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(54) Titre : ADJUVANT SOUS FORME DE PARTICULES POUR UN TRAITEMENT HIFU ET SON UTILISATION
(54) Title: PARTICLE ENHANCEMENT AGENT FOR HIGH INTENSITY FOCUSED ULTRASOUND TREATMENT AND
USE THEREOF

(57) **Abrégé/Abstract:**

The present invention discloses a particle enhancement agent for high intensity focused ultrasound (HIFU) treatment, which can increase acoustic energy deposition at the target location during HIFU treatment. The enhancement agent comprises a discontinuous phase comprised of a core material encapsulated by a membrane-forming material and a continuous phase comprising of aqueous medium. The discontinuous phase is uniformly dispersed in the continuous phase and the particle size of the discontinuous phase ranges from 0.1-8µm; the amount of the membrane-forming material in the enhancement agent is 0.1-100g/L; the core material is comprised of a liquid that does not undergo a liquid-gas phase transition at 38-100°C, and the amount of core material in the enhancement agent is 5-200g/L. The particle enhancement agent for HIFU treatment of the present invention can significantly change the acoustic environment of the target location and can increase acoustic energy deposition at the target location during HIFU treatment. Eventually, the ability of clinical HIFU treatment to ablate tumor cells can be significantly improved. Accordingly, the present invention discloses use of a particle enhancement agent for HIFU treatment during HIFU treatment.

ABSTRACT

The present invention discloses a particle enhancement agent for high intensity focused ultrasound (HIFU) treatment, which can increase acoustic energy deposition at the target location during HIFU treatment. The enhancement agent comprises a discontinuous phase comprised of a core material encapsulated by a membrane-forming material and a continuous phase comprising of aqueous medium. The discontinuous phase is uniformly dispersed in the continuous phase and the particle size of the discontinuous phase ranges from 0.1-8 μ m; the amount of the membrane-forming material in the enhancement agent is 0.1-100g/L; the core material is comprised of a liquid that does not undergo a liquid-gas phase transition at 38-100°C, and the amount of core material in the enhancement agent is 5-200g/L. The particle enhancement agent for HIFU treatment of the present invention can significantly change the acoustic environment of the target location and can increase acoustic energy deposition at the target location during HIFU treatment. Eventually, the ability of clinical HIFU treatment to ablate tumor cells can be significantly improved. Accordingly, the present invention discloses use of a particle enhancement agent for HIFU treatment during HIFU treatment.

**PARTICLE ENHANCEMENT AGENT FOR HIGH
INTENSITY FOCUSED ULTRASOUND TREATMENT AND
USE THEREOF**

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FIELD OF THE PRESENT INVENTION

The present invention is related to the fields of medicine and medical treatment, specifically to the field of ultrasound treatment, and more particularly to a particle enhancement agent for HIFU treatment, which can increase acoustic energy deposition at the target location during HIFU treatment, and use thereof.

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BACKGROUND OF THE PRESENT INVENTION

High-intensity focused ultrasound (HIFU) as a new technique to treat tumors and other diseases has already been recognized in clinical applications. HIFU employs focused ultrasound, which provides continuous, high-intensity ultrasound energy at the focus, resulting in instantaneous thermal effects (65-100°C), cavitation effects, mechanical effects and sonochemical effects, to selectively cause coagulative necrosis at the focus, and prevent tumors from proliferation, invasion and metastasis.

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It was demonstrated that the acoustic energy was attenuated exponentially as the transmission distance increased during ultrasound transmission within the body (Baoqin Liu et al., *Chinese Journal of Ultrasound in Medicine*, 2002, 18(8):565-568). In addition, the energy during ultrasound transmission in soft tissues was attenuated due to tissue absorption, scattering, refraction, diffraction and the like, among which the tissue absorption and scattering are mainly responsible for the energy loss (Ruo Feng and Zhibiao Wang as editors in chief, *Practical Ultrasound Therapeutics*, Science and

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Technology Reference Publisher of China, Beijing, 2002.14).
Therefore, when the HIFU treatment is used to treat deep-seated and
large-sized tumors, the acoustic energy transmitted to the target
would be relatively low. Thus, therapeutic efficiency would
5 decrease and treatment time would be prolonged due to the acoustic
energy attenuation.

Of course, although the transmitting power of the therapeutic
transducer might be increased in order to improve the therapeutic
efficiency, the normal tissue along the pathway of the ultrasound
10 transmission is more likely to be burned in a high-intensity
ultrasound environment.

In addition, at present, when the HIFU technique is clinically
applied to a hepatic tumor that is blocked by the ribs in the pathway
of the ultrasound transmission, the ribs are usually removed in order
15 to increase the energy deposition at the target location, shorten the
treatment time and improve therapeutic effects. Thus the
noninvasiveness of HIFU treatment cannot be ensured, which is
undesirable for the patients and doctors.

The above problems have disadvantageously limited the use of the
20 HIFU treatment as a technique for clinical practice. Therefore, the
technical problems with respect to increasing the energy deposition at
target location, effectively treating the deep-seated tumors without
damaging the surrounding normal tissue in the acoustic pathway, and
treating a hepatic tumor that is blocked by the ribs without removal of
25 the ribs, need to be solved urgently.

SUMMARY OF THE INVENTION

One objective of the present invention is to provide a particle
enhancement agent for HIFU treatment, which can enhance the acoustic
30 energy deposition at target tissue during HIFU treatment.

Another objective of the present invention is to provide a method for enhancing acoustic energy deposition at the target location during HIFU treatment using the particle enhancement agent for HIFU treatment of the present invention.

5 A further objective of the present invention is to provide use of a particle enhancement agent for HIFU treatment to enhance the effectiveness of HIFU treatment.

10 In order to achieve the above objectives, in one embodiment, the present invention provides a particle enhancement agent for HIFU treatment. The enhancement agent of the present invention is a substance that can enhance the acoustic energy absorption at target location to be treated with HIFU after its administration to a biological body, i.e. a substance that can be used to reduce the acoustic energy needed to cause lesions of a target tissue (tumor and non-tumor tissue) per unit volume of the tissue during HIFU treatment. In the present invention, the types of substances used as enhancement agents for HIFU treatment are not particularly limited, as long as the substances are lipid emulsions (e.g., fat emulsion or emulsified iodized oil) and can change the acoustic environment of the target tissue and promote therapeutic acoustic energy absorption and deposition at the target tissue.

20 As used herein, the term "lesion" refers to the substantial change in the physiological state of a tumor or normal tissue, generally refers to the coagulative necrosis of a tumor or normal tissue. Energy efficiency factor (EEF) can be used to quantify the acoustic energy needed to cause lesions of a target tissue per unit volume of the tissue. EEF is presented by the expression $EEF = \frac{\eta P t}{V}$ (unit: J/mm³), and refers to the acoustic energy needed to cause lesions of a tumor or normal tissue per unit volume of the tissue, wherein, η refers to the focusing coefficient of a HIFU transducer, which reflects the ultrasound energy focusing capacity of the transducer, here $\eta=0.7$; P refers to the

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total acoustic power of a HIFU source (unit: W), t refers to the total time of HIFU treatment (unit: s); and V refers to the volume of HIFU-induced lesions (unit: mm^3). A substance that greatly decreases the EEF of the target tissue after its administration is more suitable to be used as the enhancement agent for HIFU treatment according to the present invention.

The enhancement agent for HIFU treatment greatly decreases the EEF of the target tissue after its administration. As a result, the ratio between the EEF of the target tissue measured before the administration of the enhancement agent (i.e. $\text{EEF}_{(\text{base})}$) and the EEF of the target tissue measured after the administration of the enhancement agent (i.e. $\text{EEF}_{(\text{measurement})}$) is more than 1, preferably more than 2, and more preferably over 4. The upper limit of the ratio is not particularly limited and a higher ratio is preferred.

Specifically, the enhancement agent for HIFU treatment of the present invention comprises a discontinuous phase comprised of a core encapsulated by a membrane-forming material and a continuous phase comprised of aqueous medium. The discontinuous phase is uniformly dispersed in the continuous phase and the particle size of the discontinuous phase ranges from $0.1\text{-}8\mu\text{m}$, preferably $0.5\text{-}5\mu\text{m}$ and more preferably $2.5\text{-}5\mu\text{m}$; the amount of the membrane-forming material in the enhancement agent is $0.1\text{-}100\text{g/L}$, preferably $5\text{-}50\text{g/L}$ and more preferably $5\text{-}20\text{g/L}$; the core is comprised of a liquid that does not undergo a liquid-gas phase transition at $38\text{-}100^\circ\text{C}$, and the amount of the core material in the enhancement agent is $5\text{-}200\text{g/L}$, preferably $10\text{-}100\text{g/L}$, and more preferably $20\text{-}80\text{g/L}$.

In the above embodiment of the present invention, the membrane-forming material includes: lipids, such as 3-sn-phosphatidylcholine, 1,2-dipalmitoyl-sn-glycero-3-phosphatidylglycerol sodium salt,

1,2-distearoyl-sn-glycero-3-phosphatidylcholine, sodium
1,2-dipalmitoyl-sn-glycero-3-phosphatide,
1,2-dipalmitoyl-sn-glycero-3-phosphatidylcholine, phosphatidylserine
and hydrogenated phosphatidylserine, cholesterol, and glycolipide;
5 saccharides, including, for example, glucose, fructose, sucrose, starch
and the degradation products thereof; proteins, such as albumin,
globulin, fibrinogen, fibrin, hemoglobin, and the degradation products
of plant proteins and the like.

10 In the above embodiment of the present invention, the core
material includes water, saturated fatty acid, unsaturated fatty acid,
such as soybean oil and peanut oil, and iodized oil. The core material is
preferably oil, selected from soybean oil and iodized oil.

15 The membrane-forming material of the particle enhancement agent
for HIFU treatment according to the present invention is preferably a
biocompatible and degradable biomaterial, such as a lipid, such that the
enhancement agent can be injected intravenously, transported through
the blood circulation smoothly, and then phagocytosed quickly by the
tissues of the human body, which are full of reticuloendothelial cells.
Therefore, a mass of enhancement agent can be deposited in the tissues
20 of the human body in a certain time, significantly changing the acoustic
environment of the target tissue. Thus, the ultrasound absorption
capacity of the tissue can be significantly enhanced, the acoustic energy
deposition at the target tissue during HIFU treatment can be increased,
and eventually the ability of clinical HIFU treatment to ablate tumor
25 cells can be improved greatly.

In the above embodiment of the present invention, the aqueous
medium is distilled water, physiological saline or glucose solution. The
concentration of the glucose solution can be up to 50% (w/v). However,
the glucose solution cannot be used as the aqueous medium for the
30 particle enhancement agent for HIFU treatment in diabetic patients.

When oil is used as the core material, the enhancement agent may contain an emulsifier. The emulsifier is typically selected from a group consisting of ethylene glycol mono-C₁₆₋₁₈-fatty acid esters, diethylene glycol mono-C₁₆₋₁₈-fatty acid esters, diethylene glycol di-C₁₆₋₁₈-fatty acid esters, triethylene glycol mono-C₁₆₋₁₈-fatty acid esters, sorbitan fatty acid ester (Span type) emulsifiers, polysorbate (Tween type) emulsifiers, polyethylene glycol monolaurate-based emulsifiers, polyoxyethylene laurate-based emulsifiers, 3-sn-phosphatidylcholine (lecithin), cholic acid, and the like. The amount of emulsifier in the enhancement agent is 5-150g/L. In addition, the enhancement agent may also contain a stabilizing agent, such as carboxymethylcellulose sodium (CMC-Na), carboxymethylcellulose potassium, carboxyethylcellulose sodium, carboxyethylcellulose potassium, carboxypropylcellulose sodium, carboxypropylcellulose potassium, glycerin, and the like. The amount of the CMC-Na contained in the enhancement agent is 0.01-10g/L, preferably 0.05-0.6g/L, and more preferably 0.1-0.3g/L. The amount of the glycerin contained in the enhancement agent is 5-100g/L.

In a more preferred embodiment, in order to increase the stability of the enhancement agent, the enhancement agent is adjusted to pH 7.0-9.0, preferably 7.5-8.5. Inorganic or organic acids or bases may be used to adjust the pH value of the enhancement agent.

Additionally, in order to make the particle enhancement agent for HIFU treatment according to the present invention target a specific tumor tissue or focus, substances having specific affinity to the tumor tissue or the focus, such as a tumor-specific antibody, may be added to the enhancement agent.

In another embodiment, the present invention provides a method for preparing the particle enhancement agent for HIFU treatment. The method comprises:

(1) weighing and mixing a membrane-forming material and a core material to obtain 0.1-100g/L membrane-forming material and 5-200g/L core material, to form an oil phase;

(2) adding an aqueous medium to the oil phase prepared in step (1) up to a predetermined volume, and stirring the mixture to form a coarse emulsion;

(3) emulsifying the coarse emulsion prepared in step (2) by sonication with a power of 300W to 500W for 30 seconds to 3 minutes.

In the method for preparation of the particle enhancement agent for HIFU treatment of the present invention, it is preferable that the membrane-forming material and the core material are fully dissolved by heating to form the oil phase in the step (1). And it is more preferable that a stabilizing agent may be added to the mixture before the membrane-forming material and the core material are fully dissolved. The aqueous medium in step (2) may contain an emulsifier.

The present invention is further directed to a method for increasing energy deposition at the target location during the HIFU treatment, wherein, the method comprises administering an effective dosage of the particle enhancement agent of the present invention intravenously via continuous and rapid IV instillation or bolus injection to a patient at 0-24h before applying HIFU treatment to a patient. The effective dosage mentioned above varies with the type of tumor, weight of patient, location of tumor, volume of tumor and the like. However, a doctor or a pharmacist can easily determine the suitable dosage for different patients. For example, the dosage can be selected from the range of 0.01-5ml/kg, preferably 0.01-2.5ml/kg.

DETAILED DESCRIPTION OF THE INVENTION

Example 1

The following materials were mixed: 4g iodized oil for injection

(purchased from Shanghai Chemical Reagent Company), 0.6g yolk lecithin for injection (purchased from Shanghai Chemical Reagent Company) and 1.25g glycerin for injection (purchased from Shanghai Chemical Reagent Company), and this mixture was dissolved and formed an oil phase after heating to 70°C. Distilled water containing 1% (w/v) F-68 emulsifier (purchased from Sigma Company) was added to the oil phase to a final volume of 17.5ml. The mixture was agitated to obtain a coarse emulsion. The coarse emulsion, which was poured into a boiling tube, was emulsified by sonication with a power of 350W for 2 minutes. The resulting uniformly emulsified iodized oil was sterilized through flowing steam at 100°C for 30 minutes. The final product had a pH of 7.5-8.5, iodine content of 0.13g/ml, particle size of less than 1µm, and osmotic pressure of 350mosm/kg H₂O.

Examples 2 to 4

Examples 2 to 4 were prepared according to the same method and procedures described in Example 1 except that the iodized oil for injection was replaced with soybean oil for injection as the core material, and the yolk lecithin for injection was replaced with lecithin as the membrane-forming material. The particle enhancement agent for HIFU treatment of the present invention was obtained according to the formulation set forth below in Table 1. The enhancement agents were obtained as white emulsion liquids, which can be administered to animals and human beings via intravenous injection. The parameters of the products were also shown in Table 1.

Table 1

	Example 2	Example 3	Example 4
Concentration of Soybean oil for injection in the enhancement agent (w/v)	10%	20%	10%
Amount of Soybean oil for injection	100g	200g	100g
Amount of Lecithin for injection	12g	12g	12g
Amount of Glycerin for injection	22g	22g	16.7g
Final volume after Water for injection added	1000ml	1000ml	1000ml
pH (c.a.)	8	8	8
Particle size of the discontinuous phase	0.1-2 μ m	1-5 μ m	0.5-2 μ m
Osmotic pressure (mosm/kg H ₂ O)	300	350	310
Energy MJ (kcal)	4.6 (1100)	8.4 (2000)	12.6 (3000)

The animal tests are presented below to show the effects of the enhancement agent for HIFU treatment of the present invention in combination with use of HIFU Tumor Therapeutic Devices.

Animal test 1 Combined use of the particle enhancement agent for HIFU treatment as prepared in Example 3 and HIFU Therapeutic System Model-JC

Fifty New Zealand white rabbits (about 3 months old) with no limitation on sex, which were provided by the Laboratory Animals Center of Chongqing University of Medical Sciences, were equally divided into Group A and Group B. The rabbits in Group A and

Group B weighed $2.22 \pm 0.21\text{kg}$ and $2.24 \pm 0.19\text{kg}$ ($P > 0.05$), respectively.

The New Zealand white rabbits were anaesthetized through intramuscular injection, fastened to the treatment bed of a High-intensity Focused Ultrasound Tumor Therapeutic System Model-JC manufactured by Chongqing Haifu (HIFU) Technology Co. Ltd., and then treated with this System. The High-intensity Focused Ultrasound Tumor Therapeutic System Model-JC is composed of an adjustable power generator, a B-mode ultrasound monitoring system, a therapeutic transducer, a mechanical motion control system, a treatment bed, and an acoustic coupling device. The therapeutic transducer of the System, with a working frequency of 1MHz, diameter of 150mm, and focal distance of 150mm, using standard circulating degassed water with a gas content of no more than 3ppm, can produce a focal region of $2.3 \times 2.4 \times 26\text{mm}$ and deliver an average acoustic intensity of $5500\text{W}/\text{cm}^2$.

The rabbit livers were pre-scanned by the B-mode scanner of the HIFU therapeutic system. Two slices with an interval of at least 2cm at exposure depth of 2.0cm were measured. For each rabbit of Group A, the left side of the rabbit liver (the left/middle lobe) was considered as the control lobe (which was administered with physiological saline solution), and the right side of the rabbit liver (the right lobe) was considered as the experimental lobe (which was administered with the enhancement agent for HIFU treatment as prepared in Example 3, and also called the enhancement agent side). The control lobe and experimental lobe were reversely positioned in Group B. The exposure depth of HIFU treatment (i.e., the distance from the skin surface to the focal point) was also 2.0cm. After the liver slices were chosen, the physiological saline solution was delivered via rabbit ear border vein at 50-60 drops/min. After 20

minutes, the left side of the rabbit liver (Group A) or the right side of the rabbit liver (Group B) was exposed to HIFU under single pulse exposure or multi-pulse exposure (line length: 1cm, scanning speed: 3mm/s), and gray scale changes and exposure time in the target location were recorded. Then the focal point of the HIFU therapeutic system was moved over to the opposite site. Instead of the physiological saline solution, the enhancement agent for HIFU treatment as prepared in Example 3 was administered intravenously, the injection speed and the time being the same as that of the control lobe of liver. Then the right side of the rabbit liver (Group A) or the left side of the rabbit liver (Group B) was exposed to HIFU. The treatment modes used for both sides of the liver of the same rabbit were the same.

The rabbits were sacrificed and dissected at 24 hours after HIFU treatment. The dimensions (length, width and thickness) of the coagulation necrosis zone of the rabbit liver lesions were measured. The volume of coagulation necrosis was calculated according to the formula of $V = \frac{4}{3}\pi \times \frac{1}{2} \text{ length} \times \frac{1}{2} \text{ width} \times \frac{1}{2} \text{ thickness}$. The EEF was calculated according to the expression $EEF = \frac{\eta Pt}{V}$ (J/mm³). The EEFs were compared between and within Group A and Group B. A substance that greatly decreases the EEF of the target tissue after its administration is more suitable to be used as the enhancement agent for HIFU treatment according to the present invention. The results are shown in Table 2.

Table 2 EEF of the control lobe and the experimental lobe

	Group A	Group B	Totaling	P value
Control lobe	7.09±4.11	6.67±3.13	6.87±3.60	> 0.5*
Experimental lobe	2.73±1.64	3.43±2.07	3.10±1.89	> 0.5*
P value	< 0.001	< 0.001	< 0.001	

The results in Table 2 indicate that there were no notable differences between the rabbits in Group A and those in Group B that were administered with physiological saline solution; and also that there were no notable differences between rabbits in Group A and those in Group B that were administered with the particle enhancement agent for HIFU treatment as prepared in Example 3. However, when comparing the experimental results of the control lobe with those of the experimental lobe, there were significant differences between the control lobes and the experimental lobes in Group A or in Group B. When combining the results of Group A and Group B, it could be seen that the EEF of the experimental lobe greatly decreased. In fact, the EEF of the control lobe which was administered with physiological saline solution is about 2.22 times as much as the EEF of the experimental lobe.

Animal test 2 Combined use of the emulsified iodized oil as prepared in Example 1 and HIFU Therapeutic System Model-JC

Thirty New Zealand white rabbits each weighing approximately 2kg, which were provided by the Laboratory Animals Center of Chongqing University of Medical Sciences, were divided into an experimental group and a control group randomly with 15 rabbits for each group. Two exposure spots were introduced for each rabbit. The

rabbits in the control group were administered with physiological saline solution (dosage: 2.5ml/kg) by rapid injection via rabbit ear border vein. The rabbits in the experimental group were administered with emulsified iodized oil as prepared in Example 1 (dosage: 2.5ml/kg) by rapid injection via rabbit ear border vein followed by flushing with 1ml physiological saline solution in order to ensure that the emulsified iodized oil had entered into the body completely. One hour later, a High-intensity Focused Ultrasound Tumor Therapeutic System Model-JC manufactured by Chongqing Haifu (HIFU) Technology Co. Ltd. was used to radiate the livers of the white rabbits in the experimental group and the control group under single pulse exposure. The power for exposure was 220W; the frequency was 1.0MHZ; the exposure depth was 20mm and the exposure was stopped when coagulative necrosis occurred. The measured data were expressed with mean value $\pm$ SD, processed by the statistics software SPSS 10.0 for Windows using independent and paired sample tests. The enumeration data was determined by using chi-square (χ^2) test. The comparisons between the EEF of the control group and the EEF of the experimental group were shown in Table 3.

Table 3 Comparisons between the EEFs of the control group and the experimental group

Group	N	EEF ($\bar{\chi}\pm s$) (J/mm ³)
Control group	30	31.05 $\pm$ 2.68
Experimental group	30	7.16 $\pm$ 1.38*

N refers to the numbers of the exposure spots.

* P < 0.001 when compared to the control group.

The results in Table 3 show that the emulsified iodized oil as prepared in Example 1 could greatly reduce the level of EEF for

causing lesions of the hepatic tissue with HIFU treatment.

Animal test 3 *In vitro* study of the enhancement agent as prepared in Example 3

5 Ten New Zealand white rabbits (about 3 months old) with no limitation on sex, which were provided by the Laboratory Animals Center of Chongqing University of Medical Sciences, were randomly divided into an experimental group (which was administered with enhancement agent for HIFU treatment as prepared in Example 3) and
10 a control group (which was administered with physiological saline solution). The rabbits in the two groups weighed $2.40 \pm 0.45\text{kg}$ and $2.32 \pm 0.08\text{kg}$ ($P > 0.5$), respectively. These rabbits were fasted for 24 hours before experiments. HIFU gynaecological therapeutic apparatus CZF-1 manufactured by Chongqing Haifu (HIFU) Technology Co.
15 Ltd. was used to radiate the rabbit livers. The HIFU gynaecological therapeutic apparatus CZF-1 was composed of a power source, an applicator, and circulating water as described in Chinese Patent No. 01144259.X. The parameters in this test were set up as follows: power: 4.05W; frequency: 11MHz; and pulse: 1000Hz.

20 After the white rabbits were anaesthetized through intramuscular injection, the enhancement agent for HIFU treatment as prepared in Example 3 was delivered via rabbit ear border vein to the rabbits in the experimental group at 50-60 drops/minute for 20 minutes and the physiological saline solution was delivered to those in the control
25 group at 50-60 drops/minute for 20 minutes.

One hour after transfusion, the rabbit was fastened to a workbench in supine position. For each rabbit, the laparotomy was carried out with a 4-5cm incision in the midsection and the rabbit liver in the abdominal cavity was exposed and pulled out slightly
30 after the abdomen wall was opened layer by layer. One or two

exposure spots on each liver lobe were introduced for each exposure duration of 3s, 6s, and 9s. The experiments were carried out using the parameters as mentioned above after the exposure spots were introduced. After the lesions were generated, the rabbit liver was put back to the abdominal cavity and the abdomen wall was sutured layer by layer.

The next day, the rabbits were sacrificed with excessive anaesthetization. The livers were removed and photographed. The dimensions of lesions were measured and the EEF was calculated. All data was expressed with mean value $\pm$ SD, processed by the statistics software SPSS 10.0 for Windows and the independent sample test. The statistics was significant when P value was less than 0.05. In this test, 21 exposure spots for each exposure duration of 3s, 6s, and 9s and 63 (21 $\times$ 3) exposure spots in total were obtained in the control group; 30 exposure spots for each exposure duration of 3s, 6s, and 9s and 90 (30 $\times$ 3) exposure spots in total were obtained in the experimental group. The EEF was calculated with the above-mentioned expression, and the results are shown in Table 4.

Table 4 The EEF of the control group and the experimental group

	n	Exposure duration		
		3s	6s	9s
Control group	21	0.2749 $\pm$ 0.2409	0.1783 $\pm$ 0.0733	0.1846 $\pm$ 0.0896
Experimental group	30	0.1177 $\pm$ 0.0609	0.1367 $\pm$ 0.0613	0.1463 $\pm$ 0.069
P Value		< 0.01	< 0.05	> 0.05

The results in Table 4 show that the EEF for each exposure duration of 3s, 6s, and 9s in the control group were 2.34, 1.30 and

1.26 times of the EEF for each exposure duration of 3s, 6s, and 9s in the experimental group, respectively. In fact, the mean of the EEF in the control groups (3s, 6s, and 9s) is 1.59 times as much as the mean of the EEF in the experimental groups (3s, 6s, and 9s). If the data obtained in the exposure duration of 9s, which the difference of the EEF between the control group and the experimental group was not statistically significant, were not considered, the mean of the EEF in the control groups (3s, and 6s) is 1.78 times as much as the mean of the EEF in the experimental groups (3s, and 6s).

INDUSTRIAL APPLICABILITY

The particle enhancement agent for HIFU treatment of the present invention can change the acoustic environment of the target location greatly and can reduce the acoustic energy needed to cause lesions of a target tissue (tumor/non-tumor tissue) per unit volume of the tissue during HIFU treatment. Accordingly, deep-seated and large-sized tumors can be treated with HIFU treatment more effectively under a certain acoustic power without damaging the normal tissues along the acoustic pathway. It becomes possible to use the enhancement agent for HIFU treatment of the present invention to treat a patient with hepatic tumor that is blocked by the ribs without removal of the ribs.

Although the present invention has been described in connection with the preferred embodiments, it is not intended to limit the scope of the present invention by the above descriptions of the embodiments. It should be understood that various modifications and changes to which the present invention may be applicable will be readily apparent to those skilled in the art. The claims are intended to cover the scope of the present invention.

WHAT IS CLAIMED IS:

1. An enhancement agent for high intensity focused ultrasound (HIFU) treatment, wherein, the enhancement agent comprises a discontinuous phase composed of a core material encapsulated by a membrane-forming material, and a continuous phase comprised of aqueous medium, the discontinuous phase is uniformly dispersed in the continuous phase and the particle size of the discontinuous phase ranges from 0.1-8 μ m; the amount of the membrane-forming material in the enhancement agent is 0.1-100g/L; the core material is comprised of a liquid that does not undergo a liquid-gas phase transition at 38-100 $^{\circ}$ C and is selected from a group consisting of saturated fatty acid, unsaturated fatty acid and iodized oil, and the amount of the core material in the enhancement agent is 5-200g/L.

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2. The enhancement agent according to claim 1, wherein the discontinuous phase has particle size ranging from 0.5-5 μ m.

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3. The enhancement agent according to claim 2, wherein the discontinuous phase has particle size ranging from 2.5-5 μ m.

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4. The enhancement agent according to claim 1, wherein the membrane-forming material is one or more substances selected from a group consisting of phospholipid, cholesterol and glycolipid.

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5. The enhancement agent according to claim 4, wherein the membrane-forming material comprises phospholipid selected from a group consisting of 3-sn-phosphatidylcholine, 1,2-dipalmitoyl-sn-glycero-3-phosphatidylglycerol sodium salt, 1,2-distearoyl-sn-glycero-3-phosphatidylcholine, sodium

1,2-dipalmitoyl-sn-glycero-3-phosphatidate,
1,2-dipalmitoyl-sn-glycero-3-phosphatidylcholine, phosphatidylserine
and hydrogenated phosphatidylserine.

5 6. The enhancement agent according to claim 1, wherein the
amount of the membrane-forming material in the enhancement agent
is 5-50g/L.

10 7. The enhancement agent according to claim 6, wherein the
amount of the membrane-forming material in the enhancement agent
is 5-20g/L.

15 8. The enhancement agent according to claim 1, wherein the core
material comprises soybean oil.

 9. The enhancement agent according to claim 1, wherein the core
material comprises iodized oil.

20 10. The enhancement agent according to claim 1, wherein the
enhancement agent contains an emulsifier in an amount of 5-150g/L,
the emulsifier is selected from a group consisting of ethylene glycol
mono-C₁₆₋₁₈-fatty acid esters, diethylene glycol mono-C₁₆₋₁₈-fatty acid
esters, diethylene glycol di-C₁₆₋₁₈-fatty acid esters, triethylene glycol
mono-C₁₆₋₁₈-fatty acid esters, sorbitan fatty acid esters, polysorbate,
25 polyethylene glycol monolaurate, polyoxyethylene laurate,
3-sn-phosphatidylcholine, and cholic acid.

30 11. The enhancement agent according to claim 1, wherein the
aqueous medium comprises distilled water, physiological saline
solution or glucose solution.

12. The enhancement agent according to claim 1, wherein the amount of the core material in the enhancement agent is 10-100g/L.

5 13. The enhancement agent according to claim 12, wherein the amount of the core material in the enhancement agent is 20-80g/L.

10 14. The enhancement agent according to any one of claims 1-13, wherein the enhancement agent contains a stabilizing agent comprising carboxymethylcellulose sodium; the amount of the carboxymethylcellulose sodium in the enhancement agent is 0.01-10g/L.

15 15. The enhancement agent according to any one of claims 1-13, wherein the enhancement agent contains a stabilizing agent comprising glycerin; the amount of the glycerin in the enhancement agent is 5-100g/L.

20 16. Use of a lipid emulsion, which is used for preparing an enhancement agent for HIFU treatment according to any one of claims 1-15.

25 17. The use of the lipid emulsion according to claim 16, wherein the lipid emulsion is fat emulsion.

 18. The use of the lipid emulsion according to claim 16, wherein the lipid emulsion is emulsified iodized oil.