.: "Echokardiographie"
[Echocardiography], Thieme, Stuttgart-New York 1981; G.
30 Biamino, L. Lange: "Echokardiographie", Hoechst AG,
1983).

Since liquids -- blood as well -- yield ultrasonic
contrast in the B-scan image only if there are
differences in density with respect to the surroundings,



possibilities were investigated for making the blood and its flow visible for ultrasonic B-scan image analysis. This has indeed been made feasible by the addition of extremely fine gas bubbles.

5 The blood flow can be imaged even without contrast media by using, during ultrasonic investigation of the heart or the vessels, the weak reflections of ultrasound on the red blood corpuscles and by utilizing the so-called doppler phenomenon. However, in this method the
10 addition of small gas bubbles into the blood flow is likewise advantageous because the stronger reflections on the small gas bubbles permit better utilization of the image [Z. Kardiol, 77 : 227-232 (1988)].

15 Several methods for the production and stabilization of the small gas bubbles have been known from the literature. They can be produced, for example, prior to injection into the bloodstream by vigorous shaking or stirring of solutions, such as saline solutions, dye solutions, or previously drawn blood.

20 Although ultrasonic contrast imaging has thereby been attained, these methods display grave disadvantages manifesting themselves in poor reproducibility, greatly fluctuating size of the small gas bubbles, and -- due to a proportion of visible, large bubbles -- a certain risk
25 of embolism.

30 These drawbacks have been overcome, in part, by other manufacturing methods, such as, for example, by the process disclosed in U.S. Patent 3,640,271 wherein small bubbles of reproducible size are formed by filtration or by the use of an electrode unit under direct current. The advantage of having the possibility of being able to prepare small gas bubbles of reproducible size must be weighed against the disadvantage of considerable technical expenditure.

35 U.S. Patent 4,276,885 describes the production of small gas bubbles having a definite size, these bubbles

being surrounded by a gelatin envelop protecting against coalescence. The finished bubbles can only be stored in the "frozen" condition, for example by storage at refrigerator temperature; for use, they must again be brought to body temperature.

U.S. Patent 4,265,251 discloses the manufacture and use of small gas bubbles with a solid surrounding wall of saccharides which can be filled with a pressurized gas. If the bubbles are under normal pressure, they can be utilized as ultrasonic contrast media; when using increased internal pressure, the bubbles serve for measuring the blood pressure. Although here the storage of the solid gas bubbles does not present a problem, technical expenditure during production represents a considerable cost factor.

The risks inherent in these and other contrast media available in accordance with the state of the art are evoked by two factors: size and number of the solid particles as well as of the small gas bubbles.

The state of the art as discussed thus far permits production of ultrasonic contrast media which in all instances exhibit merely some of the required properties:

- (1) Elimination of risk of embolism
 - small gas bubbles (size and number);
 - solid particles (size and number).
- (2) Reproducibility.
- (3) Adequately long stability.
- (4) Ability of passing through the lungs, for example to obtain ultrasonic contrast of the left portion of the heart.
- (5) Ability to pass through capillaries.
- (6) Sterility and freedom from pyrogens to be displayed by the preparation.
- (7) Ease of manufacture at tolerable cost.
- (8) Storage without problems.

European Patent Application, Publication No. 52575 does disclose the production of small gas bubbles supposedly exhibiting these necessary properties. For their manufacture, microparticles of a solid crystalline compound, e.g., galactose, are suspended in a liquid vehicle; the gas that is adsorbed on the particle surface is occluded in cavities between the particles or in inter-crystalline cavities, forming the gas bubbles. The resultant suspension of small gas bubbles and microparticles is injected within 10 minutes. Although it is asserted in European Patent Application 52575 that the suspension prepared according to the disclosed method is suitable for appearing, after injection into a peripheral vein, on the right side of the heart as well as, after passing through the lungs, in the left side of the heart, and for rendering the blood and its flow visible at that location upon ultrasonic examination, this assertion collapses when subjected to analysis. Thus, it has been found that the contrast medium produced according to the method described in European Application 52575 and injected into a peripheral vein did not evoke any ultrasonic echoes in the left portion of the heart.

EP-A-77752 likewise discloses the preparation of a liquid mixture for use as contrast medium consisting, in turn, of a mixture of a tenside or an aqueous solution of the tenside, and an aqueous, viscous carrier liquid.

In a published European patent application (Publication No. 0122624), which is fully incorporated by reference herein, an agent enhancing ultrasonic contrast and containing microparticles and small gas bubbles is described which is suitable for enhancing, after intravenous administration and passage through the lungs, contrast imaging of the left side of the heart, of the myocardium, as well as other organs, such as the liver,

the spleen, and the kidneys. Although this application also cites fatty acids ["saturated or unsaturated (C₄-C₂₀)-fatty acids"] as being suitable for the production of the microparticles, confirmation by example has only been provided for their esters or salts as surfactant substances, such as, for example, ascorbyl palmitate or sucrose monopalmitate. These, however, exhibit the drawback that they are relatively quickly decomposed in the formulation even when stored under normal conditions (25°C) (see the table below). This is deleterious in regard to a commercial preparation and its purity requirements. The related imaging agent of USP 4,442,843, which disclosure is also incorporated by reference herein, is also deficient.

Summary of the Invention

Accordingly, this invention provides, inter alia, media as well as methods that do not exhibit this disadvantage. This invention employs free fatty acids (saturated) as the surfactant compounds, instead of their salts or esters, for the production of microparticles used in contrast media. In this connection, the fatty acids ~~containing 10-20 carbon atoms are especially suitable, such as, for example, lauric, myristic, palmitic, stearic, or arachic acid, or mixtures thereof.~~ ^{are employed,} Thus, the ultrasound contrast media are made up of small gas bubbles and microparticles, characterized in that they contain, as the microparticles, a mixture of at least one ^{of the above} ~~(C₁₀-C₂₀)-fatty acids~~ with at least one solid that is not a surfactant, suspended in a liquid vehicle.

The ultrasonic contrast media according to this invention, obtained by suspending the microparticles of this invention in a liquid vehicle, are capable of visualizing for ultrasound, upon intravenous administration, the blood and its flow characteristics not only on the right-hand side of the heart, but also, after passing through the capillary bed of the lungs, on the left-hand side of the heart. Moreover, they surprisingly show a higher intensification effect,



stability and better reproducibility of the ultrasonic contrast than the ultrasonic contrast media of the prior art.

TABLE - STABILITY STUDY

5

Formulation: A Galactose + 0.134% Ascorbyl
Palmitate
B Galactose + 0.1% Palmitic Acid
Chemical Stability of Additives in Dependence on
Storage Temperature and Time

10

Storage Period	F O R M U L A T I O N	
	A	B
	% (m/m) Ascorbyl Palmitate	% (m/m) Pal- mitic Acid
Start	100%	100%
6 weeks		
Room Temperature	84.3%	Not analyzed
40°C	67.9%	Not analyzed
50°C	33.6%	97.4%
12 weeks		
Room Temperature	79.8%	98.0%
40°C	53.7%	98.4%
50°C	18.7%	95.1%

15

20

25

Contrast Intensity: A reduction in additive content is accompanied by decrease in left-heart contrast.

30

The surfactant compound in the microparticles is usually utilized in a concentration of 0.01-5% by weight, preferably 0.04-1% by weight.

35

The microparticles comprise a mixture of at least one of the surfactant compounds with at least one physiologically compatible solid. Organic and inorganic materials can be utilized for this purpose, e.g., salts, such as sodium chloride, sodium

citrate, sodium acetate or sodium tartrate, monosaccharides, such as glucose, fructose or galactose, disaccharides, such as sucrose, lactose or maltose, pentoses, such as arabinose, xylose or ribose, or cyclodextrins, such as α -, β - or γ -cyclodextrin, where galactose, fructose, glucose, lactose and α -cyclodextrin are preferred. They are ^{preferably} contained in the microparticles in a concentration of 95-99.99% by weight, ^{most} preferably, 99-99.96%.

In order to prepare the microparticles, the compounds intended therefor are recrystallized under aseptic conditions. Subsequently, they are comminuted under aseptic conditions, e.g., by grinding in an air jet mill, until the desired particle size has been obtained. A desirable particle size is one comparable to erythrocytes, e.g., of $< 10 \mu\text{m}$, preferably $< 8 \mu\text{m}$. The median value of the micronized product is $1-3 \mu\text{m}$. The particle size is determined in suitable conventional measuring devices. The thus-produced microparticles consist of a mixture of a surfactant compound and a solid that is not a surfactant.

The size of the microparticles attained by the comminuting method as well as the size of the small gas bubbles contained in the contrast medium of this invention ensure hazardless passage of the capillary system and the capillary bed of the lungs, and preclude the formation of embolisms.

The gas volume required for contrast imaging is transported by the microparticles. This volume is, in part, adsorbed on the surface of the microparticles, present in the cavities between the microparticles, or occluded in intercrystalline fashion. The gas (e.g., air, nitrogen or argon) volume transported by the microparticles in the form of small gas bubbles is ^{preferably} $0.02 - 0.6 \text{ ml}$ per gram of microparticles.

The liquid vehicle can be water, aqueous solutions of one or more inorganic salts, such as physiological



sodium chloride solution and buffer solutions, aqueous solutions of mono- or disaccharides, such as galactose, glucose or lactose, mono- or polyhydride alcohols insofar as they are physiologically compatible, such as ethanol, propanol, isopropyl alcohol, polyethylene glycol, ethylene glycol, glycerol, propylene glycol, propylene glycol methyl ether, or their aqueous solutions. Preferred vehicles are water and physiological electrolyte solutions, such as physiological sodium chloride solution, as well as aqueous sugar solutions, such as, for example, galactose, glucose, fructose and lactose. If solutions are employed, the concentration of the dissolved compound is preferably 0.1-30% by weight, more preferably 0.5-15% by weight; in particular, water, 0.9% aqueous sodium chloride solution, or 5-6% aqueous galactose solution is utilized. In general, preferably 1-500, preferably 10-400 mg of microparticles are used per ml of suspension.

The invention also relates to a process for the preparation of the agent of this invention characterized in that microparticles comprising palmitic-, myristic-, stearic- or arachic- acid or mixtures thereof and at least one solid that is not a surfactant are combined with a liquid vehicle and shaken until a homogeneous suspension has been obtained.

In order to produce the ready-for-use ultrasonic contrast medium, the sterile liquid vehicle is added to the sterile combination, present in the form of microparticles, comprising palmitic-, myristic-, stearic- or arachic- acid or mixtures thereof with at least one material that is not a surfactant, and this mixture is shaken until a homogeneous suspension has been formed, for which purpose about 5-10 seconds are required. The resultant suspension is injected immediately after its preparation, but at the latest 5 minutes thereafter, in the form of a bolus into a peripheral vein or an already inserted catheter, typically administering 0.01 ml to 1 ml per kg of body weight.



For practical reasons, the components required for preparing the medium of this invention, such as the liquid vehicle (A) and microparticles comprising palmitic-, myristic-, stearic- or arachic- acid or mixtures thereof
5 and solid that is not a surfactant (B) are preferably stored sterile in the quantity required for one examination in two vessels. Both vessels (vials) preferably have seals permitting withdrawal and filling by means of an injection syringe under sterile conditions. The size of vessel B is
10 such that the content of vessel A can be transferred by injection syringe into B and the combined components can be shaken.

The use of the contrast medium according to this invention will be demonstrated by performing an
15 echocardiographic examination on a baboon weighing 10 kg:

8.5 ml of liquid vehicle (see preparation examples) is withdrawn with an injection syringe from a vial and added to 3 g of microparticles present in a second vial, and shaken for about 5-10 seconds until a homogeneous
20 suspension has been formed. Of this suspension, 2 ml is injected into a peripheral vein (V. jugularis, brachialis or saphena) by way of a three-way valve at an infusion rate of at least 1 ml/sec, better at 2-3 ml/sec. The injection of 10 ml of physiological sodium chloride solution
25 immediately follows the injection of contrast medium at the same rate, so that the contrast medium bolus remains intact as long as possible. Before, during and after injection, a commercially available transducer for echocardiography is held against the thorax of the test animal so that a
30 typical cross section is obtained through the right and left heart. This testing arrangement corresponds to the state of the art and is known to those skilled in the art.

Once the ultrasonic contrast medium has reached the



right heart, an observation can be made in the 2-D echo image or in the M-mode echo image of how the blood labeled by the contrast medium first reaches the level of the right atrium, then the level of the right
5 ventricle and the pulmonary artery, homogeneous filling prevailing for a time period adequate for diagnostic examination. While the cavities of the right heart become empty again in the ultrasonic image, the blood labeled with contrast medium reappears, after passing
10 through the lungs, in the pulmonary veins, fills the left atrium, the left ventricle, and the aorta in a homogeneous fashion, the contrast remaining longer than on the right side of the heart. In addition to imaging of the blood flow through the cavities of the left
15 heart, a contrast image of the myocardium is likewise obtained, reflecting blood circulation.

The use of the ultrasonic contrast medium of this invention is, however, not limited to rendering the bloodstream visible in the arterial portion of the heart
20 after venous administration; rather, with excellent success, the contrast medium is also employed in the examination of the right heart and other organs by contrast medium.

The use and administration of the contrast medium of this invention is analogous to the procedures
25 described, e.g., in the disclosures cited above.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description; utilize the present invention to its
30 fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

In the foregoing and in the following examples, all
35 temperatures are set forth uncorrected in degrees Celsius and unless otherwise indicated, all parts and

right heart, an observation can be made in the 2-D echo image or in the M-mode echo image of how the blood labeled by the contrast medium first reaches the level of the right atrium, then the level of the right
5 ventricle and the pulmonary artery, homogeneous filling prevailing for a time period adequate for diagnostic examination. While the cavities of the right heart become empty again in the ultrasonic image, the blood labeled with contrast medium reappears, after passing
10 through the lungs, in the pulmonary veins, fills the left atrium, the left ventricle, and the aorta in a homogeneous fashion, the contrast remaining longer than on the right side of the heart. In addition to imaging of the blood flow through the cavities of the left
15 heart, a contrast image of the myocardium is likewise obtained, reflecting blood circulation.

The use of the ultrasonic contrast medium of this invention is, however, not limited to rendering the bloodstream visible in the arterial portion of the heart
20 after venous administration; rather, with excellent success, the contrast medium is also employed in the examination of the right heart and other organs by contrast medium.

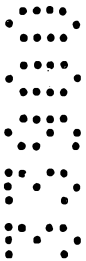
The use and administration of the contrast medium of this invention is analogous to the procedures described, e.g., in the disclosures cited above.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description; utilize the present invention to its
30 fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

In the foregoing and in the following examples, all
35 temperatures are set forth uncorrected in degrees

Celsius and unless otherwise indicated, all parts and percentages are by weight.

The entire texts of all applications, patents and publications, if any, cited above and below, and of
5 corresponding application West German P 38 34 705.9
filed October 7, 1988, are hereby incorporated by
reference.



EXAMPLE 1

(A) Liquid Vehicle: Water for purposes of
----- injection

(B) Preparation of Microparticles:

- 5 I 1,998 g of galactose in 1,080 g of water is purified,
dissolved, filtered under sterile conditions, and
cooled under aseptic conditions to 6-10° C.
- 10 II 2 g of palmitic acid is dissolved in 120 g of ethanol,
filtered under sterile conditions, and added to I
under agitation.
- 15 III The combined solutions are dried under aseptic condi-
tions at about 40° C and under a vacuum of 50 mbar.
- IV The recrystallized product is comminuted under aseptic
conditions by means of an air jet mill to the
following grain size distribution:
- $D_{10} \leq 1 \text{ } \mu\text{m}$
 $D_{50} \leq 2.5 \text{ } \mu\text{m}$
 $D_{90} \leq 5 \text{ } \mu\text{m}$
- 20 Determination of the grain size distribution takes
place after suspending the micronized product in alcohol
with the use of a particle measuring device (e.g. Cilas
Granulometer 715).
- V Packaging of the microparticles is effected into
20 ml vials at respectively 3 g.

(C) Production of Ready-For-Use Ultrasonic
Contrast Medium

By means of an injection syringe, 8.5 ml of
water for injection purposes is transferred into the
5 20 ml vial containing 3 g of microparticles, and the
vial is shaken until a homogeneous suspension is obtained
(5-10 seconds).

EXAMPLE 2

(A) Liquid Vehicle: Water for injection purposes

10 (B) Preparation of Microparticles:

I 1,998 g of galactose in 1,080 g of water is purified,
dissolved, filtered under sterile conditions, and
cooled under aseptic conditions to 6-10° C.

15 II 2 g of myristic acid is dissolved in 120 g of ethanol,
filtered under sterile conditions, and added to I
under agitation.

III The combined solutions are dried under aseptic condi-
tions at about 40° C and under a vacuum of 50 mbar.

20 IV The recrystallized product is comminuted under aseptic
conditions with an air jet mill to the following grain
size distribution:

$$D_{10} \leq 1 \text{ } \mu\text{m}$$

$$D_{50} \leq 2.5 \text{ } \mu\text{m}$$

$$D_{90} \leq 5 \text{ } \mu\text{m}$$

25 Determination of grain size distribution takes place
after suspending the micronized product in alcohol with

a particle measuring instrument (e.g. Cilas Granulometer 715).

V Packaging of the microparticles takes place into 20 ml vials with respectively 3 g.

5 (C) Production of Ready-For-Use Ultrasonic Contrast Medium

Using an injection syringe, 8.5 ml of water for injection purposes is transferred into the 20 ml vial containing 3 g of microparticles, and the vial is
10 shaken until a homogeneous suspension is produced (5-10 seconds).

EXAMPLE 3

(A) Liquid Vehicle: Water for injection purposes

(B) Preparation of Microparticles:

15 I 1,998 g of galactose in 1,080 g of water is purified, dissolved, filtered in sterile state, and cooled under aseptic conditions to 6-10° C.

II 2 g of stearic acid is dissolved in 120 g of ethanol, filtered under sterile conditions, and added to I
20 with stirring.

III The combined solutions are brought to the dry condition in an aseptic environment at about 40° C and under a vacuum of 50 mbar.

25 IV The recrystallized product is comminuted under aseptic conditions by means of an air jet mill to the following grain size distribution:

$$D_{10} \leq 1 \text{ } \mu\text{m}$$

$$D_{50} \leq 2.5 \text{ } \mu\text{m}$$

$$D_{90} \leq 5 \text{ } \mu\text{m}$$

Determination of grain size distribution is made
5 after suspending the micronized product in alcohol
using a particle measuring device (e.g. Cilas
Granulometer 715).

V The microparticles are packaged into 20 ml vials with
respectively 3 g.

10. (C) Production of Ready-For-Use Ultrasonic
Contrast Medium

With the use of an injection syringe, 8.5 ml
of water for injection purposes is transferred into the
20 ml vial containing 3 g of microparticles, and the vial is
15 shaken until a homogeneous suspension is obtained
(5-10 seconds).

EXAMPLE 4

(A) Liquid Vehicle: Water for injection purposes

(B) Preparation of Microparticles:

20 I 1,998 g of galactose in 1,080 g of water is purified,
dissolved, filtered in the sterile state, and cooled
to 6-10° C under aseptic conditions.

II 1 g of myristic acid + 1 g of arachic acid are dis-
solved in 120 g of ethanol, filtered under sterile
25 conditions, and added to I under stirring.

III The combined solutions are brought to dryness under
aseptic conditions at about 40° C and under a
vacuum of 50 mbar.

IV The recrystallized product is aseptically comminuted with the use of a jet air mill to the following grain size distribution:

5 $D_{10} \leq 1 \text{ } \mu\text{m}$
 $D_{50} \leq 2.5 \text{ } \mu\text{m}$
 $D_{90} \leq 5 \text{ } \mu\text{m}$

10 Determination of the grain size distribution takes place after suspending the micronized product in alcohol using a particle measuring device (e.g. Cilas Granulometer 715).

V The microparticles are packaged into 20 ml vials with respectively 3 g.

(C) Production of Ready-For-Use Ultrasonic Contrast Medium

15 By means of an injection syringe, 8.5 ml of water for injection purposes is transferred into the 20 ml vial containing 3 g of microparticles, and the vial is shaken until a homogeneous suspension is obtained (5-10 seconds).

20 EXAMPLE 5

(A) Production of Liquid Vehicle:

25 55 g of galactose is dissolved in water for injection purposes, filled up to a volume of 1,000 ml, filtered through a 0.2 μm filter, respectively 10 ml of the filtered solution is dispensed into 10 ml vials, and sterilized for 15 minutes at 121° C.

(B) Preparation of Microparticles:

- I 1,998 g of galactose in 1,080 g of water is purified, dissolved, filtered under sterile conditions, and aseptically cooled to 6-10° C.
- 5 II 1 g of palmitic acid + 1 g of stearic acid are dissolved in 120 g of ethanol, filtered under sterile conditions, and added to I under agitation.
- III The combined solutions are aseptically dried at about 40° C and under a vacuum of 50 mbar.
- 10 IV The recrystallized product is comminuted under aseptic conditions with an air jet mill to the following grain size distribution:
- $D_{10} \leq 1 \text{ } \mu\text{m}$
- $D_{50} \leq 2.5 \text{ } \mu\text{m}$
- 15 $D_{90} \leq 5 \text{ } \mu\text{m}$
- Determination of the grain size distribution is effected after suspending the micronized product in alcohol, using a particle size measuring device (e.g. Cilas Granulometer 715).
- 20 V The microparticles are packaged into 20 ml vials with respectively 3 g.

(C) Production of Ready-For-Use Ultrasonic
Contrast Medium

Using an injection syringe, 8.5 ml of
galactose solution A is transferred into the 20 ml vial
5 which contains 3 g of microparticles, and the vial is
shaken until a homogeneous suspension is obtained
(5-10 seconds).

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A contrast medium for ultrasonic diagnostics comprising a liquid vehicle containing (a) suspended
5 microparticles comprising palmitic-, myristic-, stearic- or arachic- acid or mixtures thereof and at least one solid that is not a surfactant and (b) small gas bubbles.
2. A medium of claim 1, wherein the microparticles
10 comprise 0.01-5% by weight of myristic, palmitic, stearic or arachic acid or a mixture thereof.
3. A medium of claim 1, wherein the microparticles
15 comprise 0.04-1% by weight of a myristic, palmitic, stearic or arachic acid or a mixture thereof.
4. A medium of claim 1, wherein the microparticles contain, as the solid that is not a surfactant, a cyclodextrin, a monosaccharide, a disaccharide, a
20 trisaccharide, a polyol, or an inorganic or organic salt physiologically acceptable for diagnostic use.
5. A medium of claim 2, wherein the microparticles contain, as the solid that is not a surfactant, a
25 cyclodextrin, a monosaccharide, a disaccharide, a trisaccharide, a polyol, or an inorganic or organic salt physiologically acceptable for diagnostic use.
6. A medium according to claim 1, wherein the
30 microparticles comprise, as the solid that is not a surfactant, galactose, fructose, glucose, lactose or α -cyclodextrin.
7. A medium according to claim 2, wherein the
35 microparticles comprise, as the solid that is not a surfactant, galactose, fructose, glucose, lactose or α -cyclodextrin.



8. A medium of claim 1, wherein the physiologically compatible liquid vehicle is water, a physiological electrolyte solution, an aqueous solution of a mono- or polyhydric alcohol or of propylene glycol methyl ether,
5 or an aqueous solution of a mono- or disaccharide.

9. A medium of claim 8, wherein said alcohol is glycerol or polyethylene glycol.

10 10. A medium of claim 1, wherein the physiologically compatible liquid vehicle is water, a physiological sodium chloride solution, or a 5-6% aqueous galactose solution.

15 11. A medium of claim 7, wherein the physiologically compatible liquid vehicle is water, a physiological sodium chloride solution, or a 5-6% aqueous galactose solution.

20 12. A medium of claim 1, comprising microparticles comprising a mixture of palmitic acid and galactose, suspended in water.

13. A medium of claim 1, comprising microparticles
25 comprising a mixture of myristic acid and galactose, suspended in water.

14. A medium of claim 1, comprising microparticles comprising a mixture of stearic acid and galactose,
30 suspended in water.

15. Solid microparticles comprising (a) an admixture of at least one C_{10} - C_{20} -fatty acid and at least one solid that is not a surfactant and (b) gas.
35

16. Solid particles of claim 15, of a size less than about $10\mu m$.



17. Solid particles of claim 15, wherein said solid that
is not a surfactant is a cyclodextrin, monosaccharide,
disaccharide, trisaccharide, polyol, or inorganic or
organic salt physiologically acceptable for diagnostic
5 use.

18. Solid particles of claim 17, wherein the acid is
myristic, palmitic or stearic acid.

10 19. Solid particles of claim 18, wherein the solid which
is not a surfactant is galactose.

20. Solid particles of claim 19, wherein the acid is
palmitic acid.

15

21. A method of preparation of the contrast medium of
claim 1 comprising:

combining said microparticles with a liquid vehicle
and shaking until a homogeneous suspension of said
20 microparticles is obtained.

22. A contrast medium made in accordance with any one of
Examples 1 to 5 described herein.

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