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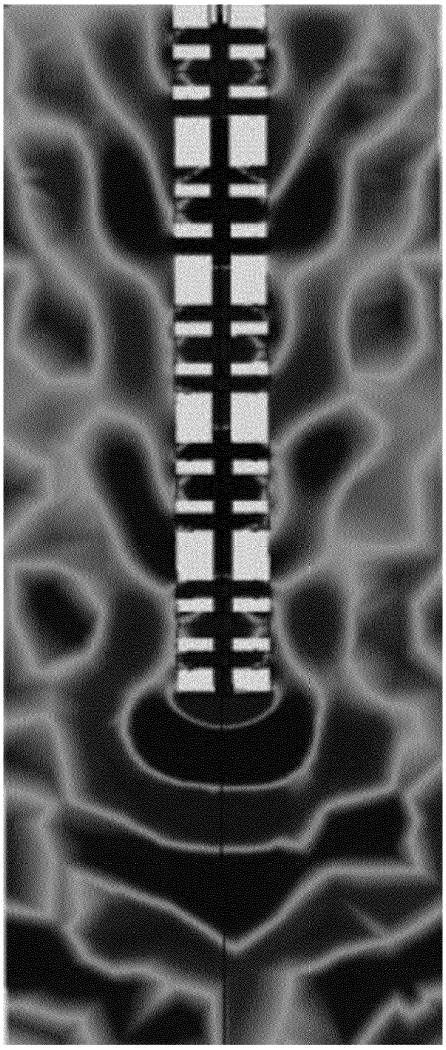
(54) ULTRASONIC PROCESSOR FOR NANOEMULSIONS AND NANOLIPOSOMES PRODUCTION

(57) The invention describes a new ultrasonic processor equipped with ultrasonic generator, piezoelectric transducers and sonotrode submerged in liquid container, designed for the production of nanoemulsions and nanoliposomes **characterized in that** the sonotrode has at least one standing wave length at the average working frequency, is equipped in an axial channel and two perpendicular radial through holes located at a node of the sonotrode and at least two additional radial through holes located at the distance not greater than 30 mm for the node of the sonotrode, while ultrasonic generator works in an frequency sweeping mode with at least 500 Hz frequency span.

Fig. 2



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Description

[0001] Due to the ever-increasing applications of nanoemulsions and nanoliposomes in biophysics, physiology and medicine, many techniques have been developed over recent years to manufacture them. Micro and nano sized emulsions and liposomes can be utilized as carriers of encapsulated drugs. All existing methods to produce these emulsions have serious drawbacks, namely rate of production, high production costs, low efficiency, low quality, end-product contamination with metal particles during production, short operating life of used ultrasonic processors and difficult scale-up procedures. Specifically, for human drug delivery, liposomes (in the order of micro and nano size) are of growing interest as carriers of drugs. For medical applications, these micro and nano spherical shaped liposome carriers are of such a size to be able to travel freely throughout the human body and through the body tissue. The liposomes may also be addressed by means of specific coatings such as sugars and proteins to target them only to specific tissues within the body. Through this new and innovative system of nanoemulsions and nanoliposomes production (high efficiency, selective sizing, batch, or continuous methods for commercial production) to produce the required liposomes, a highly effective liposomal drug delivery can be achieved.

[0002] The formation of nanoemulsions and nanoliposomes requires intense shear forces and significant energy deposition to break the original particles down to the nanometer scale. High ultrasonic amplitudes are required for efficient nanoemulsions and nanoliposomes production. The necessary shear forces are created by ultrasonic cavitation, which produces violently and asymmetrically imploding vacuum bubbles and causes microjets that disperse and break up the original oil droplets and liposomes down to the nanometer scale. Known for many decades, this effect of high-amplitude ultrasound has been extensively studied and successfully used in laboratory-scale research. However, none of the existing ultrasonic liquid processors can generate the required amplitudes on the industrial scale. Commercial implementation of high-power ultrasound has, therefore, been limited to processes for which low amplitudes are sufficient (cleaning, simple deagglomeration, mixing, macroemulsification, etc.). As the high intensity ultrasonics can produce nanosized liposomes, the moderate intensity can also agglomerate them thus rapid leaving of the cavitation zone is of essence to high-yield production.

[0003] The invention describes an improved ultrasonic system based on Multifrequency, Multimode, Modulated Sonic & Ultrasonic Vibrations, also known as MMM, enables a resolution of the typically known and current production disadvantages, especially for nanoliposomes production, in both laboratory and commercial batch and continuous modes. The improved method enables a much narrower size distribution of resulting particles (typically 5nm to 100nm) along with a much shorter production time (which lies between factor 10 and 100 shorter of typical and known production times) along with a completely non-contamination of the product.

[0004] Ultrasonic processor designed to produce nanoemulsions and nanoliposomes accordingly to the invention is equipped with ultrasonic generator, piezoelectric transducers and sonotrode submerged in liquid container, characterized in that the sonotrode has at least one standing wave length at the average working frequency, is equipped in an axial channel and two perpendicular radial through holes located at a node of the sonotrode and at least two additional radial through holes located at the distance not greater than 30 mm for the node of the sonotrode, while ultrasonic generator works in an frequency sweeping mode with at least 500 Hz frequency span.

[0005] The invention is based on a novel sonotrode which consist set of channels realizing sequential and progressive flow of the processed liquid. The processed liquid enters the cavitation zone through holes located near the node and due to differential pressure are pumped towards antinode direction through the axial channel and leaves the system through the other set of holes. To ensure the pumping effect dimeter of inlet hole (located at the node) must be greater than outlet holes. Additionally, node-hole provides certain flexibility of the system making the intensity of ultrasonics greater via Multimode-cavitation thus increased total intensity of ultrasound.

[0006] In addition, sequential and progressive waves pumping and fluid circulating effect are realized via axial hole, enabled fluid under processing to supply perpendicular and lateral holes that are producing vortices additionally intensifying cavitation effect. As the processed liquid is leaves the zone of high intensity cavitation rapidly there is no secondary effect of liposome coagulation.

[0007] Ultrasonic processor accordingly to the invention can operate in different Continuous Wave, or Periodic Pulse-trains, including arbitrary and forced carrier signal modulations, this way producing wideband and complex spatially distributed ultrasonic field structures.

[0008] Sonotrode accordingly to the invention, thanks to its geometry or shape and complex acoustic field structure, is producing effects of particles size reduction, particles agglomerations, multiphase liquids mixing and homogenization, forced and accelerated solid particles precipitation and sedimentation. In addition, sonotrode according to the invention is producing spherical shaping of complex inorganic, biological or organic molecules (mostly based on different turbulent, vortex and spherical ultrasonic field's formations, belonging to non-linear acoustics with Shear fields and evolving transient waving effects). Long, stable, stationary, continuous ultrasonic irradiation (like most of contemporary ultrasonic fluids processing equipment), is not at all producing mentioned vortices and spherical fields formations necessary for non-linear acoustic liquids processing.

[0009] Turbulence is created in a mixture of small sin-

gle particles or molecules within a carrier liquid. Turbulence, in the form of numerous small vortices within the bulk liquid mixture, are created so enabling the agglomerate and sticking together of individual particles and molecules in a highly concentrated and fast twisting or cyclonic manner.

[0010] The turbulence or vortices described above are created using a special submerged rod like resonating element which is activated via a special external power supply or electro-acoustic (or ultrasonic) generator. The resonating rod has axial and perpendicular holes and channels, designed in a way that all of them are synchronously resonating, producing different wave motions, vortices, and shear waves in both axial and radial directions, when submersed. Subsequently, the uniquely designed resonating bar can produce and propagate the required liquid vortices via a combination of low frequency oscillations, ultrasonic frequency oscillations, including forced and frequency- sweeping oscillating regimes with different signal modulations.

[0011] Operation of the generator in frequency sweeping mode is critical to activate various vibrational modes of the sonotrode accordingly to the invention and provide cavitation effect of the highest intensity.

Example and figures explanation:

[0012] The system accordingly to the invention was equipped with 14 nF, 20 kHz Langevin-type piezoelectric transducers, 2 kW MMM-type ultrasonic generator, 20 l liquid container and sonotrode as show on Fig. 1, submerged in the liquid container. The sonotrode was manufactured from Φ60x610 mm Ti6Al4V alloy treated and aged rod which corresponds to 2,5 λ (standing wavelength at 20 kHz in Ti6Al4V) and was equipped in axial through hole of 20 mm diameter and two perpendicular, radial through holes of 20 mm diameter located at each node and two sets of three through holes of 10 mm diameters per each node located at the distance of 25 mm for each node. The sonotrode was submerged in liquid container providing pressure field as show in Fig. 2 and was processing water with 1% polyethylene glycol 1% iron acetate, providing 50-100 nm liposomes at 90% yield after 30 minutes.

Claims

1. Ultrasonic processor equipped with ultrasonic generator, piezoelectric transducers and sonotrode submerged in liquid container, designed for the production of nanoemulsions and nanoliposomes **characterized in that** the sonotrode has at least one standing wave length at the average working frequency, is equipped in an axial channel and two perpendicular radial through holes located at a node of the sonotrode and at least two additional radial through holes located at the distance not greater than 30 mm for the node of the sonotrode, while ultrasonic generator works in an frequency sweeping mode with at least 500 Hz frequency span.

Fig. 1

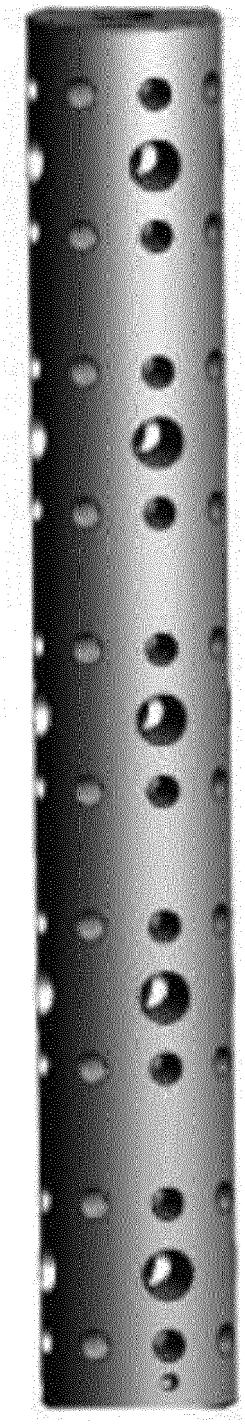
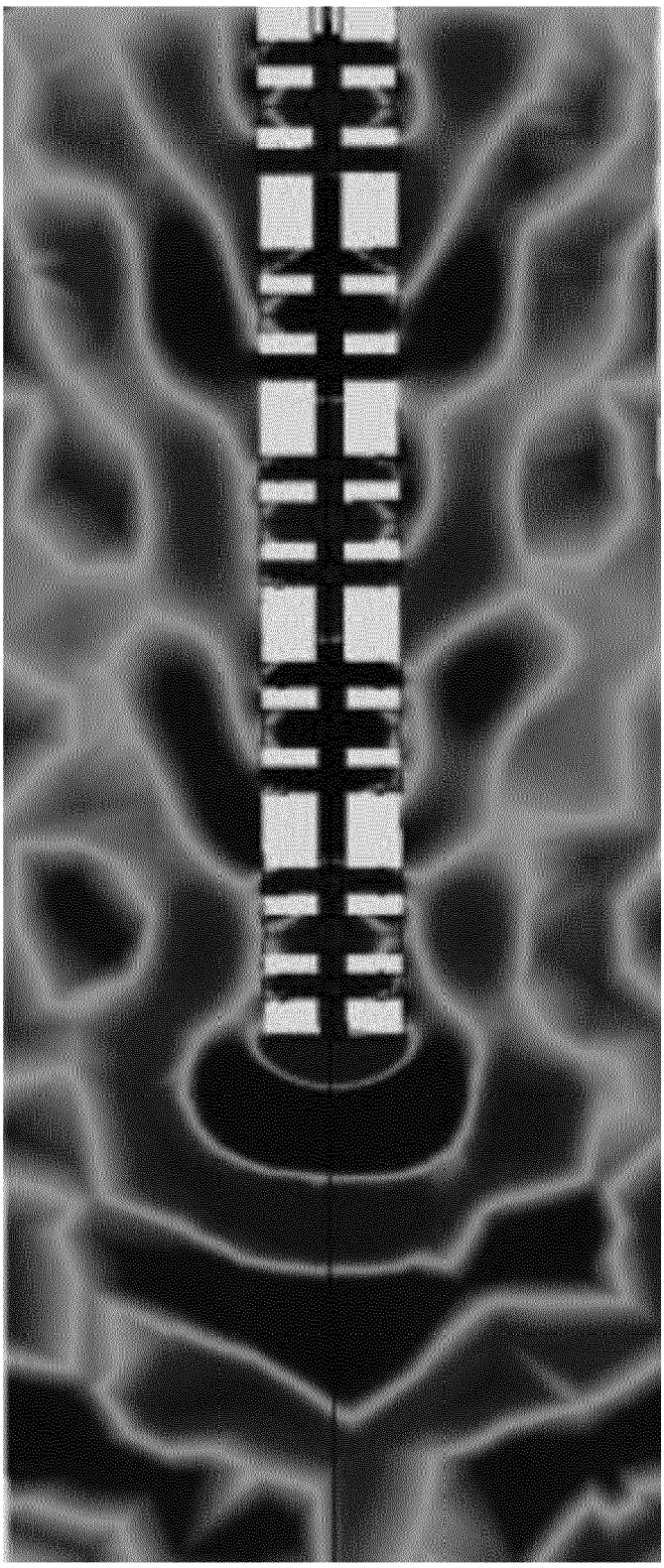


Fig. 2



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EUROPEAN SEARCH REPORT

Application Number
EP 21 02 0302

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X	CH 714 039 A2 (MIODRAG PROKIC LIVINGSTONE [CH]) 15 February 2019 (2019-02-15) * the whole document *	1	INV. B01F23/411 B01F31/85

TECHNICAL FIELDS SEARCHED (IPC)

B01F

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	25 October 2022	Real Cabrera, Rafael

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
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P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
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ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 21 02 0302

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
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25-10-2022

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
CH 714039 A2	15-02-2019	NONE	

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82