US 20060008531A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2006/0008531 A1**

Shekunov et al. (43) **Pub. Date: Jan. 12, 2006**

(54) **METHOD FOR PRODUCING SOLID-LIPID COMPOSITE DRUG PARTICLES**

(75) Inventors: **Boris Y. Shekunov**, Aurora, OH (US); **Pratibhash Chattopadhyay**, North Royalton, OH (US); **Robert W. Huff**, North Royalton, OH (US)

Correspondence Address:
RANKIN, HILL, PORTER & CLARK, LLP
925 EUCLID AVENUE, SUITE 700
CLEVELAND, OH 44115-1405 (US)

(73) Assignee: **FERRO CORPORATION**, Cleveland, OH (US)

(21) Appl. No.: **11/160,367**

(22) Filed: **Jun. 21, 2005**

Related U.S. Application Data

(63) Continuation-in-part of application No. 10/434,426, filed on May 8, 2003.

Publication Classification

(51) **Int. Cl.**
A61K 9/14 (2006.01)

(52) **U.S. Cl.** **424/489**

(57) **ABSTRACT**

A method of producing solid composite lipid/drug nanoparticles that includes the steps of: (1) dissolving a lipid and a drug in a suitable organic solvent to form a solution; (2) emulsifying the solution in a liquid to form an emulsion having a discontinuous phase of micelles comprising the organic solvent, the drug and the lipid, and a continuous phase comprising the liquid; and (3) contacting the emulsion with a supercritical fluid under conditions suitable to keep the supercritical fluid in a supercritical state, whereby the supercritical fluid extracts the organic solvent from the micelles, causing them to precipitate as organic-solvent free solid composite lipid/drug nanoparticles suspended or dispersed in the liquid.

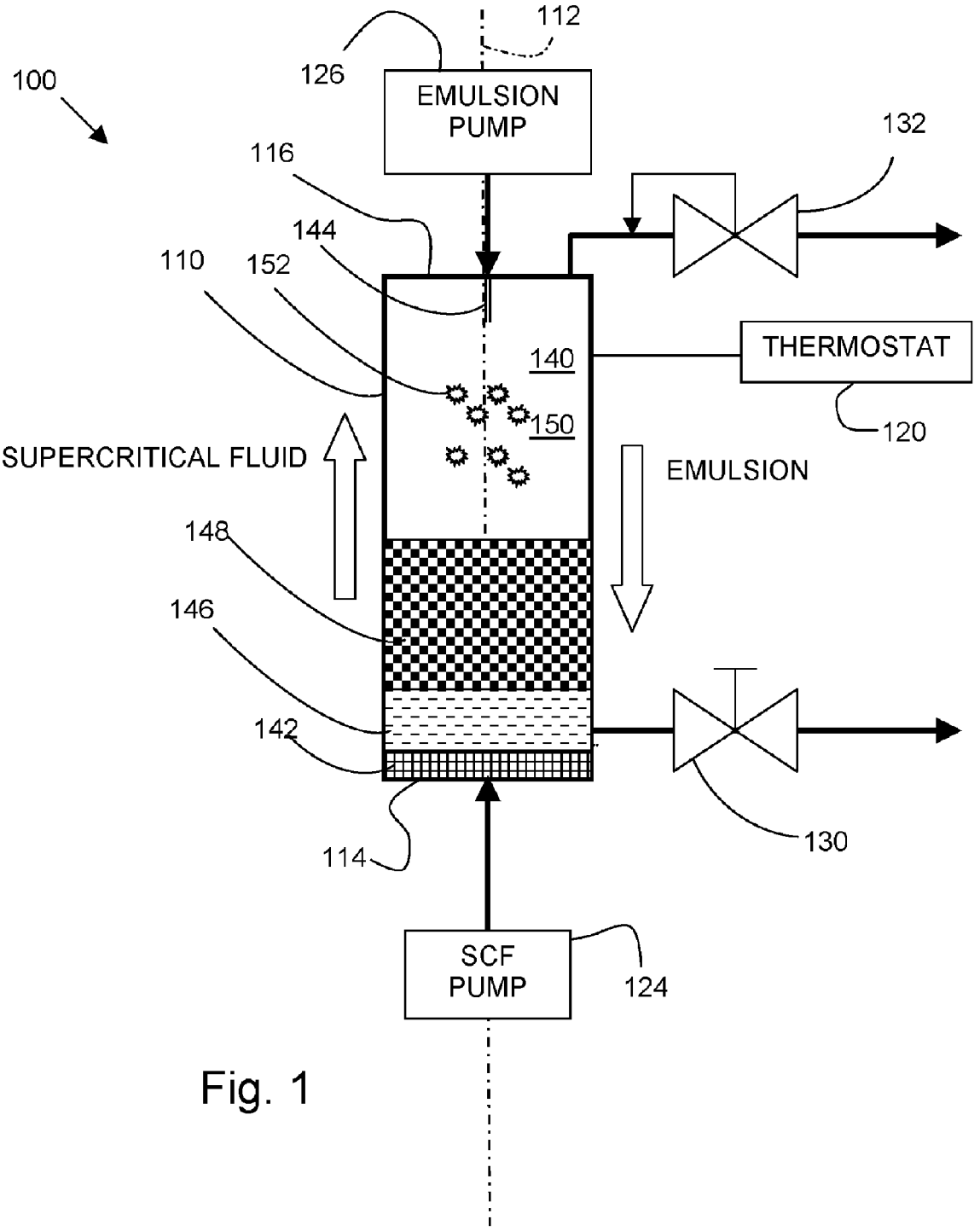
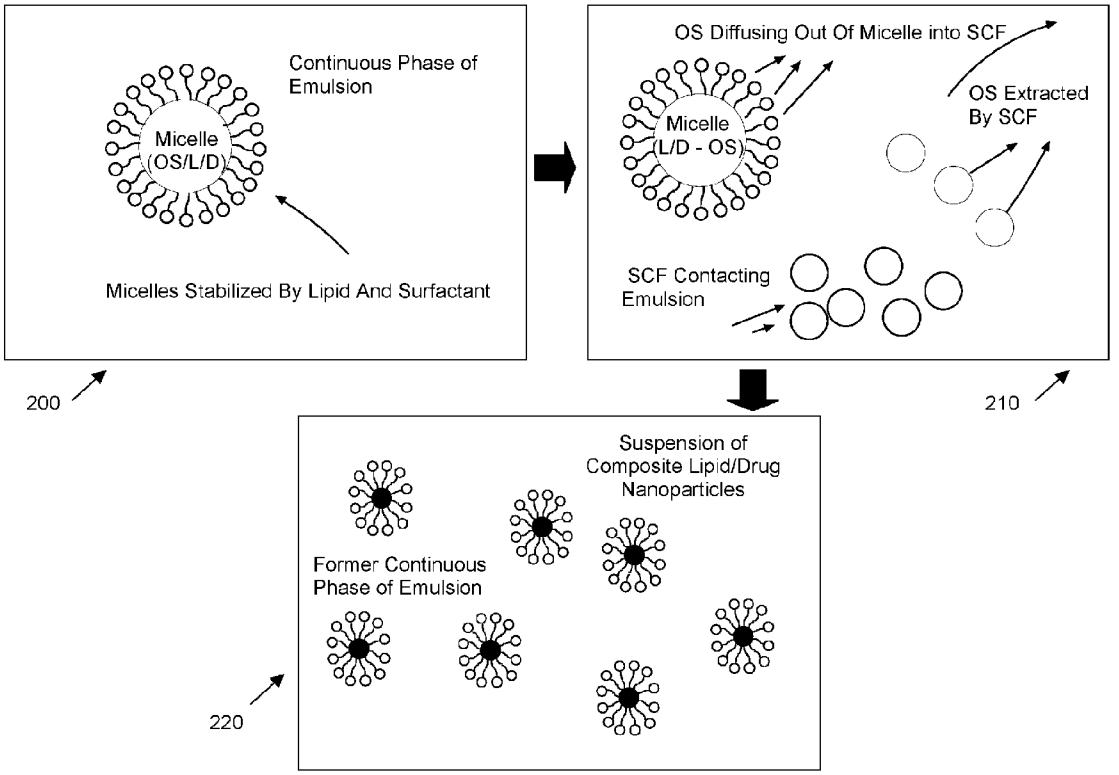

100
112
126
EMULSION PUMP
132
116
144
110
152
140
THERMOSTAT
120
150
SUPERCRITICAL FLUID
EMULSION
148
146
142
114
130
SCF PUMP
124

Fig. 1

Fig. 2


Continuous Phase of Emulsion
Micelle (OS/L/D)
Micelles Stabilized By Lipid And Surfactant
200
OS Diffusing Out Of Micelle into SCF
Micelle (L/D - OS)
OS Extracted By SCF
SCF Contacting Emulsion
210
Suspension of Composite Lipid/Drug Nanoparticles
Former Continuous Phase of Emulsion
220

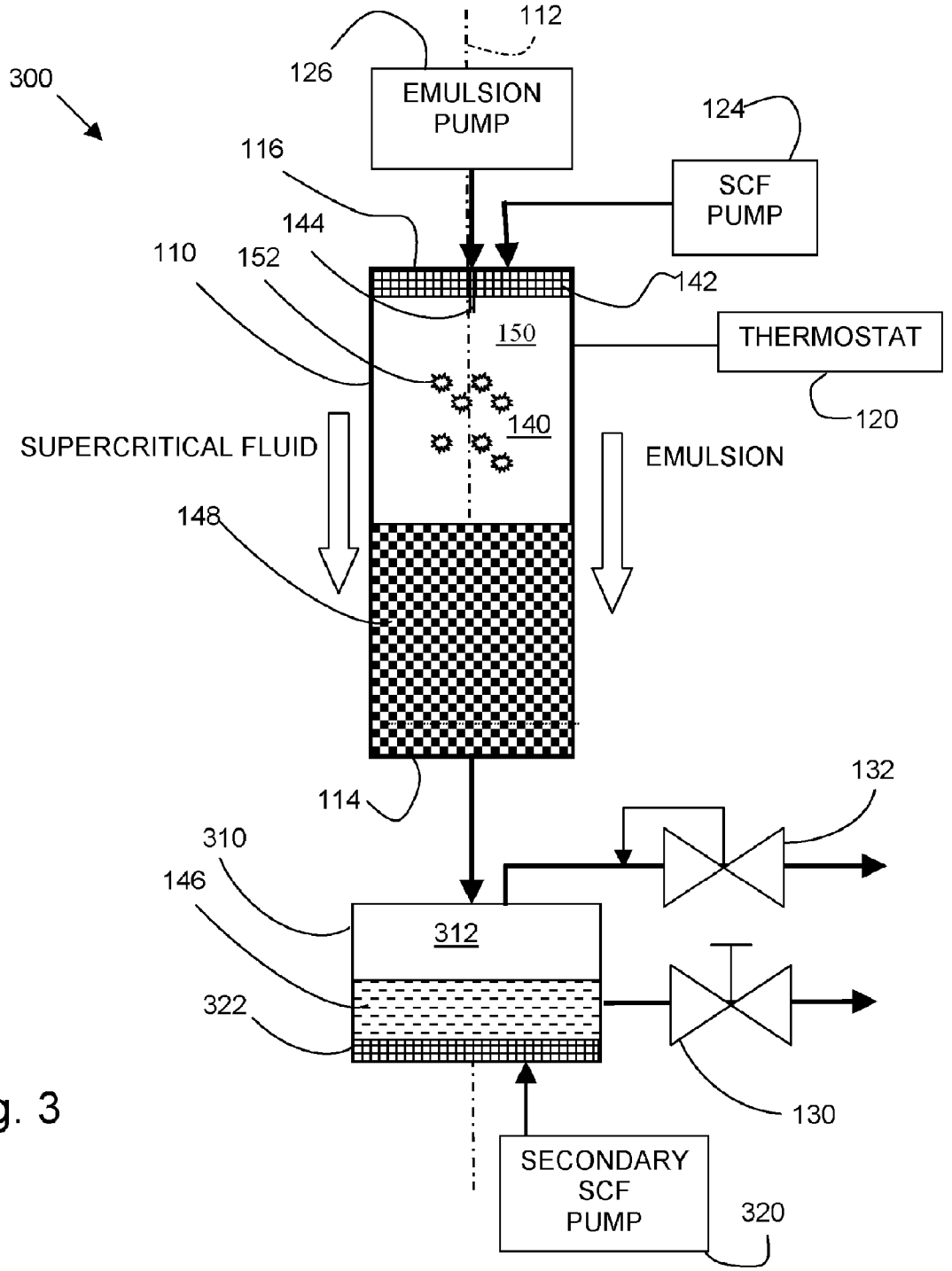
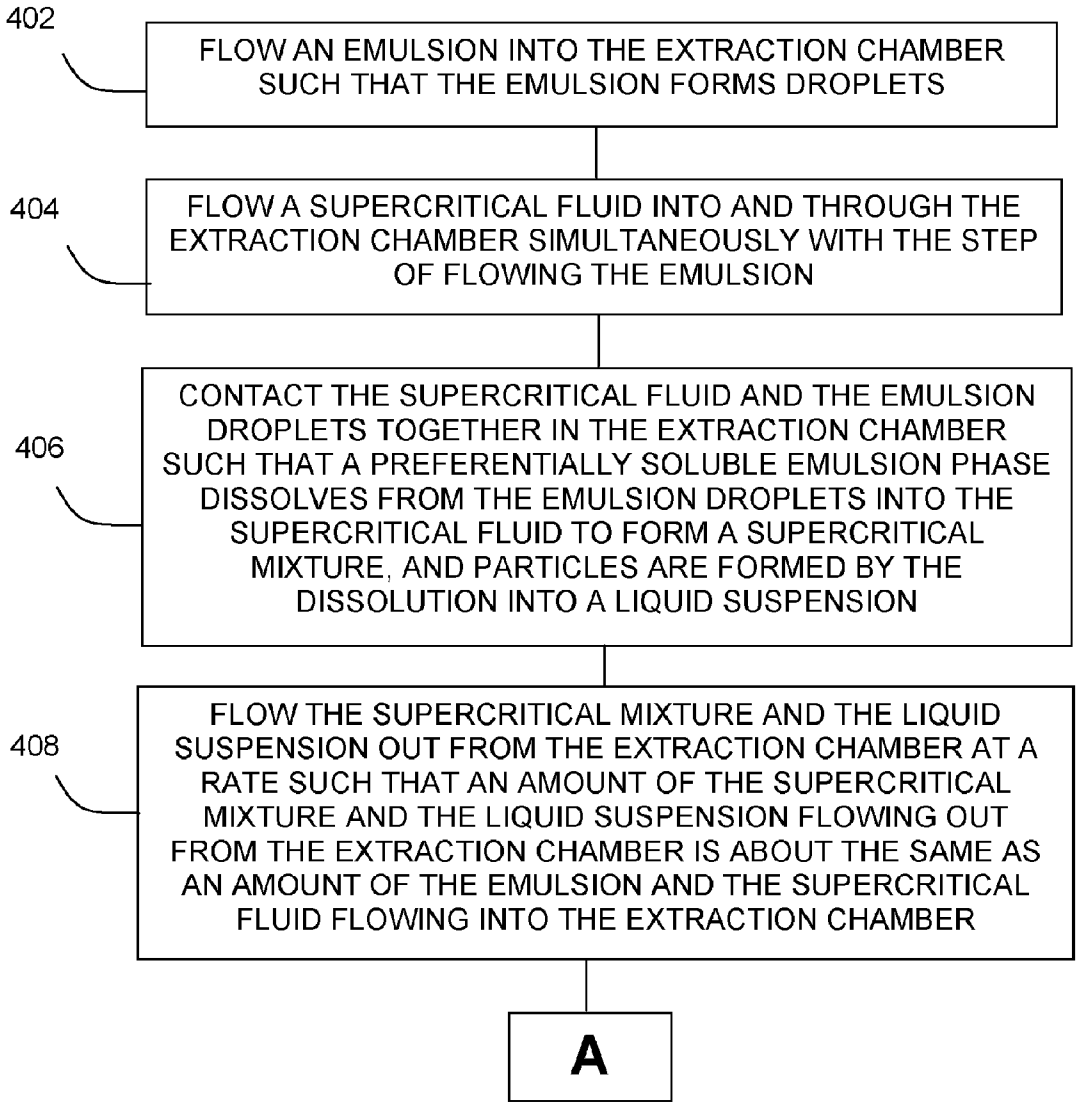

300
112
126
EMULSION PUMP
124
SCF PUMP
116
144
110
152
142
150
THERMOSTAT
120
140
SUPERCRITICAL FLUID
EMULSION
148
114
132
310
146
312
322
130
SECONDARY SCF PUMP
320

Fig. 3

Fig. 4


402
FLOW AN EMULSION INTO THE EXTRACTION CHAMBER SUCH THAT THE EMULSION FORMS DROPLETS
404
FLOW A SUPERCRITICAL FLUID INTO AND THROUGH THE EXTRACTION CHAMBER SIMULTANEOUSLY WITH THE STEP OF FLOWING THE EMULSION
406
CONTACT THE SUPERCRITICAL FLUID AND THE EMULSION DROPLETS TOGETHER IN THE EXTRACTION CHAMBER SUCH THAT A PREFERENTIALLY SOLUBLE EMULSION PHASE DISSOLVES FROM THE EMULSION DROPLETS INTO THE SUPERCRITICAL FLUID TO FORM A SUPERCRITICAL MIXTURE, AND PARTICLES ARE FORMED BY THE DISSOLUTION INTO A LIQUID SUSPENSION
408
FLOW THE SUPERCRITICAL MIXTURE AND THE LIQUID SUSPENSION OUT FROM THE EXTRACTION CHAMBER AT A RATE SUCH THAT AN AMOUNT OF THE SUPERCRITICAL MIXTURE AND THE LIQUID SUSPENSION FLOWING OUT FROM THE EXTRACTION CHAMBER IS ABOUT THE SAME AS AN AMOUNT OF THE EMULSION AND THE SUPERCRITICAL FLUID FLOWING INTO THE EXTRACTION CHAMBER
A

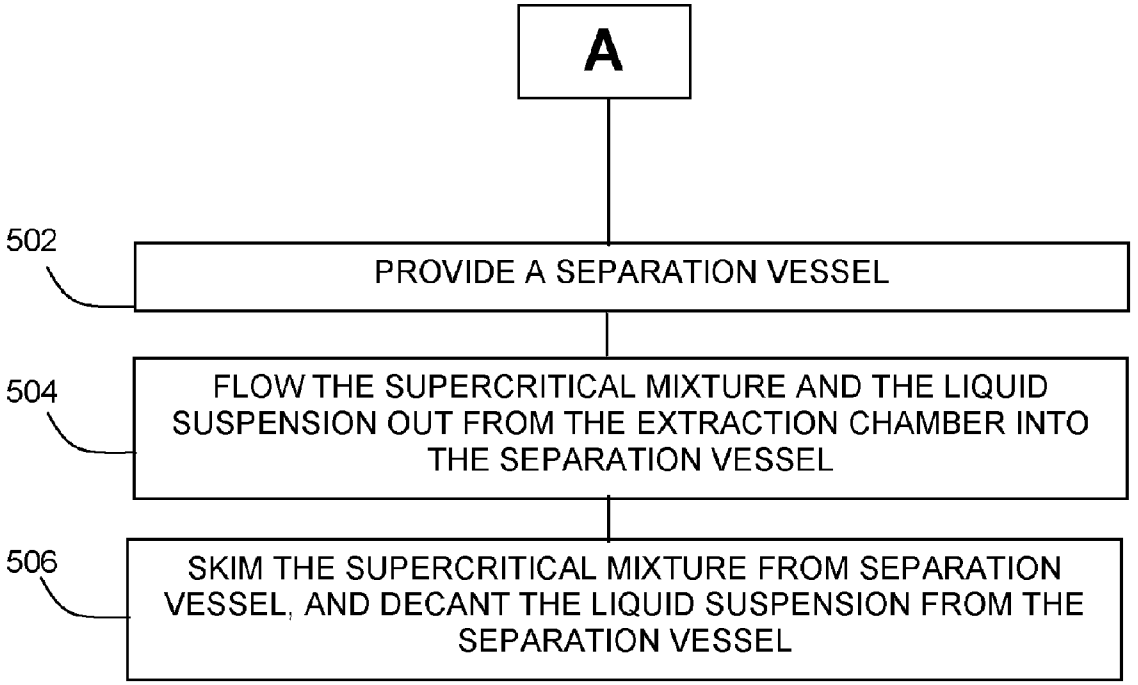

A
502
PROVIDE A SEPARATION VESSEL
504
FLOW THE SUPERCRITICAL MIXTURE AND THE LIQUID SUSPENSION OUT FROM THE EXTRACTION CHAMBER INTO THE SEPARATION VESSEL
506
SKIM THE SUPERCRITICAL MIXTURE FROM SEPARATION VESSEL, AND DECANT THE LIQUID SUSPENSION FROM THE SEPARATION VESSEL

Fig. 5

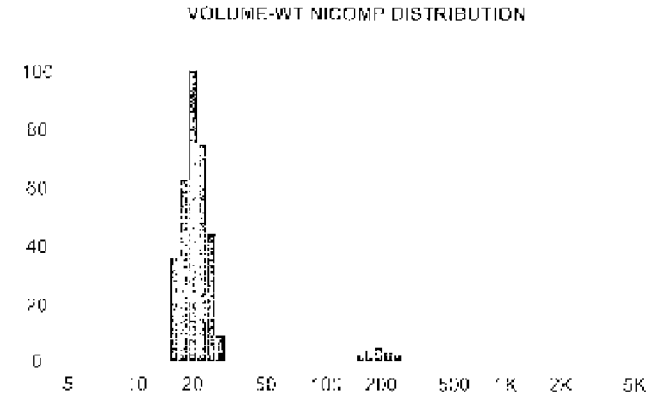


Fig. 6a

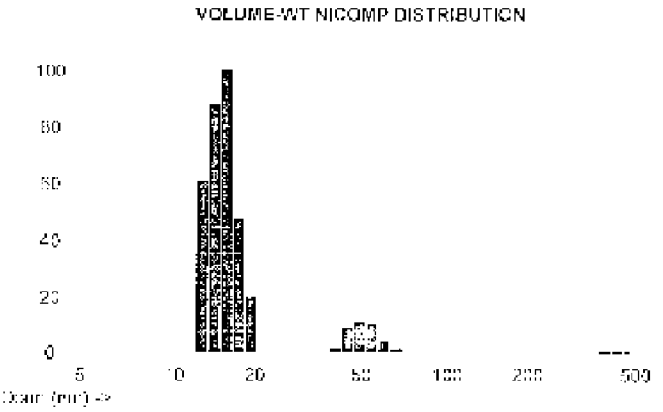


Fig. 6b

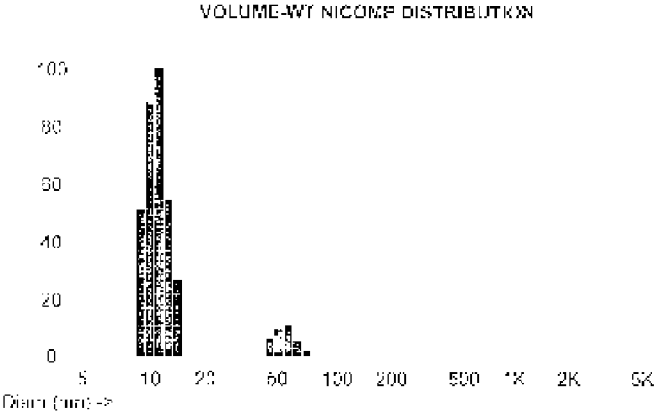


Fig. 6c

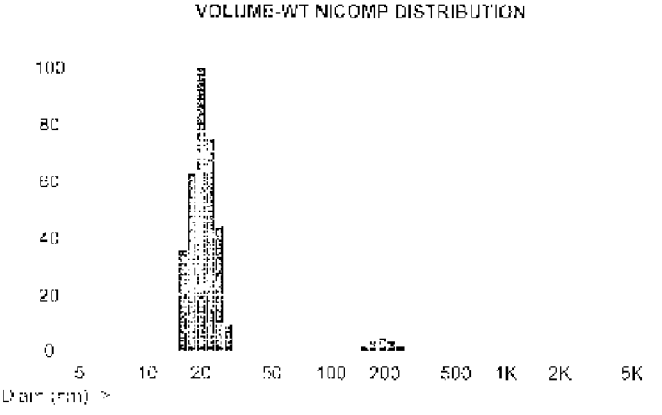


Fig. 6d

METHOD FOR PRODUCING SOLID-LIPID COMPOSITE DRUG PARTICLES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application is a continuation-in-part of application Ser. No. 10/434,426, filed May 8, 2003.

BACKGROUND OF THE INVENTION

[0002] 1. Field of Invention

[0003] The present invention relates generally to an apparatus and a method of producing solid-lipid composite drug particles.

[0004] 2. Description of Related Art

[0005] In recent years, solid composite lipid/drug particles have been used for oral, pulmonary and parenteral drug delivery as an alternative to traditional drug delivery systems such as emulsions, liposomes and biodegradable polymer nanoparticles. Solid lipid/drug composite particles provide the advantages of traditional drug delivery systems, such as improved dissolution and controlled release, but avoid some of the disadvantages of traditional drug delivery systems. The use of drug-containing emulsions, for example, is limited by the physical stability of the drug-containing emulsions, and also by the low dissolution of most drugs in the triglycerides used to form the emulsions. Liposome based drug delivery systems are limited by the non-availability of inexpensive pharmaceutical liposomes, and also by the low solubility of most drugs in the liposome membrane. Biodegradable polymer nanoparticles are limited by the cytotoxicity of certain polymers in the human body.

[0006] Most lipids are well tolerated by the human body and do not cause undesirable side effects upon delivery. Thus, they are particularly suitable for use in delivering drugs. Conventional methods of making solid composite lipid/drug particles include: the high-pressure homogenization process, which is described by Lucks et al. in EP 0 605 497; the microemulsion process, which is described by Gasco in U.S. Pat. No. 5,250,236; the precipitation process, which is described by Siekmann and Westesen in *Preparation And Physicochemical Characterization Of Aqueous Dispersions Of Coenzyme Q_{10} Nanoparticles,* Pharm Res. 1995;12:201-208; and the nanopelletization process, which is described by Domb in U.S. Pat. No. 5,188,837.

[0007] There are some inherent limitations on the conventional methods of forming solid composite lipid/drug particles. The high-pressure homogenization process, for example, is limited by the solubility of the drug in the molten lipid, and cannot be used to effectively produce solid composite lipid/drug particles having an average particle diameter of less than 100 nm. The average particle size of solid composite lipid/drug particles produced via the microemulsion process tends to be quite small, but the dispersion obtained using this process is extremely dilute and is thus not suitable for drug delivery applications. And, although the precipitation process can be used to produce fine particles having average diameters in the nanometer range, large processing times are required in order to achieve low residual solvent content. Scale up of the process is also problematic.

BRIEF SUMMARY OF THE INVENTION

[0008] The present invention provides an apparatus and a method of producing solid composite lipid/drug nanoparticles for controlled drug delivery that offers several advantages over conventional processing techniques, including the consistent production of solid composite lipid/drug particles having an average diameter below 100 nm, high drug loading and low temperature processing. The method of the invention is sometimes referred to herein by the acronym PSFEE, which stands for Particles from Supercritical Fluid Extraction of Emulsions ("PSFEE"), and involves the steps of: (1) dissolving a lipid and a drug in a suitable organic solvent to form a solution; (2) emulsifying the solution in a liquid to form an emulsion having a discontinuous phase of micelles comprising the organic solvent, the drug and the lipid, and a continuous phase comprising the liquid; and (3) contacting the emulsion with a supercritical fluid under conditions suitable to keep the supercritical fluid in a supercritical state, whereby the supercritical fluid extracts the organic solvent from the micelles, causing them to precipitate as organic-solvent free solid composite lipid/drug nanoparticles suspended or dispersed in the liquid.

[0009] The foregoing and other features of the invention are hereinafter more fully described and particularly pointed out in the claims, the following description setting forth in detail certain illustrative embodiments of the invention, these being indicative, however, of but a few of the various ways in which the principles of the present invention may be employed.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] **FIG. 1** is a schematic drawing of a first apparatus for use in accordance with a method of the invention;

[0011] **FIG. 2** is a schematic flow chart that illustrates the steps of the method;

[0012] **FIG. 3** is a schematic drawing of a second apparatus for use in accordance with another method of the invention;

[0013] **FIG. 4** is a block diagram of a method according to the invention;

[0014] **FIG. 5** is a block diagram of another method according to the invention; and

[0015] FIGS. **6**(*a*) through **6**(*d*) are graphs showing the particle size distribution of the solid composite lipid/drug nanoparticles produced in Example 1.

DETAILED DESCRIPTION OF THE INVENTION

[0016] The present invention provides a method of producing solid composite lipid/drug nanoparticles that are dispersed or suspended in a liquid. Throughout the instant specification and in the appended claims, the term "lipid" refers to fats and fat derived materials (e.g., fatty acids, fatty acid esters, fatty alcohols, sterols, and waxes) that are relatively insoluble in water, are utilizable by animal organisms and are solids phase materials at 1 atmosphere pressure and 15° C. temperature. A preferred lipid for use in the invention is polyethylene gylcol-32 glyceryl palmitostearate, which is available from Gattefosse SA as GELUCIRE 50/13. Another preferred lipid is tripalmitin.

[0017] The term "drug" refers to any substance that is intended for use in the diagnosis, cure, mitigation, treatment or prevention of diseases or health conditions and/or to affect the structure or function of the body. Included within the definition are synthetic and natural medicinal agents, pharmaceuticals, dietary supplements and vitamins.

[0018] The term "liquid", unless otherwise specifically defined, refers to substances that are liquid phase fluids at 1 atmosphere pressure and 15° C. temperature. Water is the preferred liquid for use in the invention, but other liquids that can emulsify an organic solution comprising a dissolved lipid and drug can also be used.

[0019] In accordance with the method of the invention, at least one lipid and at least one drug are dissolved in at least one organic solvent to form a solution. The weight ratio of drug(s) to lipid(s) dissolved in the organic solvent can be from about 0.1:99.9 to about 50:50. More preferably, however, the weight ratio of drug(s) to lipid(s) will be from about 5:95 to about 40:60. The amount of organic solvent in the solution will depend upon the solvating power of the organic solvent with respect to the lipid and drug, and the desired viscosity of the resulting solution. Typical drug/lipid loadings are from about 1% to about 50% by weight of the organic solvent. Suitable organic solvents for use in the invention include, for example, chloroform, toluene, hexane, ethyl acetate and other organic solvents that have good solvating power for lipids and drugs and which can be emulsified in water or other liquids.

[0020] The organic solution is emulsified in a liquid to form an emulsion having a discontinuous phase of micelles comprising the organic solvent, the drug and the lipid, and a continuous phase comprising the liquid. Surfactants can, if necessary, be present in the liquid before the emulsifying step. Co-surfactants can, if necessary, be present in the organic solution before the emulsifying step. Surfactants and co-surfactants can help stabilize the emulsion and the resulting particles formed upon processing. The surfactants and co-surfactants are preferably biodegradable and pharmaceutically accepted surfactants. However, emulsion systems can also be formed with very little or no surfactant to achieve short-term emulsion stability required for the duration of a supercritical fluid process according to the invention. Preferred surfactants include non-ionic, anionic and cationic surfactants. Preferred emulsifiers include poly(vinyl pyrrolidone), polyglycerol, polyricinoleate, poly(vinyl alcohol), and block copolymers.

[0021] Once the emulsion is formed, it is contacted with a supercritical fluid under conditions suitable to keep the supercritical fluid in a supercritical state. The contacting step is preferably accomplished by injecting the emulsion and the supercritical fluid into a heated pressure vessel. The organic solvent must be soluble in the supercritical fluid, such that the supercritical fluid extracts the organic solvent from the micelles, causing them to precipitate as organic-solvent free solid composite lipid/drug nanoparticles that become suspended or dispersed in the liquid. The supercritical fluid is preferably supercritical carbon dioxide ("CO_2"). However, supercritical fluids such as trifluoro methane, ammonia, nitrous oxide, dimethylether, straight chain or branched C1-C6 alkanes, alkenes, alcohols, and combinations thereof could be used. The supercritical fluid is chosen generally with reference to the solubility of at least one of the solvents present in the emulsion. Supercritical CO_2 is very effective in removing organic solvents from organic solutions comprising dissolved lipids and drugs.

[0022] **FIG. 1** is a schematic representation of an apparatus **100** for producing solid composite lipid/drug nanoparticles in accordance with the method of the invention wherein the emulsion and the supercritical fluid are introduced into the pressure vessel using a "contra-current" flow. The apparatus **100** includes a reactor or extractor **110**, which is preferably tubular and defines an axis **112** and having first and second ends **114**, **116** that are spaced axially apart. Preferably, the axis **112** is oriented vertically such that the first end **114** is below the second end **116**. That is, the second end **116** is UP and the first end **114** is DOWN when moving along the axis **112**. The extractor **110** is preferably about 1 to about 5 meters long, although other lengths and configurations can be employed.

[0023] A thermostat **120** communicates with heating elements (not shown) that are located proximate to the extractor **110**. A supercritical fluid pump **124** communicates with the first end **114** of the extractor **110**, and an emulsion pump **126** communicates with the second end **116** of the extractor **110**. A release valve **130** and a backpressure regulator **132** also communicate with the extractor **110**.

[0024] The extractor **110** has an inner surface that defines an extraction chamber **140**. Preferably disposed within the extraction chamber **140** are optional parts, for example a frit **142**, a nozzle **144** and a packed bed **148**. If an optional packed bed **148** is employed, the portion of the chamber **140** that is not occupied by the packed bed **148** defines an upper portion or headspace **150**.

[0025] The supercritical fluid pump **124** is preferably a P-200 high-pressure reciprocating pump commercially available from Thar Technologies, Inc. (Pittsburgh, Pa). Suitable alternative pumps include diaphragm pumps and air-actuated pumps that provide a continuous flow of supercritical fluid. Preferably, the supercritical fluid pump **124** can be supplemented with a surge tank and metering valve (not shown) so as produce a pulse-free flow. The source of the supercritical fluid can be a virgin source or can be a recycled source. If recycled, the "dirty" or solvent bearing supercritical fluid is expanded to separate the solvent from the supercritical fluid. The supercritical fluid is then compressed and reused as the supercritical fluid supply or source.

[0026] The frit **142** is preferably stainless steel and has a pore size of preferably about 0.5 micrometer (μm) or smaller. The frit **142** overlays the inner surface of the extractor **110** at the extractor first end **114**. The supercritical fluid pump **124** is in fluid communication with the frit **142** and supplies supercritical fluid through the frit **142** into the extraction chamber **140**. The frit **142** is micro-porous and the supercritical fluid flows through the frit **142** and breaks into a plurality of dispersed flow streams.

[0027] The solution pump **126** is preferably a high-pressure liquid-chromatography (HPLC) reciprocating pump such as the model PU-2080, which is commercially available from Jasco Inc. (Easton, Md.). Suitable alternative pumps include syringe type pumps, such as the 1000D or 260D pumps, which are commercially available from Isco Inc. (Lincoln, Nebr.).

[0028] The nozzle **144** is preferably a capillary-type nozzle and extends from the inner surface of the extractor

110 at the second end 116 into the extraction chamber 140. The emulsion pump 126 is in fluid communication with the nozzle 144 and supplies an emulsion (discussed in further detail hereinbelow) through the nozzle 144 into the extraction chamber 140. A head or end of the nozzle 144 that extends into the extraction chamber 140 may define a plurality of openings having very small diameters of uniform size. The diameter of the openings can affect the droplet size. Thus, controlling the opening diameters can control the size of the resultant emulsion droplets. Alternatively, a nozzle is provided such that, rather than spraying, the emulsion is pumped through the chamber 140. It is preferably that a pumped emulsion has an increased retention time and/or an increased volume of packed bed so as to effect a sufficient contact time and surface area between the flows of supercritical fluid and emulsion.

[0029] The packed bed 148 is preferred but optional. Use of a packed bed 148 can increase the extraction efficiency of an extraction column. If present, the packed bed 148 occupies a substantial volume of the extraction chamber 140. The packed bed 148 is preferably Raschig rings, which are commercially available from Labglass, Inc. an SP Industries Company (Vineland, N.J.). In alternative embodiments, the packed bed is comprised of glass beads, ceramic pellets, glass wool, zeolite, catalyst, stainless steel wool, and/or the like. Alternatively, the packed bed 148 is a series of trays that extend a flow path length through the expansion chamber 140. The remaining, upper portion 150 of the extraction chamber 140 is generally unobstructed so that the emulsion and the supercritical fluid can flow therethrough. The headspace or upper portion 150 is preferably occupied or precharged with supercritical fluid.

[0030] Upon contacting the supercritical fluid, the organic solvent is extracted from the discontinuous phase of the emulsion (i.e., the micelles) causing the lipid and drug to precipitate into the liquid as a dispersion or suspension of solid composite lipid/drug nanoparticles 146, which is preferably separate from the supercritical fluid bearing the organic solvent. The liquid suspension or dispersion of solid composite lipid/drug nanoparticles collects adjacent to the frit 142 at the first end 114, or bottom, of the chamber 140. A release valve 130 is in fluid communication with this portion of the chamber, and allows for the removal of the liquid dispersion or suspension of solid composite lipid/drug nanoparticles 146. The release valve 130 is preferably a standard commercially available valve and is interchangeable with other like valves that are known to those of ordinary skill in the art.

[0031] A backpressure regulator 132 is preferably a 26-1700 type regulator, which is commercially available from Tescom, USA (Elk River, Minn.) is used to remove supercritical fluid bearing the organic solvent.

[0032] During a contra-current operation of the apparatus 100, the extractor 110 is maintained at constant operating temperature by the thermostat 120. The extraction chamber 140 is brought up to a predetermined pressure, preferably using the supercritical fluid pump 124. The upper portion 150 fills with supercritical fluid.

[0033] With reference to FIGS. 1 and 4, the emulsion pump 126 supplies emulsion (step 402), and the supercritical fluid pump 124 supplies supercritical fluid (step 404), to the extractor 110. The supercritical fluid is dispersed upward into the extraction chamber 140 through the frit 142 at the first end 114 of the extractor 110.

[0034] Simultaneously, the emulsion is sprayed or pumped downward into the extractor 110 through the nozzle 144 at the upper second end 116. The supercritical fluid flows through the extraction chamber 140 by passing through the frit 142, the liquid phase 146, the packed bed 148, and the space 150 in the upward direction as indicated by the directional arrow labeled SUPERCRITICAL FLUID.

[0035] Preferably, the emulsion is sprayed or jetted into the space 150 and forms very small droplets 152 (step 402). As the emulsion jet is introduced into the extraction space 150, it is atomized into the small droplets 152 by a jet breakup caused by the passage through the openings in the nozzle 144. Mass transfer between the solvent contained in the emulsion droplets and supercritical fluid results in both supersaturation and precipitation of the solid within the droplets in the form of fine particles. The flow rates of both the emulsion and supercritical fluid are optimized and tuned in order to provide maximum removal of the solvent from the emulsion. The upper or maximum solid particles size is limited by the amount of solute or material dissolved within the droplets 152, that is, the concentration of the solute can affect particle size. The rate of solvent extraction provides control of the particle precipitation rate, and therefore influences both the number and solid-state properties (e.g. crystallinity and polymorphism) of produced particles. Composite particles can be obtained by co-precipitation of solutes or by material encapsulation a multiple emulsions system.

[0036] The droplets 152 are urged downward both by gravity and by the force of the emulsion, and flow in the direction indicated by the directional arrow labeled EMULSION. The emulsion droplets 152 travel or are carried through the packed bed 148 and into the liquid phase 146. Accordingly, the droplets 152 and the supercritical fluid form contra-current flows with the supercritical fluid flowing in a first direction and the droplets 152 flowing in an opposite second direction.

[0037] The supercritical fluid intermingles with and contacts the emulsion droplets 152 during the countercurrent current flows (step 406). The packed bed 148 increases the surface area, and thus the contact, between the emulsion and the supercritical fluid. The solvent in the emulsion droplet 152 is dissolved into the flow of supercritical fluid. The supercritical fluid thus removes the solvent from the emulsion droplet 152. The solvent removal results in the material of interest that was dissolved in the emulsion droplet 152 precipitating into the remaining phase, thus forming a particle suspension in the phase that is relatively less soluble in the supercritical fluid.

[0038] The particle suspension continues to flow downward toward, and into, the liquid phase 146. The liquid phase/suspension is purged from the extraction chamber 140 via the release valve 130. The aqueous suspended particles are recovered from the purged liquid phase.

[0039] The supercritical fluid bears the dissolved solvent upward to the backpressure regulator 132. The supercritical fluid and solvent exit the extraction chamber 140 via the backpressure regulator 132. Optionally, the supercritical fluid and solvent are recovered for reuse.

[0040] The apparatus 100 operates in a continuous manner with the aid of the backpressure regulator 132 and the

release valve **130**. The backpressure regulator **132** and the release valve **130** communicate with the pumps **124**, **126**, and cooperate with each other to maintain the balance of feed and exit flows of the supercritical fluid and the emulsion (step **508**). The method shown in **FIG. 4** can end at step **508**, alternatively the process can continue as described hereinbelow.

[**0041**] **FIG. 2** is a schematic representation showing various aspects of the method of the invention. Box **200** shows a representative emulsion micelle comprising an organic solvent (OS) having a lipid (L) and a drug (D) dissolved therein. The micelle depicted in Box **200** represents the discontinuous phase of the emulsion formed by emulsifying the organic solution containing the dissolved drug and lipid in a liquid. A co-surfactant may also be present in the micelle, and a surfactant may be present in the liquid that constitutes the continuous phase of the emulsion.

[**0042**] Box **210** shows the organic solvent diffusing out of the micelle and into the supercritical fluid (SCF), which is contacting the emulsion while the supercritical fluid is being maintained in a supercritical state. In Box **210**, the supercritical fluid is shown in the form of bubbles, which can be formed by pumping the supercritical fluid through the frit.

[**0043**] Box **220** shows that as the organic solvent continues to be extracted from the micelles, the solvating power of the organic solvent remaining in the micelles diminishes, and the lipid and drug supersaturate the solution and precipitate as solid composite lipid/drug nanoparticles. The supercritical fluid bearing the organic solvent flows away from the solid lipid/drug composite nanoparticles, which are dispersed or suspended in the liquid. The dispersion or suspension of solid composite/lipid nanoparticles in the liquid can be removed from the pressure vessel, depressurized, and used to deliver drugs to an animal organism such as a human being. Alternatively, the suspension or dispersion of solid composite lipid/drug nanoparticles can be further processed to obtain a paste or dry powders. The solid composite lipid/drug nanoparticles preferably consist essentially of one or more lipids and one or more drugs, but may also consist of small amounts of one or more surfactants and/or a co-surfactants and very small amounts (<~20 ppm) of one or more residual organic solvents.

[**0044**] A second embodiment of the invention comprising an apparatus **300** for use with another method according to the invention is shown in **FIG. 3**. The apparatus **300** has many parts that are substantially the same as corresponding parts of the apparatus **100**; this is indicated by the use of the same reference numbers in **FIGS. 1 and 3**. Similar to the first embodiment, the apparatus **300** simultaneously disperses an emulsion and a supercritical fluid. However, the flows of the emulsion and the supercritical fluid are parallel or co-current in the second embodiment, rather than counter to each other.

[**0045**] The apparatus **300** includes a separation vessel **310** (step **502** in **FIG. 5**). The separation vessel **310** an inner surface defining a separation chamber **312**. The separation vessel **310** preferably has cyclone or cylinder geometry. The supercritical fluid pump **124** communicates with the second end **116** of the extractor **110**, rather than the first end **114**, and the frit **142** overlays the second end **116** rather than the first end **114**, as in the first embodiment.

[**0046**] A secondary supercritical fluid pump **320** supplies supercritical fluid to the vessel **310** through a secondary frit **322**. The secondary frit **322** overlays a bottom portion of the inner surface of the vessel **310** inside the chamber **312**.

[**0047**] The separation vessel **310** can also be used in conjunction with other embodiments of the invention. For example, the separation vessel **310** can be placed in fluid communication with the apparatus **100**, and therefore used with a contra-current continuous flow apparatus. The addition of the separation vessel **310** to an extraction device according to the invention can increase the purity and/or reduce the residual solvent content of the resultant particles.

[**0048**] During operation of the apparatus **300**, the thermostat **120** controls the temperature of the extractor **110** to a predetermined and equilibrated temperature. The supercritical fluid pump **124** supplies supercritical fluid to the extractor chamber **140** at the first end **116** of the extractor **110**. The supercritical fluid flows through the frit **142** and downward into the chamber **140**. Simultaneously, the emulsion pump **126** supplies emulsion to the extractor **110** through the nozzle **144**. The emulsion flows through the nozzle **144** and downward into the chamber **140**. The emulsion breaks into the droplets **152** as it exits the nozzle **144** through the nozzle openings. The droplets **152** and the supercritical fluid flow co-currently together downward through the chamber **140** and further through the packed bed **148**. The co-current flow is a multi-phase flow.

[**0049**] The droplets **152** intimately contact the supercritical fluid during the co-current flow. Because of the contact, the solvent present in the emulsion is dissolved or extracted into the supercritical fluid. Material dissolved in the emulsion precipitates out in the form of small particles as a result of the solvent extraction.

[**0050**] With reference to **FIGS. 3 and 5**, the multi-phase flow and the particles produced by the extraction process are communicated to the separation vessel **310** (step **504**). The steps illustrated in **FIG. 5** end with step A and the steps illustrated in **FIG. 5** begin with step A to indicate that the optional additional process steps shown in **FIG. 5** may be performed subsequent to or concurrent with the steps shown in **FIG. 4**.

[**0051**] In the separation vessel **310**, the aqueous suspension of particles and supercritical fluid mixture (supercritical fluid+solvent) are separated (step **504**). The liquid suspension is generally heavier than the supercritical fluid mixture. Thus, the separator **310** can decant the liquid suspension layer **146** and skim the supercritical fluid mixture layer (which occupies a substantial remaining portion of the chamber **312**). Preferably, the separation vessel **310** has heaters (not shown) that communicate with the thermostat **120**. The thermostat **120** controls the temperature in the separation vessel **310**.

[**0052**] The secondary supercritical fluid pump **320** can supply supercritical fluid into the chamber **312** through the secondary frit **322**. The secondary supercritical fluid pump **320** can both control the pressure in the chamber **312**, and also provide a second flow of supercritical fluid through the liquid suspension layer **146** so as to remove residual solvent and further purify the precipitated particles.

[**0053**] The apparatus **300** operates in a continuous manner with the aid of the backpressure regulator **132** regulating the supercritical fluid flow, and the release valve **130** controlling the liquid suspension flow. The regulator **132** and release

valve **130** together adjusting the exit flows with reference to inflows by the pumps **124**, **126**.

[**0054**] The apparatus and methods described in the present application can be used scaled up for continuous commercial-scale production of dispersions or suspensions of solid composite lipid/drug nanoparticles in water or other liquids, which can, if desired, be further processed to obtain dry powders or concentrated to form pastes. The method is particularly effective for the production of nanosuspensions with average particle sizes as small as 5 nm. By varying the concentration of the lipid, drug, organic solvent and the fluid, robust size control of the resulting solid composite lipid/drug nanoparticles can be obtained. The particles tend to be monodisperse, and can have drug loadings up to 50%. Particles having an average particle size of from about 5 nm to about 100 nm are particularly preferred.

[**0055**] The method and apparatus produce a high yield of solid composite lipid/drug nanoparticles, which can be recovered at relatively high concentration dispersed or suspended in the liquid. The solid composite lipid/drug nanoparticles exhibit very low residual solvent content (<20 ppm), and can be produced using non-toxic organic solvents. The process is a low shear, low temperature process, which prevents degradation of the drug during processing.

[**0056**] In a further embodiment of the method of the invention, the suspension of solid composite lipid/drug nanoparticles can be further be converted into a solid porous mass via lyophilization with a cryoprotectant. The solid porous mass can be easily redispersed in an aqueous media.

[**0057**] Solid composite lipid/drug nanocomposites according to the invention can increase the bioavailability of drugs in animal organisms. The lipid aids in the absorption or uptake of the drug into the animal tissue. The solid lipid/drug composite nanoparticles according to the invention are suitable for injections, topical/ophthalmic preparations and aerosols.

[**0058**] The following examples are intended only to illustrate the invention and should not be construed as imposing limitations upon the claims. Unless specified otherwise, all ingredients are commercially available from such common chemical suppliers as Sigma Aldrich, Inc. (St. Louis, Mo.) and/or Fisher Scientific International, Inc. (Hanover Park, Ill.).

EXAMPLE

[**0059**] Preparation of Emulsions

[**0060**] Four organic solutions (Examples 1-4, respectively) were prepared by dissolving 5 percent of a lipid (GLUCIRE 50/13) and the amounts shown in Table 1 of either Indomethacin or Ketoprofen in chloroform (all amounts are specified as weight percents relative to the weight of the organic solvent). The resulting organic solutions were then dispersed in an aqueous 0.13% w/w of sodium glychocholate solution in the amounts shown in Table 1 in parts by weight relative to water to form coarse oil-in-water (O/W) emulsions. The resulting emulsions were then homogenized using a homogenizer commercially available from Microfluidics, Inc. (Newton, Mass.) at 16,000 p.s.i. in 3 passes.

TABLE 1

Example	Drug	Weight % of Drug in Solvent	Weight % of Organic Solution in Water
1	Indomethacin	15	10
2	Indomethacin	10	30
3	Indomethacin	15	30
4	Ketoprofen	15	30

[**0061**] Precipitation of Nanoparticles

[**0062**] An apparatus such as shown in **FIG. 1** was used to precipitate solid composite lipid/drug nanoparticles as a suspension in water. About, 100-200 milliliters (ml) of each emulsion was pumped using an emulsion pump into an extraction chamber at a constant flow rate. Simultaneously, a supercritical fluid pump was used to pump supercritical CO_2 into the extraction chamber through a frit. The extraction chamber was maintained at a constant pressure and temperature of 8 megapascal (MPa) and 318 Kelvin (K), respectively. The flow rates of the supercritical CO_2 and the emulsion through the extraction chamber were maintained constant: 50 g/min for CO_2; and 5 ml/min for the emulsions. Counter current extraction of the solvent from the emulsion droplets caused the solid composite lipid/drug nanoparticles to precipitate into an aqueous liquid. The solid composite lipid/drug nanoparticles were suspended in the aqueous liquid, and were stabilized by the surfactants present in the emulsion. The suspension was removed from the extraction chamber at a constant rate of 55 g/min through the release valve. The suspensions of solid composite lipid/drug nanoparticles were then analyzed.

[**0063**] Analysis of the Nanoparticles

[**0064**] Analysis of the aqueous colloidal suspensions of solid composite lipid/drug nanoparticles was performed using a DLS. **FIGS. 6***a* through **6***d* are graphs illustrating the particle size distribution of the solid composite lipid/drug nanoparticles obtained from Examples 1 through 4, respectively. The analysis of the particles is numerically illustrated in Table 2 below:

TABLE 2

Example	Vol. Avg.	Std. Dev.	No. Avg.	Std. Dev.
1	27 nm	27 nm	17 nm	17 nm
2	22 nm	17 nm	13 nm	10 nm
3	39 nm	32 nm	21 nm	17 nm
4	22 nm	13 nm	10 nm	7 nm

[**0065**] Additional advantages and modifications will readily occur to those skilled in the art. Therefore, the invention in its broader aspects is not limited to the specific details and illustrative examples shown and described herein. Accordingly, various modifications may be made without departing from the spirit or scope of the general inventive concept as defined by the appended claims and their equivalents.

1. A method of producing a suspension or dispersion of solid composite lipid/drug nanoparticles in a liquid comprising:

dissolving a lipid and a drug in a suitable organic solvent to form a solution;

emulsifying the solution in the liquid to form an emulsion having a discontinuous phase of micelles comprising the organic solvent, the drug and the lipid, and a continuous phase comprising the liquid; and

contacting the emulsion with a supercritical fluid under conditions suitable to keep the supercritical fluid in a supercritical state, whereby the supercritical fluid extracts the organic solvent from the micelles, causing the micelles to precipitate into the liquid and thus form the suspension or dispersion of solid composite lipid/drug nanoparticles in the liquid.

2. The method according to claim 1 wherein the liquid is water.

3. The method according to claim 2 wherein a surfactant is dissolved in the water before the solution is emulsified in the water.

4. The method according to claim 3 wherein a co-surfactant is dissolved in the solution before the solution is emulsified in the water.

5. The method according to claim 2 wherein the supercritical fluid is supercritical carbon dioxide.

6. The method according to claim 5 wherein the organic solvent is chloroform.

7. The method according to claim 1 wherein the weigh ratio of the drug to the lipid in the solution is from about 0.1:99.9 to about 50:50.

8. The method according to claim 1 wherein the average particle size of the solid composite lipid/drug nanoparticles is from about 5 nm to about 1000 nm.

9. The method according to claim 1 wherein the emulsion and the supercritical fluid contact each other as contra-current flows in an extraction chamber.

* * * * *