(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 April 2001 (12.04.2001)

PCT

(10) International Publication Number
WO 01/24917 A1

(51) International Patent Classification[7]: B01F 3/12, 5/02, A61K 9/16

(21) International Application Number: PCT/US00/27743

(22) International Filing Date: 5 October 2000 (05.10.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/414,470 7 October 1999 (07.10.1999) US

(71) Applicant: **BATTELLE MEMORIAL INSTITUTE** [US/US]; Pacific Northwest Division, Intellectual Property Services, P.O. Box 999, Richland, WA 99352 (US).

(72) Inventors: **FULTON, John, L.**; 1809 Hunt Avenue, Richland, WA 99352 (US). **DEVERMAN, George, S.**; 1256 El Monte Court, Richland, WA 99352 (US). **MATSON, Dean, W.**; 4104 West 17th Avenue, Kennewick, WA 99337 (US). **GRAFF, Gordon, L.**; 3750 West Lake Drive, West Richland, WA 99353 (US). **PHELPS, Max, R.**; 2035 Newcomer Avenue, Richland, WA 99352 (US).

(74) Agent: **MAY, Stephen, R.**; Battelle Memorial Institute, Pacific Northwest Division, Intellectual Property Services, P.O. Box 999, MSIN: K1-53, Richland, WA 99352 (US).

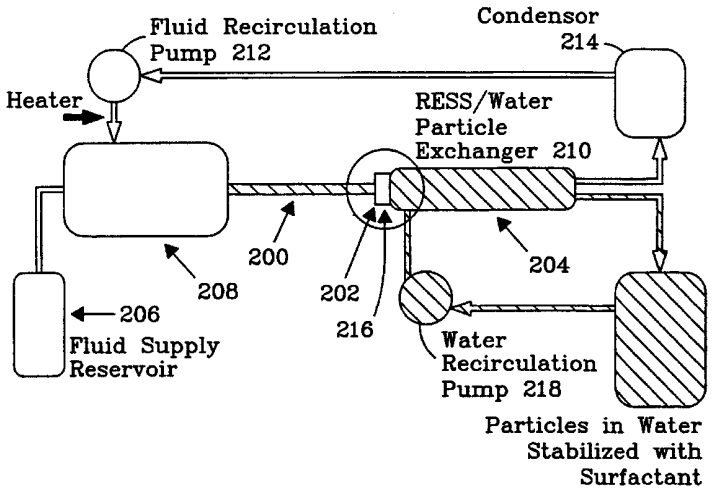
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHOD AND APPARATUS FOR OBTAINING A SUSPENSION OF PARTICLES



(57) Abstract: The present invention is a method and apparatus for obtaining a suspension of fine particles. The method has the steps of incorporating a compound in a variable density fluid as a fluid premixture, discharging the fluid premixture through a nozzle into a receiving liquid and forming particles of the compound. For certain compounds, mixing a surfactant with the receiving liquid prevents and retards agglomeration of the particles, and heating the nozzle prevents the formation of ice. The compound is preferably a pharmaceutical, and a biocompatible supercritical solvent maximizes solubility of the compound in the premixture. Fine particles of the compound are produced by rapid expansion of the supercritical fluid premixture in the receiving liquid.

WO 01/24917 A1

METHOD AND APPARATUS FOR OBTAINING A SUSPENSION OF PARTICLES

FIELD OF THE INVENTION

The present invention relates generally to a method and apparatus for obtaining a suspension of particles. More specifically, the invention describes a method and apparatus for producing an aqueous solution that contains high concentrations of fine particles suspended for long periods of time by biocompatible surfactants.

BACKGROUND OF THE INVENTION

Administration of therapeutic drugs via inhalation has been in practice for many years. Ideally, the therapeutic drug would be in the form of particles of a size that would travel as an aerosol into the furthest recesses of the lung. However, most materials at that size are not stable and tend to agglomerate into larger particles that do not travel to the furthest recesses of the lung. Target particle size is from 1 – 5 μm.

Presently, inhalation systems are unable to produce particles or droplets of the therapeutic drug with more than about 10% of the particles of the target particle size.

In unrelated literature, small particles have been produced using supercritical fluids.

U.S. patent 4,582,731 to RD Smith (B-781) describes a method for forming a fine powder by first dissolving a solid material into a supercritical fluid then rapidly expanding the solution through an orifice into a low pressure region wherein the fine powder is formed. The low pressure region contains a passive gas at about atmospheric pressure or less. The patent does not indicate the size of the particles and makes no mention or suggestion of making a stable suspension of the particles.

The paper, PARTICLE FORMATION WITH SUPERCRITICAL FLUIDS-A REVIEW; JW Tom, PG Debenedetti; J. Aerosol Sci., Vol. 22, No. 5, pp555-564, 1991, mentions that dissolution of low vapor pressure solids with supercritical fluids was first done in 1879 by Hannay and Hogarth. It further mentions that rapid expansion leading to particle formation was done in 1987 by Matson et al. and termed rapid expansion of supercritical solutions (RESS). The paper points out that much smaller particles are obtained compared to conventional processes of mechanical (crushing, grinding, milling) or equilibrium (crystallization from solution) methods. Particles have been made with RESS from materials of inorganics/ceramics, organics/pharmaceuticals, polymers, and two-soluble systems. For organics/pharmaceuticals, it is necessary to select low-critical temperature solvents to avoid damage of the organic/pharmaceutical. RESS is capable of producing particles of a size (1-3 μm) and uniformity necessary for effective delivery into the lung.

The paper, Krukonis V. (1984), Supercritical Fluid Nucleation of Difficult-to-Comminute Solids, paper 140f, AIChE meeting, San Francisco, November reports using carbon dioxide at 55 °C and 345 bar with ferrocene, dodecanolatam, β-estradiol, soy bean lecithin, and navy blue dye. Particle size of the β-estradiol was sub-micron and uniform.

The paper Chang, CJ and Randolph, AD (1989) AIChE J. 35, 1876, reports precipitation of β-carotene from ethylene at 70 °C and 306 bar both by free expansion and into gelatine solution. Although the precipitation into the gelatine resulted in smaller particles (0.3 μm compared to 1-20 μm from free expansion), an additional step is needed to separate the particles from the gelatine.

The paper Schmitt, WJ et al. (1995), Finely-Divided Powders by Carrier Solution Injection into a Near or Supercritical Fluid, AIChE Journal Vol 41, No. 11, November, points out that compounds of pharmaceutical interest are either too polar or of too high a molecular weight to be more than sparingly soluble in commonly used supercritical fluids. Accordingly they suggest addition of an

entrainer or cosolvent to improve solubility, but point out the challenge of separation of entrainer from the pharmaceutical.

The paper Alessi P et al. (1996), Particle Production of Steroid Drugs Using Supercritical Fluid Processing, Ind. Eng. Chem. Res. 1996, 35, 4718-4726, investigated solubility of progesterone and medroxyprogesterone in supercritical carbon dioxide and found that solubility was a function of temperature and pressure. In addition, by reducing temperature upstream of the nozzle, solubility was maintained throughout the expansion and precipitation process.

All of the previous references address the problem of making the particles, but none discuss the problem of administering the particles for therapeutic benefit.

Sievers et al. discuss both the making and administering of the particles. U.S. patent 5,301,664 discusses methods and apparatus for delivering physiologically active compounds. The apparatus is hand-held and has a chamber for the high pressure supercritical mixture of supercritical fluid and pharmaceutical compound.

The paper Hybertson, BM et al. (1993) Pulmonary Drug Delivery of Fine Aerosol Particles from Supercritical Fluids, Journal of Aerosol Medicine, Vol. 6, No. 4, 1993, shows an apparatus with a supercritical fluid pump, temperature control water bath, supercritical fluid drug delivery cell connected to an inhalation chamber.

Both of these apparati suffer from the disadvantage of issues surrounding high pressure vessels for public use.

Hence, there remains a need for a method and an apparatus for making a stable suspension of particles, especially particles of a size less than 20 μm, that may be administered or deployed from a low pressure apparatus.

SUMMARY OF THE INVENTION

The present invention is a method and apparatus for obtaining particles in a suspension. The present invention has elements and steps for

(a) incorporating a compound in a variable density fluid as a premixture;

(b) discharging the premixture through a nozzle into a receiving liquid and forming the particles of the compound that remain in suspension in the receiving liquid.

Advantages of the present invention over prior art include obtaining particle size as little as less than 1 μm in diameter, and obtaining gram quantities in less than 10 minutes.

An object of the present invention is to provide a method and apparatus to make particles that are stably suspended.

The subject matter of the present invention is particularly pointed out and distinctly claimed in the concluding portion of this specification. However, both the organization and method of operation, together with further advantages and objects thereof, may best be understood by reference to the following description taken in connection with accompanying drawings wherein like reference characters refer to like elements.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1a is a thermodynamic diagram showing the region of fluid density above the critical density of the fluid.

FIG. 1b is a thermodynamic diagram showing the region above the critical temperature and critical pressure of a fluid.

FIG. 2 is a schematic diagram of the present invention.

FIG. 3 is a schematic detail of the nozzle according to the present invention.

FIG. 4a is a schematic diagram of a counterflow steam mixing apparatus.

FIG. 4b is a schematic diagram of a cyclone mixing apparatus.

DESCRIPTION OF THE PREFERRED EMBODIMENT(S)

The present invention is a method and apparatus for obtaining particles in a suspension. The present invention has elements and steps for:

(a) incorporating a compound in a variable density fluid as a premixture;

(b) discharging premixture through a nozzle into a receiving liquid and forming the particles of said compound that remain in suspension in said receiving liquid.

Variable density fluid includes fluid that is a gas at standard temperature and pressure and at a density greater than a critical density of the variable density fluid as illustrated in **FIG. 1a** as the cross-hatched region **100**. Region **102** (non-cross hatched) is below the critical density. Tests to date have been done in the subregion **100a**. Variable density fluid also includes fluid that is a liquid at standard temperature and pressure and at a temperature greater than a critical temperature of the variable density fluid and at a pressure greater than a critical pressure of the fluid as illustrated in **FIG. 1b** as the cross-hatched region **110**. Because the cross-hatched region **110** can be a common region, a combination of variable density fluid that is a gas at standard temperature and pressure with a variable density fluid that is a liquid at standard temperature and pressure is possible when operating in region **110**. The properties of a variable density fluid that is a gas at standard temperature and pressure and at a density greater than a critical density of the variable density fluid were set forth in U.S. patent 5,158,704 hereby incorporated by reference. The variable density fluid that is a gas at standard temperature and pressure includes but is not limited to organic fluids, particularly hydrocarbons, such as alkanes, for example methane, ethane, ethylene, propane; inorganic fluids, for example, fluorocarbons (e.g. chlorodifluoromethane, R22), ammonia, carbon dioxide, nitrous oxide, xenon sulfur hexafluoride; and combinations thereof. The variable density fluid that is a liquid at standard temperature and pressure includes but is not limited to organic fluids, for example pentane; alcohols, for example methanol, ethanol isopropanol, isobutanol, cyclohexanol; aromatics, for example benzene, toluene, cyclohexane; others for example chlorofluoromethane, monofluoromethane, pyridine, m-cresol, decalin, o-xylene, tetralin, aniline, camphor; inorganic fluids, for example water. For pharmaceutical use, it is preferred that the variable

density fluid be biocompatible, for example carbon dioxide, R22, and combinations thereof.

The basic problem that is addressed by the present invention is the fact that presently there are two steps from raw material to suspension when particles are made from a premixture. The two steps are (1) making the particles with or in one fluid medium and (2) placing the particles in a suspension in a different fluid medium or receiving liquid. According to the present invention, the particles are made in the liquid intended as the final suspending medium, i.e. receiving liquid. For example, pharmaceutical compounds are generally delivered in an aqueous solution, possibly a saline solution. Other particle receiving liquid combinations including but not limited to ceramic particle pigment in paint and organic dye particles in textile dyes. The present invention provides the compound(s) of particle size and distribution achievable with rapid expansion of supercritical solutions (RESS) directly into the receiving liquid (e.g. aqueous solution) by having the RESS nozzle outlet into the receiving liquid.

Because certain combinations of compounds and receiving liquids result in agglomeration of the particles in the receiving liquid, a surfactant may be mixed with the receiving liquid to prevent and retard agglomeration of the particles.

Thermodynamic cooling of the nozzle as the premixture expands may cause solid phase formation (e.g. ice from aqueous solution) of the receiving liquid on the nozzle thereby blocking the nozzle. In those situations, the nozzle may be heated to prevent the formation of a solid phase of said receiving liquid.

The compound is any compound soluble in any fluid as defined herein or combination of fluids or fluid with surfactant. Preferably the compound is a pharmaceutical compound including but not limited to anti-inflammatory agents such as steroids, antibiotics, anti-viral agents, anti-neoplastic agents such as etoposide, antihistamines, peptides, proteins, and combinations thereof.

Solubility of the compound in the fluid may be enhanced by addition of a polar modifier, for example addition of several weight percent of ethanol to carbon dioxide. Solubility may also be enhanced by addition of a surfactant, for example a fatty acid,dipalmitoyl-phosphatidyl choline, quaternary ammonium

salts such as didodecydimethylammonium bromide, alkyl sulfonate such as Bis-2ethylhexyl sulfosuccinate sodium salt (AOT) and combinations thereof. This list is shown in Table 1.

To successfully suspend particles at relatively high concentrations (15%) requires the use of ionic surfactants that provide the highly repulsive electrostatic interactions that overcome the van der Waals forces that would normally lead to agglomeration. In order to maximize the stability of the suspension the electric double layer thickness or Debye length must be as high as possible. This is best achieved by (1) using de-ionized water and high purity drugs with no ionic impurities. Slight improvements in stability are achieve by operating at lower temperatures. Improvement of stability may be achieved by addition of a surfactant as shown in Table 1, specifically, addition of quaternary ammonium salts such as cetyltrimethyl ammonium bromide, tetradecyltrimethylammonium bromide (TTAB), alkyl sulfate; anionic surfactant such as sodium dodecyl sulfate, natural surfactants such as oleic acid and combinations thereof.

For pharmaceutical uses, the selection of surfactant will strongly depend upon its biocompatibility at the concentration needed for particle suspension. For pharmaceuticals, it is preferred that the surfactant be of the low- or non-toxic surfactants. In Table 1, the order, from most compatible to least compatible is: DPPC, LPPC, oleic acid, nonionic surfactants and then the cationic and anionic surfactants. The quaternary ammonium salts and the alkyl sulfates can be rather caustic.

Table 1. Biocompatible surfactants and their type of application.

Name	Receiving Liquid Stabilizer	RESS Modifier
Quaternary Ammonium Salts		
Cetyl trimethylammonium bromide	X	
Tetradecytrimethylammonium bromide	X	
Cetyl pyridinium chloride	X	
Didodecydimethylammonium bromide		X
Anionic surfactants		
Sodium dodecyl sulfate	X	
Bis-2ethylhexyl sulfosuccinate sodium salt (AOT)		X
Nonionic Surfactants		
Ethoxylated surfactants ($C_{12}EO_n$)		X
"Natural" surfactants		
Lysophosphatidylcholine (LPPC)	X	
Sodium glycocholate	X	
Oleic acid	X	
Glycyrrthetinic acid	X	
DPPC	X	
L-a-phosphatidylcholine		X

According to the present invention, the apparatus (**FIG. 2**) includes a premixture supply **200**, a rapid expansion nozzle **202**, and a receiving liquid reservoir **204** into which the rapid expansion nozzle **202** extends.

Upstream of the variable density fluid supply **200** may be a compound reservoir **206,** and a premixture reservoir **208**. For complete variable density fluid handling, there may also be a variable density fluid recirculation pump **212**, and a variable density fluid condensor **214**. For receiving liquids that form a solid phase (freeze) upon expansion of the variable density fluid, a nozzle heater **216** may be added.

The fluid premixture is discharged through the rapid expansion nozzle **202** into the receiving liquid, which is circulating through the receiving liquid reservoir **204** via the receiving liquid recirculation pump **218**. The receiving liquid is preferably water. The rapid expansion nozzle **202** is located at one end of the particle exchange chamber **210** and is submerged in the stream of receiving liquid (with surfactant).

In a preferred embodiment, the nozzle heater **216** is a source of steam **300** as shown in **FIG. 3**. The rapid expansion nozzle **202** is inside a steam tube **302** co-injecting steam during rapid expansion of the fluid premixture to prevent icing at the tip **304** of the rapid expansion nozzle **202**. A receiving liquid tube **306** may be co-axial as shown for co-injecting the recirculating receiving liquid to prevent overheating in the expansion region.

The fluid premixture is discharged through the rapid expansion nozzle **212** directly into the receiving liquid resulting in the production of ultra-fine particles of compound. In the extreme conditions of the expansion region, the receiving liquid is in intimate contact with the micro-bubbles that are formed at the tip of the rapid expansion nozzle **202**. Thus, the particles rapidly migrate from the expanded-gas phase of the supercritical fluid premixture to the aqueous phase of the receiving liquid. For compounds that tend to agglomerate in the receiving liquid, addition of a receiving liquid surfactant prevents agglomeration. Receiving liquid surfactants include but are not limited to cationic surfactant, anionic surfactant, amphoteric surfactant and combinations thereof.

This process produces an aqueous solution that contains high concentrations of fine particles (~ 0.5 μm) suspended in the receiving liquid. For pharmaceutical compound in an aqueous solution, the suspension may be placed in a standard delivery device. Hand held delivery devices are typically operated at pressures much lower than necessary to maintain supercritical or near critical conditions.

Example 1

An experiment was conducted to produce particles of etopiside then suspend them in a liquid in separate steps.

The pulmonary drug etoposide was dissolved into R22 and then sprayed through a nozzle into a 5 liter bell jar to generate the ultra-small particles in the gas phase. Particles of ~1 μm diameter were produced that would be suitable for the delivery of the etoposide via direct inhalation of the effluent gas stream. The white "smoke" of dispersed particles persisted for about 10 minutes, consistent with the settling times of 1 μm particles.

A large "saturation" cell filled with solid etoposide and held at a certain temperature and pressure, is all that is needed to dissolve a controlled amount of the etoposide into the fluid prior to the expansion region of the nozzle. This is because the phase behavior is one of the solid-fluid equilibrium type.

This experiment demonstrated that:

Etoposide is unaffected by extended exposure to 130°C in R22. Particles in the range of 0.5 μm were formed. Particle morphology indicates a "cotton ball" appearance. Most likely involves a mass of extremely small crystallites. Individual crystallites cannot be resolved by the current SEM method. Extremely high surface area of crystallite ball may aid in drug uptake. The much lower density of the cores of these particles may affect deposition rates of the aerosol powder. Much larger particles may be necessary. Because of the morphology, re-dispersion of a collected powder may not be possible because of agglomeration. When spraying liquid or near-critical R22, the temperature of the jet, 3 cm downstream, is about -40°C. Under these conditions a layer of solid R22 immediately forms on the tip of the thermocouple probe. When spraying supercritical R22 with upstream temperatures of 165 or 200°C, the temperature is almost uniformly -4°C at 3 cm downstream. At a distance of 25 cm beyond the nozzle tip the temperature of the plume is about 20°C. This is due to the entrainment of a large amount of air into the jet stream. When spraying into a 4-liter bell jar, an aerosol is created that has the appearance of a white "smoke" that persists for about 5-10 min after the flow is stopped. The performance of the 50μm sapphire orifice is satisfactory.

Example 2

An experiment was conducted to directly transport particles into an aqueous phase. The premixture was a fluid of R22, and the compound solvent blue 36 (SB36). Solvent blue 36 is a polyacrylic organic that is a surrogate for some pharmaceuticals. Premixture flow was countercurrent to a flow of saturated steam (**FIG. 4a**). However, this method experienced severe particle agglomeration in the condensed droplets before the surfactant could be "administered" to stabilize the particles.

Example 3

Another experiment was conceived to directly transport particles into an aqueous phase. **FIG. 4b** shows premixture flow into a first cyclone inlet **400** and a receiving liquid flow into a second cyclone inlet **402**. The premixture may be as in Example 2. The receiving liquid may be water with a cationic surfactant known as tetradecyltrimethyl ammonium bromide. Aqueous particle suspension is removed from the cyclone outlet **404**. Particle size must be greater than or equal to 0.2 μm. Performance is expected to be better than Example 2 but not as good as Example 4.

Example 4

Another experiment was conducted to directly transport particles into an aqueous phase with the apparatus of **FIG. 2**. The premixture was as in Example 2. The receiving liquid was as in Example 3. Additional details are shown in Table E4-1.

The SB36 particles generated in the AISE process were characterized using several techniques. An optical micrograph of the particles in solution showed them to have a particle size of about 0.5 μm. This is at the limit of resolution for optical spectroscopy (~0.2 μm). When viewed directly, particles can be seen to undergo vigorous translation and rotation due to Brownian motion. The particle concentrations are high enough (0.1 wt%) that in this single field of view and depth of view there are hundreds of particles. All of the particles in solution were removed by filtering with a 20μm filter. Even though the dye was a blue color the scattered light was red. It was hypothesized that the red scattering was due to the particles retaining crystallinity even with very small size.

Table E4-1. Process conditions

Parameter	Range/setpoint
Feed Annuli	
RESS restrictor, PEEK	0.005 or 0.0025 in ID, 1/16 in OD x 11.25 in
Steam feed	1/8 in OD x 0.1 in ID
Recycle solution	¼ in OD x 0.21 ID x 6 in long OR 3/8 in OD x 5/16 ID x 3 in long
Insulation on steam line	¼ in OD x 0.21 ID x 6 in. Teflon (Used with 3/8 in recycle tube.)
Receiver tube	1.5 in OD x 1.25 in ID x 10 in, Acrylic, tilted 45°
Discharge end	split to gas and liquid effluent streams
Recycle solution flow rate	300 ml/min
Receiver tank	350 ml volume, 10°C jacket temperature
Surfactant concentration	1 to 2.5 mM
Steam source	1/16 in OD x 0.04 in ID x 2 ft tube wound on 2.5 in heated core
Steam temperature	100-120 °C
Steam feed rate	60-200 ml/hr water equivalent
RESS fluid	Chlorodifluoromethane, R22
RESS fluid temperature	100°C
RESS pressure	2000-6000 psi
RESS feed rate	3-15 ml/min
RESS mixing cell	50 ml volume, "CSTR" mode
Solute concentration	0.15 to 0.5% (wt/vol)

Other conclusions include: The preliminary trials demonstrated the stabilization of lower concentrations of particles in water (0.1% wt). The concentration of the surfactant in the aqueous solution was below the critical micelle concentration at about 1mM. If the temperature of the aqueous surfactant solution is too high (>40°C) then the particles undergo rapid crystal growth. This process is further aided by the presence of an excess of surfactant. The dye solubilization in the cores of the micelles is a transport mechanism that

feeds the larger crystallites. There is evidence that the SB36 particles underwent crystal growth in the water solution at room temperature over a 1 day time frame. Cooling of the sample inhibited this growth and stabilized the suspension.

Example 5

An experiment was conducted as in Example 4, but with etoposide as the compound. Only a few process conditions were changed in order successfully process the etoposide. First of all, the solubility of etoposide in water is slight but appreciable (about 0.3 mg/ml), therefore, prior to the run, the receiving liquid was saturated with the drug. Finally, the steam feed line was optimized to minimize the heat transfer to the receiving liquid in order minimize the heating. Recycle temperatures below 20°C were achieved.

The particle suspensions were evaluated using optical microscopy. No particles could be resolved meaning that the size was well below 0.5 μm. A second qualitative test was completed. The solution was filtered through a 0.1 μm filter result in about 50% reduction in the Tyndall scattering. The solution was filtered through 0.02 μm filter resulting in total removal of the particles. Thus there is a substantial part of the distribution contains particles that are below 0.1 μm but all particles are larger than 0.02 μm.

When the etoposide particle concentration became too high (0.5 wt%) in the recycle solution, nucleation to larger (10 μm) macroscopic crystals occurred in about 15 minutes. Below this concentration the particles do not recrystallize and have remain stably suspended for 4 weeks. Whereas SB36 was stabilized by the surfactant at higher concentrations, etoposide was not.

There were some unusual crystal phase transitions that occurred in room temperature aqueous solutions of etoposide. The material, as supplied, was very deliquescent. The uptake of water maybe hydrated the polar sites on the molecules. This altered the morphology of the crystals in the aqueous solution. The starting solution was stable to temperature changes of at least -15° C without evidence of any crystal formation.

CLOSURE

While a preferred embodiment of the present invention has been shown and described, it will be apparent to those skilled in the art that many changes and modifications may be made without departing from the invention in its broader aspects. The appended claims are therefore intended to cover all such changes and modifications as fall within the true spirit and scope of the invention.

CLAIMS

We claim:

1. A method for obtaining particles in a suspension, said method comprising the steps of:

(a) incorporating a compound in a variable density fluid as a premixture; and

(b) discharging the premixture through a nozzle into a receiving liquid and forming said particles of said compound that remain in suspension in said receiving liquid.

2. The method as recited in claim 1, wherein said variable density fluid is a gas at standard temperature and pressure and at a density greater than a critical density of the variable density fluid.

3. The method as recited in claim 2, wherein said variable density fluid is organic or inorganic.

4. The method as recited in claim 3, wherein said variable density fluid that is organic is a hydrocarbon.

5. The method as recited in claim 4, wherein said hydrocarbon is an alkane.

6. The method as recited in claim 5, wherein said alkane is selected from the group consisting of methane, ethane, ethylene, propane and combinations thereof.

7. The method as recited in claim 3, wherein said variable density fluid that is inorganic is a fluorocarbon.

8. The method as recited in claim 7, wherein said fluorocarbon is selected from the group consisting of chlorodifluoromethane, ammonia, carbon dioxide, nitrous oxide, xenon sulfur hexafluoride; and combinations thereof.

9. The method as recited in claim 1, wherein said variable density fluid is a liquid at standard temperature and pressure and is at a temperature greater than the critical temperature of said variable density fluid and is at a pressure above a critical pressure of said variable density fluid.

10. The method as recited in claim 9, wherein said variable density fluid is organic or inorganic.

11. The method as recited in claim 10, wherein said variable density fluid that is organic is a hydrocarbon.

12. The method as recited in claim 11, wherein said hydrocarbon is selected from the group consistent of pentane, alcohol, aromatic, other and combinations thereof.

13. The method as recited in claim 12, wherein said alcohol is selected from the group consisting of methanol, ethanol isopropanol, isobutanol, cyclohexanol and combinations thereof.

14. The method as recited in claim 12, wherein said aromatic is selected from the group consisting of benzene, toluene, cyclohexane and combinations thereof.

15. The method as recited in claim 12, wherein said other is selected from the group consisting of chlorofluoromethane, monofluoromethane, pyridine, m-cresol, decalin, o-xylene, tetralin, aniline, camphor and combinations thereof.

16. The method as recited in claim 10, wherein said variable density fluid that is inorganic is water.

17. The method as recited in claim 1, further comprising mixing a surfactant with said receiving liquid to prevent and retard agglomeration of said particles.

18. The method as recited in claim 1, further comprising the step of heating said nozzle to prevent the formation of a solid phase of said receiving liquid.

19. The method as recited in claim 1 wherein said compound is immiscible within said receiving liquid.

20. The method as recited in claim 1 wherein said receiving liquid is de-ionized water.

21. The method as recited in claim 17 wherein said surfactant is an ionic surfactant that binds to said particles.

22. The method as recited in claim 21 wherein said ionic surfactant is selected from the group consisting of Cetyl trimethylammonium bromide, Tetradecytrimethylammonium bromide, Cetyl pyridinium chloride, Sodium dodecyl sulfate, Lysophosphatidylcholine (LPPC), Sodium glycocholate, Oleic acid, Glycyrrthetinic acid, and DPPC.

23. The method as recited in claim 1 wherein said compound is a pharmaceutical.

24. The method as recited in claim 23 wherein said pharmaceutical comprises etoposide, carboplatin, cisplatin and combinations thereof.

25. The method as recited in claim 1, wherein a surfactant is added to said variable density fluid.

26. An apparatus for obtaining particles in a suspension, said apparatus comprising:

(a) a source of a compound in a variable density fluid as a premixture; and

(b) a nozzle for discharging the premixture into;

(c) a vessel containing a receiving liquid and therein forming said particles of said compound that remain in suspension in said receiving liquid.

27. The apparatus as recited in claim 26, wherein said variable density fluid is a gas at standard temperature and pressure and at a density greater than a critical density of the variable density fluid.

28. The apparatus as recited in claim 26, wherein said variable density fluid is a liquid at standard temperature and pressure and is at a temperature greater than the critical temperature of said variable density fluid and is at a pressure above a critical pressure of said variable density fluid.

29. The apparatus as recited in claim 26, wherein said nozzle has a first orifice for said premixture.

30. The apparatus as recited in claim 29, wherein said nozzle has a second orifice for a heating fluid.

31. The apparatus as recited in claim 30, wherein said nozzle has a third orifice for circulating said receiving liquid.

32. The apparatus as recited in claim 26, wherein said receiving liquid includes a surfactant to prevent and retard agglomeration of said particles.

33. The apparatus as recited in claim 26 wherein said compound is immiscible within said receiving liquid.

34. The apparatus as recited in claim 26 wherein said receiving liquid is de-ionized water.

35. The apparatus as recited in claim 26 wherein said surfactant is an ionic surfactant that binds to said particles.

36. The apparatus as recited in claim 35 wherein said ionic surfactant is selected from the group consisting of Cetyl trimethylammonium bromide, Tetradecytrimethylammonium bromide, Cetyl pyridinium chloride, Sodium dodecyl sulfate, Lysophosphatidylcholine (LPPC), Sodium glycocholate, Oleic acid, Glycyrrthetinic acid, and DPPC.

37. The apparatus as recited in claim 26 wherein said compound is a pharmaceutical.

38. The apparatus as recited in claim 37 wherein said pharmaceutical comprises etoposide, carboplatin, cisplatin and combinations thereof.

39. The apparatus as recited in claim 26, wherein said fluid includes a surfactant.

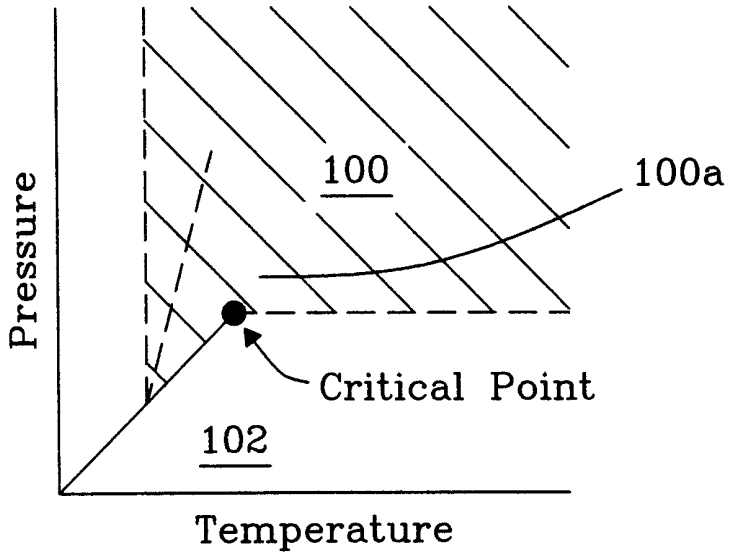

Pressure
100
100a
Critical Point
102
Temperature

Fig. 1a

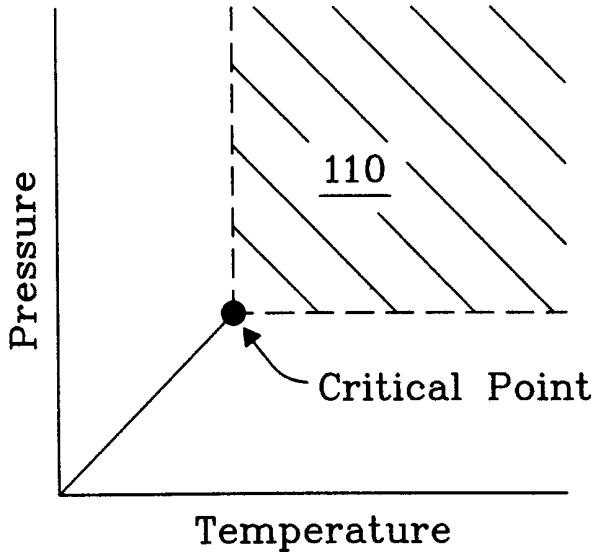

Pressure
110
Critical Point
Temperature

Fig. 1b

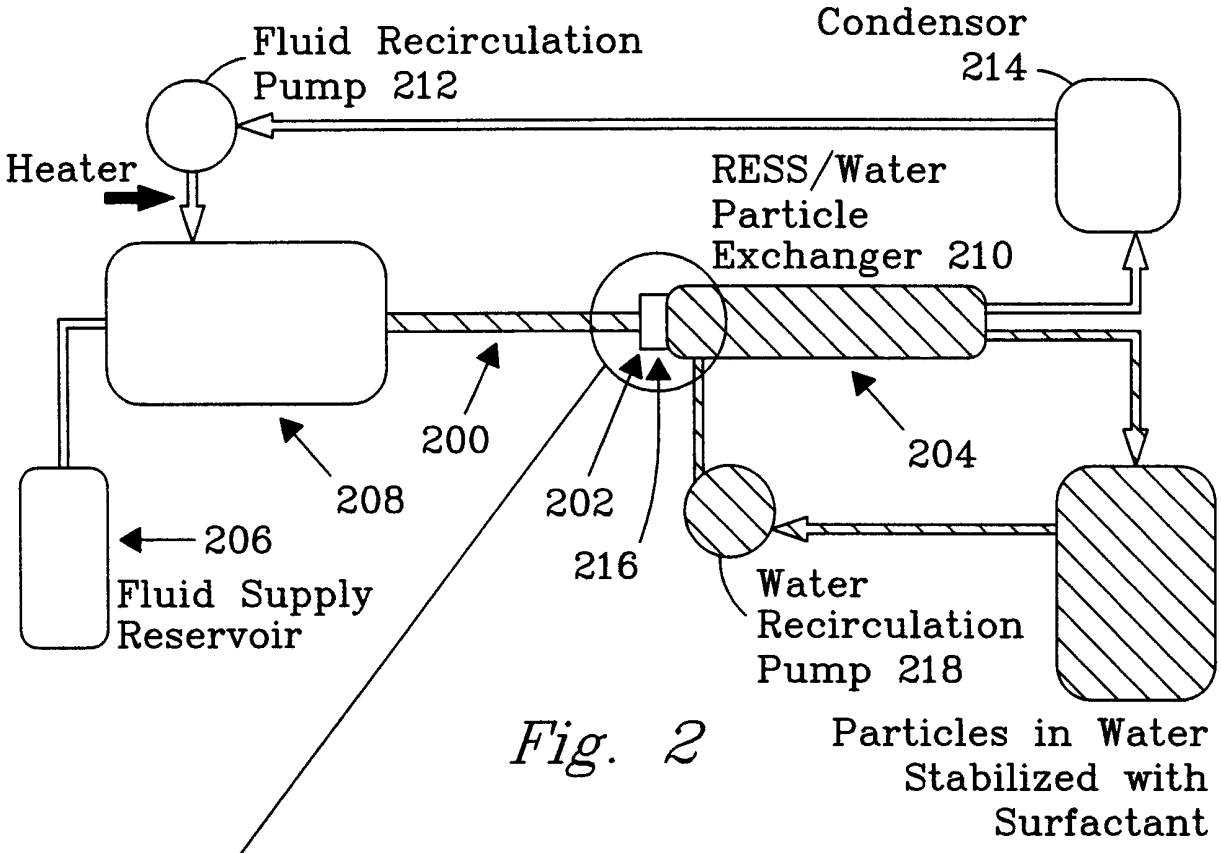

Fluid Recirculation Pump 212
Condensor 214
Heater
RESS/Water Particle Exchanger 210
200
204
208
202
206
Fluid Supply Reservoir
216
Water Recirculation Pump 218
Particles in Water Stabilized with Surfactant

Fig. 2

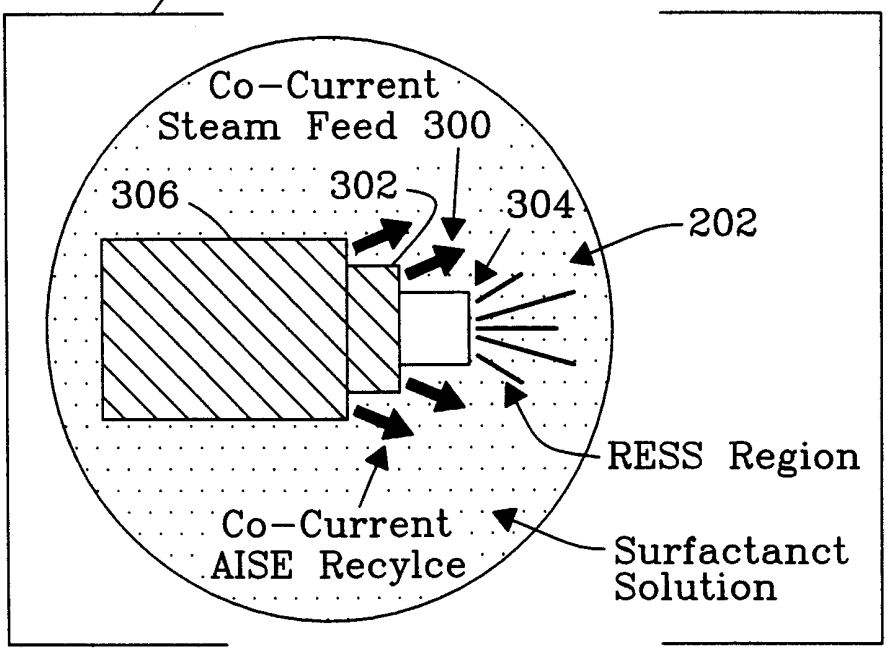

Co-Current Steam Feed 300
306
302
304
202
RESS Region
Co-Current AISE Recylce
Surfactanct Solution

Fig. 3

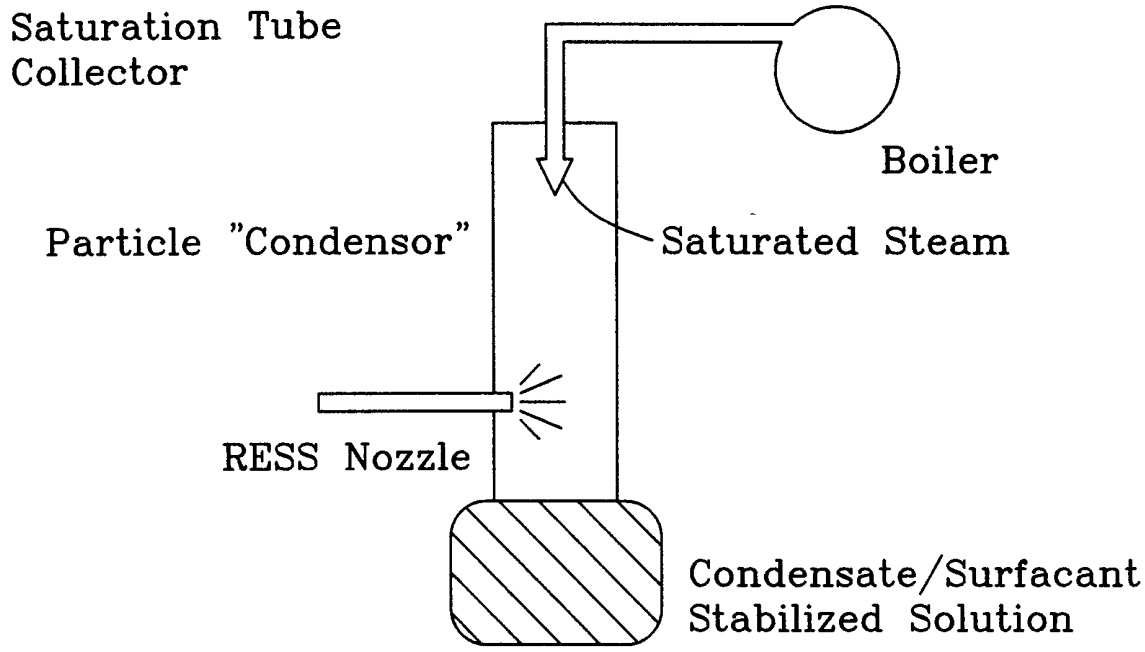

Saturation Tube
Collector
Boiler
Particle "Condensor"
Saturated Steam
RESS Nozzle
Condensate/Surfacant
Stabilized Solution

Fig. 4a

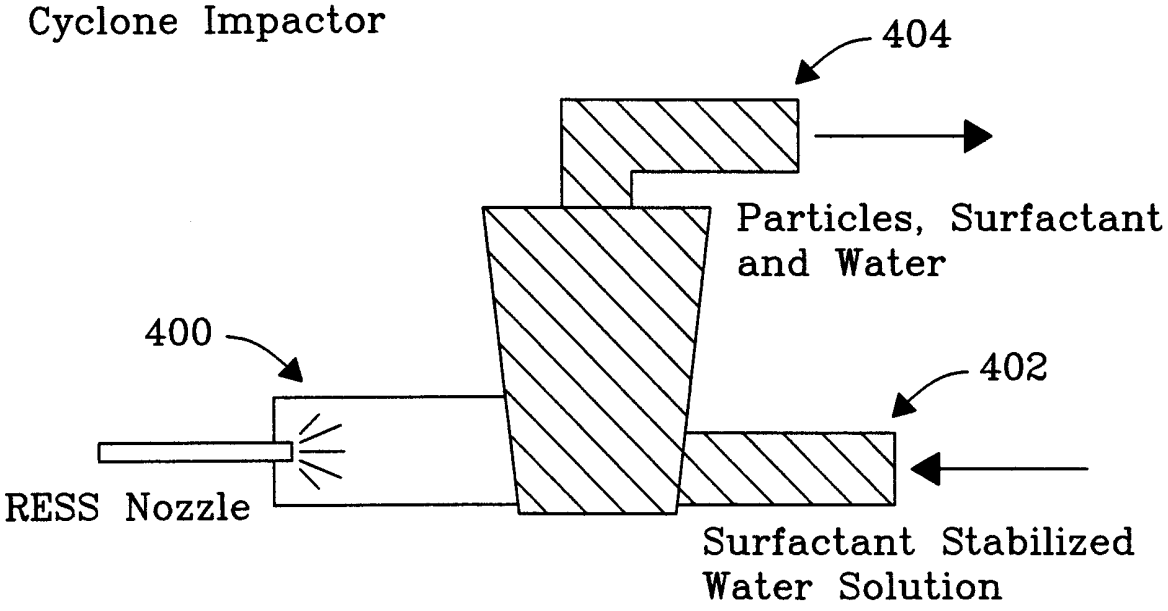

Cyclone Impactor
404
Particles, Surfactant
and Water
400
402
RESS Nozzle
Surfactant Stabilized
Water Solution

Fig. 4b

INTERNATIONAL SEARCH REPORT

Inte .ional Application No
PCT/US 00/27743

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 B01F3/12 B01F5/02 A61K9/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 B01F A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 850 682 A (INOUE MFG INC) 1 July 1998 (1998-07-01) the whole document ---	1-10, 16-20, 25-30, 33,39
X	WO 97 14407 A (PACE GARY W ;MAWSON SIMON (US); UNIV TEXAS (US); HENRIKSEN INGE B) 24 April 1997 (1997-04-24) the whole document ---	1,9,10, 17-24, 26-29, 32-39
X	US 5 487 965 A (ODELL PETER G) 30 January 1996 (1996-01-30) the whole document --- -/--	1,9-12, 17-22, 26-29, 32-36

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 March 2001	23/03/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Labeeuw, R

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte .ional Application No
PCT/US 00/27743

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 99 65469 A (RTP PHARMA INC) 23 December 1999 (1999-12-23) the whole document -----	1-28, 32-39

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte ional Application No
PCT/US 00/27743

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0850682 A	01-07-1998	JP 10192670 A	28-07-1998
		CN 1185990 A,B	01-07-1998
		SG 60111 A	22-02-1999
		US 5921478 A	13-07-1999
WO 9714407 A	24-04-1997	AU 709262 B	26-08-1999
		AU 7461796 A	07-05-1997
		EP 0855906 A	05-08-1998
		JP 11514367 T	07-12-1999
US 5487965 A	30-01-1996	NONE	
WO 9965469 A	23-12-1999	AU 4693899 A	05-01-2000
		SE 0004620 A	08-02-2001