



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : B01F 5/06, 7/00		A1	(11) International Publication Number: WO 00/10697
			(43) International Publication Date: 2 March 2000 (02.03.00)
(21) International Application Number: PCT/GB99/02741	(22) International Filing Date: 18 August 1999 (18.08.99)		Ann-Kristin [NO/NO]; Tamburveien 13K, N-0485 Oslo (NO).
(30) Priority Data: 9818021.9 18 August 1998 (18.08.98) GB	(74) Agents: COCKBAIN, Julian et al.; Frank B. Dehn & Co., 179 Queen Victoria Street, London EC4V 4EL (GB).		
(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 60/101,224 (CIP) Filed on 21 September 1998 (21.09.98)	(81) Designated States: AE, AL, AM, AT, AT (Utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, CZ (Utility model), DE, DE (Utility model), DK, DK (Utility model), DM, EE, EE (Utility model), ES, FI, FI (Utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (Utility model), SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, 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).		
(71) Applicant (for all designated States except US): NYCOMED IMAGING AS [NO/NO]; Nycoveien 2, P.O. Box 4220 Torshov, N-0401 Oslo (NO).	(71) Applicant (for GB only): COCKBAIN, Julian [GB/GB]; Frank B. Dehn & Co., 179 Queen Victoria Street, London EC4V 4EL (GB).		
(72) Inventors; and (75) Inventors/Applicants (for US only): OMTVEIT, Tore [NO/NO]; Nycomed Imaging AS, Nycoveien 2, P.O. Box 4220 Torshov, N-0401 Oslo (NO). HONERUD,	Published <i>With international search report.</i>		

(54) Title: APPARATUS HAVING PARTIALLY GOLD-PLATED SURFACE

(57) Abstract

A change in the surface properties of apparatus for pharmaceutical preparation results from steam sterilisation. This change may be avoided by the use of apparatus with more hydrophilic post-sterilisation surfaces, e.g. those of gold. Hence there is provided a process for the preparation of a mixture comprising a discontinuous phase in a continuous phase which comprises using a mixing apparatus having a non-porous mixing surface which is repellent to the discontinuous phase and/or attractive to the continuous phase when the continuous phase is liquid or which is attractive to the discontinuous phase when the continuous phase is gaseous, whereby to improve the efficacy of the preparation of said mixture and/or to reduce physical degradation of said mixing surface, said surface if hydrophilic being more hydrophilic after sterilisation than is stainless steel and if hydrophobic being more hydrophobic after sterilisation than is stainless steel.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

APPARATUS HAVING PARTIALLY GOLD-PLATED SURFACE

5 This invention relates to improvements in and relating to apparatus used for production of a pharmaceutical product comprising a continuous aqueous phase containing a discontinuous water-immiscible phase, in particular high shear mixer apparatus.

10 In the preparation of pharmaceuticals, it is important that the apparatus used should be capable of sterilization. This is generally achieved for large scale apparatus by steam sterilization, i.e. by passing steam, usually superheated steam, through the apparatus 15 between production runs.

 Much of the large scale apparatus used in pharmaceutical production is made of stainless steel because of its chemical inertness, corrosion resistance, ease of production and simplicity of sterilization.

20 We have now found however that mixing apparatus made of stainless steel and subjected in use to high shear forces may suffer a reduction in efficacy following steam sterilization. This is particularly critical in the case of rotor:stator mixers used to 25 generate lipid-membraned vesicles for use as pharmaceuticals, e.g. gas containing vesicles for use as ultrasound contrast agents, where the steam sterilization results in a reduction in vesicle yield.

 We have found that a change in surface properties 30 of the apparatus surfaces results from steam sterilization and that this may be reduced or avoided by the use of apparatus with more hydrophilic post-sterilisation surfaces, e.g. gold surfaces.

 Thus viewed from one aspect the invention provides 35 a process for the preparation of a mixture comprising a discontinuous phase in a continuous phase which comprises using a mixing apparatus having a non-porous

- 2 -

mixing surface which is repellent to the discontinuous phase and/or attractive to the continuous phase when the continuous phase is liquid or which is attractive to the discontinuous phase when the continuous phase is 5 gaseous, whereby to improve the efficacy of the preparation of said mixture and/or to reduce physical degradation of said mixing surface, said surface if hydrophilic being more hydrophilic after sterilisation than is stainless steel and if hydrophobic being more hydrophobic after sterilisation than is stainless steel. 10

Viewed from another aspect the invention provides a process for the preparation of a product, preferably a pharmaceutical product, comprising a continuous aqueous phase containing a discontinuous water-immiscible phase, 15 said process comprising mixing an aqueous material and a water-immiscible material in a mixing apparatus, characterized in that at least part of a non-porous surface of said apparatus contacting said aqueous and water-immiscible materials is formed of a substance 20 which when sterilized (e.g. steam sterilized) is more hydrophilic than sterilized steel, e.g. of gold or of a substance as hydrophilic as or more hydrophilic than gold.

For the purposes of comparison of surface 25 hydrophilicity, it is preferred to determine receding water contact angle at 25°C after a steam sterilization cycle for 1 hour. More preferably it is determined after repeated use (ie. homogenization) and sterilization cycles, e.g. after at least two such 30 cycles, preferably after 3 to 10 cycles.

The process of the invention may yield a ready-for-use pharmaceutical composition directly as a result of the operation of the mixing apparatus or alternatively further steps may be required in the process. Such 35 steps may include dilution, concentration, sterilization, lyophilization, addition of further active or non-active ingredients (e.g. diluents,

- 3 -

antioxidants, flavours, colours, stabilizers, suspending agents, etc.), dispersion and size separation, for example as occurs in mixing apparatuses such as extruders as described in more detail below. Likewise, 5 the pharmaceutical product produced by the process of the invention may be an intermediate in the production of or a component for a pharmaceutical composition. Preferably such compositions are vesicle containing diagnostic contrast media (e.g. X-ray, MR or most 10 preferably ultrasound contrast media) or vesicle containing therapeutic compositions (e.g. compositions where a therapeutic agent, e.g. a cytotoxic agent, is contained within vesicles such as liposomes or micelles).

15 Since the mixing apparatus is used for production of a pharmaceutical product, the surfaces contacting the materials being mixed are preferably sterile and the apparatus is preferably sealed.

20 The part of the surface of the mixing apparatus which is of the more hydrophilic substance preferably includes at least part of the mixing surfaces, i.e. the portions of the apparatus surface responsible for the mixing action.

25 Such mixing surfaces may be in motion or may be static during the operation of the mixing apparatus, e.g. they may be on mixing paddles or blades, on rotors in rotor:stator devices, etc. or they may be on atomisers (e.g. spray nozzles), expansion nozzles, static mixers, deflector/diffuser plates, sonicator 30 heads or other sonicator surfaces, or on stators in rotor:stator devices. In one embodiment, the mixing surface may form part of a mixing apparatus such as an extruder as described in more detail below. Such 35 extruders are especially suitable for the production of emulsions and work advantageously when some of the surfaces of the extruder which contact the reaction mixture are coated with gold. Such extruders may also

- 4 -

reduce problems associated with filter clogging. Desirably however such surfaces are ones over which the materials being mixed flow at a rate which is higher than that at which they flow over other surfaces in the 5 mixing apparatus.

The mixing apparatus will generally comprise one or more chambers (mixing chambers) in which mixing occurs. In the process of the invention a more hydrophilic surface is preferably present in one or more, preferably 10 all, of such chambers.

If desired, all surfaces in the mixing apparatus in contact with the materials being mixed (i.e. all contact surfaces) may be of the hydrophilic substance. Generally however only mixing surfaces (rather than 15 chamber surfaces and inlet and outlet duct surfaces) will be of the hydrophilic substance.

The hydrophilic substance may be any material capable of meeting the mechanical and chemical demands of the portion of the mixing apparatus in which it 20 occurs and which after steam sterilization is more hydrophilic than steel (e.g. stainless steel) after, for example, equivalent steam sterilization. Hydrophilicity in this regard may be compared by comparing the contact angle between pure water and the hydrophilic substance 25 or steel surfaces. The larger the contact angle the less hydrophilic is the surface.

In general the hydrophilic substance will 30 preferably have a receding contact angle (measured at 25°C after sterilization for 1 hour with steam) of less than 55°, preferably less than 45°, more preferably less than 30°. One example of a suitable hydrophilic material is gold and the water receding contact angle for gold steam sterilized for 1 hour is about 26°. By contrast, the receding contact angle for stainless steel 35 steam sterilized for 1 hour is 60°. Contact angles may be measured as described by Hansen et al. in J. Colloid Interface Sci. 141 (1991) and by Hansen in J. Colloid

- 5 -

Interface Sci. 160: 209 (1993).

The hydrophilic substance may be used to form entire components of the mixing apparatus; more generally however the hydrophilic substance will form a surface on a substrate, e.g. of steel or other metal or of a ceramic. The hydrophilic substance may be a material deposited on the substrate (e.g. by electroplating, vapour deposition, fusion, lamination, film deposition, painting, etc.) or alternatively it may be a material produced by transformation of a substrate surface, e.g. by plasma treatment or particle bombardment. While gold is a particularly preferred hydrophilic substance, alternative substances include ceramics, enamels, glass and vitreous glazes. The hydrophilic material may thus comprise a surface layer of a thickness sufficient to survive normal operation of the mixing apparatus. Suitable thicknesses will depend on the nature of the hydrophilic material and geometry and nature of mixer and mixing surface. However, suitable thicknesses generally will be in the range 0.5 to 50 μm , preferably 2 to 30 μm , e.g. 3 to 20 μm , most preferably about 3 μm .

The hydrophilic surfaces, and indeed all other contact surfaces in the mixing apparatus used according to the invention will preferably be smooth and also preferably non water-porous. Smoothness in this regard is as measurable by touch as hydrophilic surfaces may be created, even on steel substrates, by particle bombardment, e.g. by glass blasting, to create roughness at a nanometer scale (nano-roughness). In general, any roughness in surfaces should be at a scale smaller than the droplet size produced by the process.

The mixing apparatus used according to the invention may be any apparatus capable of generating a composition comprising a continuous aqueous phase containing a discontinuous non-water miscible phase, e.g. an emulsion, dispersion, foam, suspension, etc.

Such apparatus will generally be provided with a power source capable of causing the mixing effect, e.g. a pressure source or pump or a motor capable of moving mixing surfaces in the apparatus. The apparatus will 5 not generally be one in which the mixing effect is achieved by the effort of the operator, e.g. by manual stirring. Moreover the apparatus will preferably be arranged for operation under computer control or under on/off control by an operator.

10 The use of gold surfaces in pharmaceutical mixing apparatus is novel and such apparatus having gold contact surfaces forms a further aspect of the invention. Viewed from this aspect the invention provides a pharmaceutical mixing apparatus, preferably 15 adapted for steam sterilization (e.g. by provision of steam inlet and drainage ports), having a surface which in use contacts the material being mixed therein, wherein at least part of said surface is of gold, e.g. is gold plated.

20 The mixing apparatus of or used according to the invention may be any of the conventional types of mixing apparatus, e.g. homogenisers, atomisers, extruders, sonicators, static mixers, expansion nozzles, capmixers, shakers, paddle or blade mixers, etc. However, the 25 apparatus is preferably one in which the material being mixed is subjected to high shear forces, e.g. high shear homogenisers and sonicators and in particular rotor:stator mixers (e.g. as supplied by Ytron or as described in WO99/08782). In rotor:stator mixers, the 30 rotor and stator surfaces over which the material being mixed passes are preferably of a hydrophilic material or provided with a surface of a hydrophilic material. Likewise in atomisers (e.g. in spray mixers) the lining 35 of the spray nozzle is preferably of a hydrophilic material or provided with a hydrophilic material surface although it is envisaged that the lining of the spray nozzle may also be a hydrophobic material or provided

- 7 -

with a hydrophobic material. The mixing apparatus of or used according to the invention may likewise be provided with inlet and outlet ports for the materials to be mixed and the resulting mixture, etc. and optionally 5 with inlet and outlet ports for flushing or cleaning or sterilizing materials. Otherwise the apparatus is preferably sealed or sealable.

The materials being mixed using the process of the invention are preferably fluids whereby an emulsion, 10 suspension or dispersion is produced on mixing. The compositions produced on mixing (and any subsequent processing steps) are preferably diagnostic imaging contrast media (particularly vesicular ultrasound, X-ray or MR contrast media, for example dispersions of gas 15 microbubbles or of MR or X-ray contrast agent containing vesicles) or therapeutic compositions (e.g. dispersions of therapeutic agent - containing vesicles).

Particularly preferably, the materials being mixed comprise an aqueous liquid, a vesicle (e.g. liposome or 20 micelle or gas microbubble) membrane forming agent (e.g.

a lipid, in particular a phospholipid or a mixture of phospholipids) and optionally and preferably a gas or 25 gas-precursor (e.g. air, nitrogen, sulphur hexafluoride or a fluorocarbon, for example a C₃₋₆ perfluorocarbon).

By gas-precursor is meant a material or mixture of 30 materials which is at least partially in the gaseous phase at 37°C and atmospheric pressure or which is reactive to generate a gas in vivo. Examples of suitable lipids, gases and gas precursors are described in WO 97/29783 (Nycomed).

The principle behind the process and apparatus of the invention may however be extended to the mixing of non-pharmaceutical compositions, e.g. cosmetics and foodstuffs, and even to the production of droplet-in-gas 35 dispersions of aqueous or hydrophilic liquids, e.g. as in spray-dryers and prilling towers. In the production of droplet-in-gas dispersions (sprays), the hydrophilic

- 8 -

surface will preferably be provided on the internal surface of the spray nozzle. Such uses and apparatus therefor form further aspects of the invention.

The principle behind the process and apparatus of the invention may likewise be applied to the production of products comprising a water-immiscible continuous phase containing an at least partially water-miscible discontinuous phase (e.g. water-in-oil emulsions) as well as to the production of droplet-in-gas dispersions (sprays) of water-immiscible liquids (e.g. of hydrocarbon fuels for example as sprayed in injection nozzles in diesel engines). In such cases, it is preferred to use in place of a hydrophilic surface, a hydrophobic surface, i.e. one which following steam sterilization is more hydrophobic than steam sterilized steel (e.g. with a water contact angle above 90°), for example a hydrophobic polymer such as a polyolefin or a fluorinated polyolefin such as PTFE, or a substance as hydrophobic as PTFE or more hydrophobic than PTFE. However, it is envisaged that a hydrophilic surface may also be effective. Such uses and apparatus therefor form still further aspects of the present invention.

Documents referred to herein are hereby incorporated by reference.

Embodiments of the invention will now be described further by way of example and with reference to the accompanying drawings in which:

Figure 1 is a cross-sectional drawing of a rotor:stator mixer substantially as described in WO99/08782);

Figure 2 is a perspective view of the rotor and stator stage in the apparatus of Figure 1; and

Figure 3 is a cross-sectional drawing of an extruder suitable for use in the preparation of liposome suspensions.

Referring to Fig. 1, there is shown a rotor: stator mixer. Gas (e.g. a perfluorocarbon such as

- 9 -

perfluorobutane) and liquid (e.g. an aqueous phospholipid mixture) are introduced through inlets 5 and 6 respectively into premixing chamber 7, the walls of which are defined by a concave section of housing 8, 5 first stator element 9, and the tip 10 of rotor drive shaft 11.

Tip 10 of rotor drive shaft 11 carries a flange 12 (seen side-on) which serves to mix gas and liquid in pre-mix chamber 7.

10 Housing 8 provides a cylindrical chamber and has a cup-shaped portion 8 and an end cap 13 with rotor drive shaft 11 entering through the base of portion 8 and sealed by a double mechanical seal 14. Drive shaft 11 is rotated for example at speeds of up to 8000 rpm by 15 externally positioned motor 15 and rotates first rotor 16 and second rotor 17 which are in interlocking engagement with first stator 18 and second stator 19. The rotors and stators are gold plated to a thickness of 2 to 30 μm and have an external diameter of about 110 20 mm.

Premix chamber 7 communicates with first mixing chamber 20 which is defined by surfaces of housing 8, first stator 18, and second stator 19 and which has an outlet 21 which corresponds to the inlet to second 25 mixing chamber 22. Second mixing chamber 22 is defined by surfaces of second stator 19 and housing 8.

In first mixing chamber 20, material from premixing chamber 7 passes radially outward through shear force zones 23a,b,c etc. between cylindrical extensions 24,25 30 of first stator 18 and first rotor 16 through fluid passageways defined by axial slots 26,27 in first rotor and first stator. Conveniently each rotor:stator assembly defines about 12 to 14 such shear force zones and the radial clearance between the cylindrical 35 extensions is conveniently about 250 μm . At the periphery of the mixing chamber the material being mixed then passes radially inward to pass from first mixing

- 10 -

chamber to second mixing chamber through outlet 21.

The cylindrical extensions of rotor and stator are not shown in the lower portion of Fig. 1 and the slots in cylindrical extensions of second rotor and second stator are likewise not shown.

In second mixing chamber 22, the mixture passes radially outward between second rotor and second stator before leaving through outlet 28 as a gas microbubble suspension.

First and second mixing chambers 20 and 22 are provided with drainage ports 29 and 30 along their lower boundary. These drainage ports may be connected to a steam trap and drain, e.g. as is conventional in pharmaceutical manufacturing apparatus. For sterilization, steam (generally superheated steam) is introduced into the mixing chambers through inlet 5. Liquid media may likewise be introduced through inlet 5; however in this instance inlet 5 is desirably provided with a valve (not shown) which provides a larger inlet diameter (e.g. 3 to 8 mm) when liquid is to be introduced than the diameter (e.g. 0.2 to 2 mm, preferably 0.5 mm) used when gas is introduced. Liquid inlet 6 likewise conveniently has a diameter of 3 to 8 mm. Moreover about their periphery, first and second mixing chambers are provided with annular temperature control means, e.g. water cooling jackets, 31 and 32, temperature controlled by monitors 33,34 and control means 35,36. Further cooling means, e.g. coolant ducts, may be provided to cool the stators, the rotor drive shaft and the mechanical seal.

In a typical example of the use of the mixer apparatus, drive shaft 11 is rotated at 8000 rpm or such a rate as to cause outer shear force zone 23 to have a relative rotor:stator speed of at least 32 m/s, e.g. 46 m/s.

Gold plated rotor:stator assemblies are novel and form a further aspect of the invention.

- 11 -

Referring to Figure 2, it may be seen that the cylindrical extensions (flanges) 24,25 and axial slots 26,27 of the stators and rotors are axially extending and comprise a plurality of axially extending "teeth" 37 5 separated by a corresponding plurality of circumferentially evenly spaced, axially and radially extending apertures 38. In use, the materials being mixed pass through these apertures into successive shear force application zones defined by the circumferential 10 sides of adjacent cylindrical extensions and axial slots.

Referring to Figure 3, there is shown a representation of an individual flange 24,25.

Referring to Figure 4, there is shown a 15 representation of a cross sectional drawing of an extruder suitable for use as a mixing apparatus according to the invention.

Extrusion is performed using a pressurised reservoir (not shown) connected to a filter house with 20 filters installed. The filter house assembly consists of the house bottom (39), the house lid (40), one or more support screens (41), bolts (42), o-ring seals (43) one or more filter membranes (44) and optionally one or more drain disks (45). Gold plating the parts which 25 contact the fluid from the reservoir (other than the filter membranes (44) itself and particularly parts 39, 40 and 41 is beneficial for the efficiency of the extrusion operation. A liposome suspension may be introduced through inlet (46) at a pressure of up to 30 approximately 300 bar. There are preferably three filter membranes (44) which may be formed from, for example, 2 μ m polycarbonate sold under the Trade name Neopore by Corning. The drain disk (45) may be formed from a perforated porous sheet and which lies on top of 35 the support screen(s) (41) which comprises a series of holes to allow the extruded liposome suspension to pass out of the extruder through outlet (47).

- 12 -

The following non-limiting examples serve to illustrate the invention.

Example 1

5

Rotor:stator assemblies as described, made of stainless steel 316 L or gold plated stainless steel 316 L were tested for yield (million/mL as determined using a Coulter Multisizer) of 3-5 μm microbubbles and for surface hydrophilicity (receding contact angle at 25°C). The assemblies were untreated (U), steam sterilized for 1 hour (1S), unplated (316), gold plated (G), roughened (E), and/or steam sterilized for 15 production/sterilization cycles, each involving 1 hour of steam sterilization (15S). The yields and contact angles are set out below:

	<u>Surface</u>	<u>Yield (million/mL)</u>	<u>Contact angle (°)</u>
	316.U	1200-2000	13
20	316.1S	500	60
	316.1SE	500	70
	G.U	1400	18
	G.1S	1200	26
	G.15S	1000	43

25

As can be seen, the gold plated assemblies did not suffer the rapid drop off in yield subsequent to sterilization associated with the unplated assemblies.

30

Example 2

Liposome Extrusion

35 Using moderate pressure, e.g. 300 bar, a liquid crystalline multilamellar liposome suspension can be forced through filters with defined pore sizes. As the layers of the multilamellar liposome deform to pass

- 13 -

through the pore, a breaking and resealing of the membranes occurs. If a liposome preparation is passed through filters many times, this process gives rise to a liposome population that reflects that of the filter 5 pore.

Extrusion can be performed using an apparatus as described in the text above with reference to Figure 4

10 Comparative study:

In a comparative study, we have found that gold plating the parts 39, 40 and 41 is beneficial for the efficiency of the extrusion operation compared to an assembly with parts 39, 40 and 41 having surfaces of stainless steel. 15 The filter membranes used were sets of three Nucleopore® track-etched membrane filters supplied by Corning. The reservoir was pressurised until a steady flow came out of the filter house, and the pressure was gradually increased further if the flow significantly reduced.

20

	Stainless Steel	Gold Plated
1 st extrusion stage	3 x 0.8 µm pore filters max. 10 barg	3x 0.8 µm pore filters max. 5 barg
2 nd extrusion stage	3 x 0.2 µm pore filters max. 120 barg - decreasing flowrate	3 x 02 µm pore filters max. 25 barg
3 rd extrusion stage	3 x 0.1 µm pore filters max. 140 barg - full clogging	3 x 0.1 µm pore filters max. 40 barg
Median size	141 nm	144 nm

30 The table shows that the liposome suspension was much easier extruded in the gold plated extruder housing.

- 14 -

CLAIMS

1. A process for the preparation of a mixture comprising a discontinuous phase in a continuous phase which comprises using a mixing apparatus having a non-porous mixing surface which is repellent to the discontinuous phase and/or attractive to the continuous phase when the continuous phase is liquid or which is attractive to the discontinuous phase when the continuous phase is gaseous, whereby to improve the efficacy of the preparation of said mixture and/or to reduce physical degradation of said mixing surface, said surface if hydrophilic being more hydrophilic after sterilisation than is stainless steel and if hydrophobic being more hydrophobic after sterilisation than is stainless steel.
2. A process as claimed in claim 1 wherein said continuous phase is an aqueous liquid.
3. A process as claimed in claim 2 wherein said surface is of gold or ceramic or is plasma oven treated.
4. A process as claimed in either of claims 2 and 3 wherein water receding contact angle of said surface after steam sterilisation is less than 55°.
5. A process as claimed in any one of claims 1 to 4 wherein said mixture is a pharmaceutical composition.
6. A process as claimed in any one of claims 1 to 5 wherein the continuous phase is an aqueous liquid and the discontinuous phase is at least partially gaseous.
7. A process as claimed in any one of claims 1 to 6 wherein said mixing apparatus is selected from homogenizers, atomizers, sonicators, cap mixers,

- 15 -

shakers, paddle mixers, blade mixers, static mixers, expansion nozzles, rotor stators, extruders and extruders.

5 8. A process as claimed in any preceding claim wherein said surface is steam sterilised before mixing.

9. A process as claimed in any one of the preceding claims being a process for the preparation of a product 10 comprising a continuous aqueous phase containing a discontinuous water-immiscible phase, said process comprising mixing an aqueous material and a water-immiscible material in a mixing apparatus, characterized in that at least part of a non-porous surface of said 15 apparatus contacting said aqueous and water-immiscible materials is formed of a substance which when sterilized is more hydrophilic than sterilized steel.

10. A process as claimed in claim 1 being a process for 20 the preparation of a product comprising a continuous hydrophobic phase containing therein an immiscible discontinuous phase, for example an aqueous phase, said process comprising admixing a hydrophobic material with a material immiscible therewith in a mixing apparatus, 25 characterized in that at least part of a non-porous surface of said apparatus contacting said materials is formed of a substance which when sterilized is more hydrophobic than sterilized steel.

30 11. A process as claimed in claim 1 being a process for the preparation of a hydrophilic droplet-in-gas spray, said process comprising passing a liquid hydrophilic material through a spray nozzle into a gas, characterised in that a surface of said nozzle in 35 contact with said hydrophilic material is more hydrophilic than sterilized steel.

- 16 -

12. A process as claimed in claim 1 being a process for the preparation of a hydrophobic droplet-in-gas spray, said process comprising passing a liquid hydrophobic material through a spray nozzle into a gas,

5 characterised in that a surface of said nozzle in contact with said hydrophobic material is more hydrophobic than sterilized steel.

13. Pharmaceutical mixing apparatus having a surface which in use contacts the material being mixed therein, wherein at least part of said surface is of gold.

14. A gold plated rotor:stator assembly.

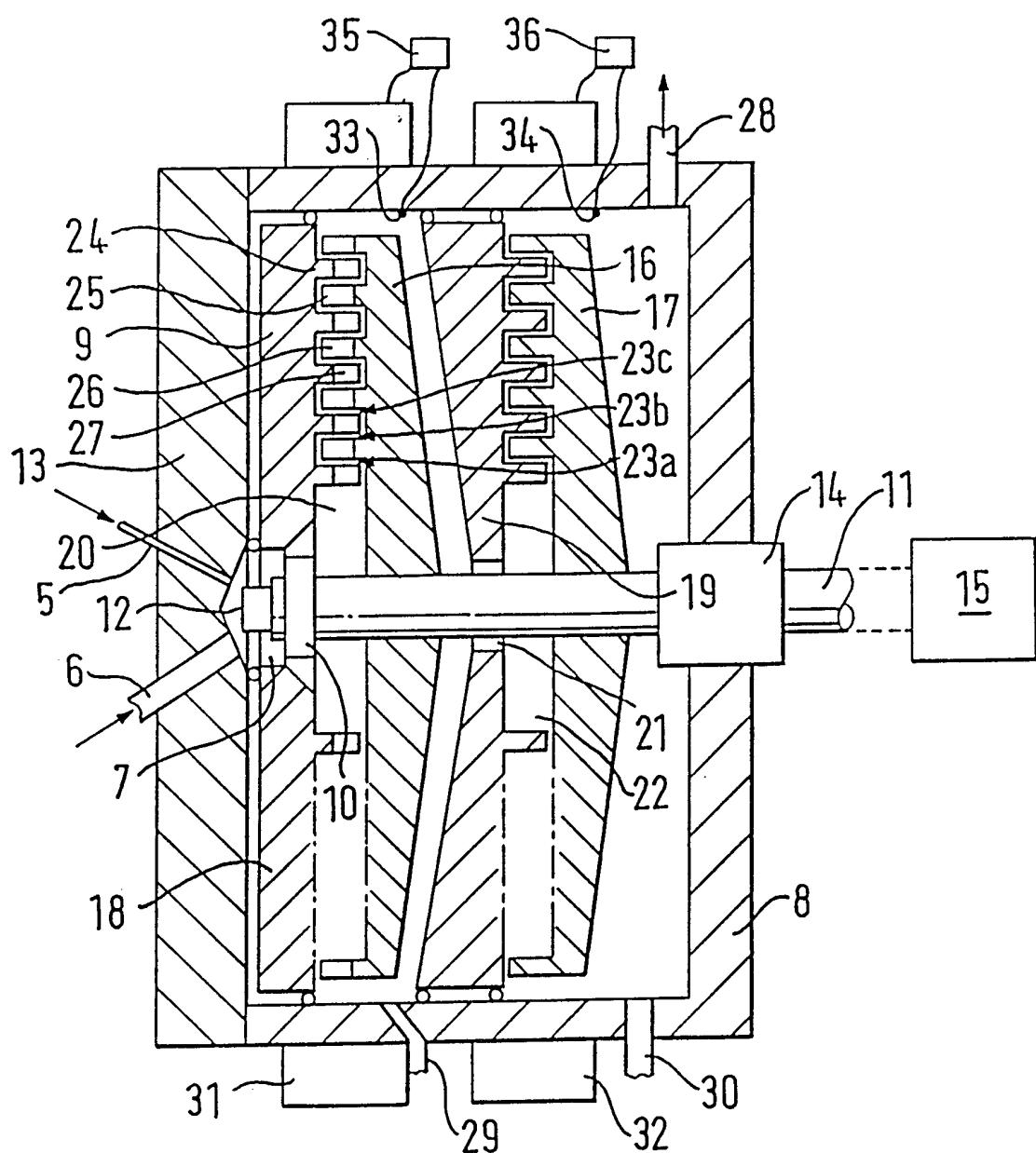
15. 15. An assembly comprising a sonicator horn or other actively vibrating surface placed in a sonicating chamber wherein at least part of the surfaces of said assembly are gold plated.

20 16. An extruder having a filter chamber comprising a filter membrane disposed on a support, characterised in that at least part of the surfaces within said chamber are gold plated.

25 17. A product obtained by a process as claimed in any one of claims 1 to 12.

1/3

FIG. 1



2/3

FIG. 2

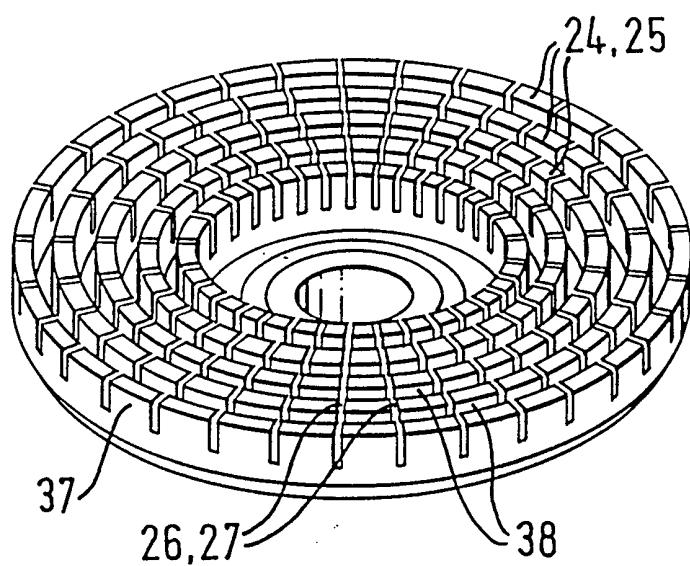
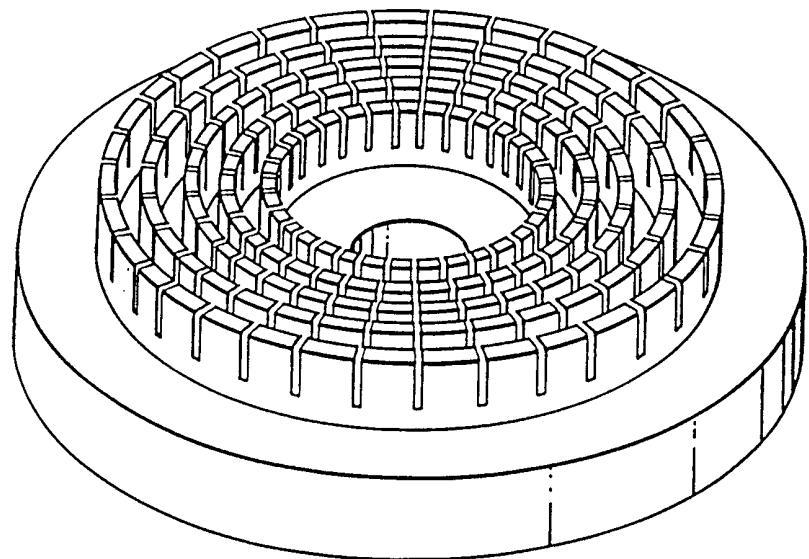
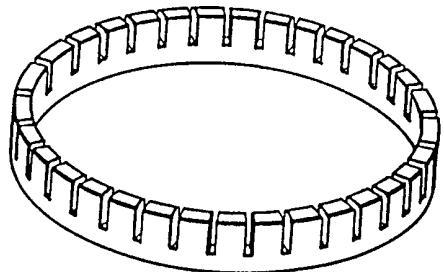


FIG. 3



3/3

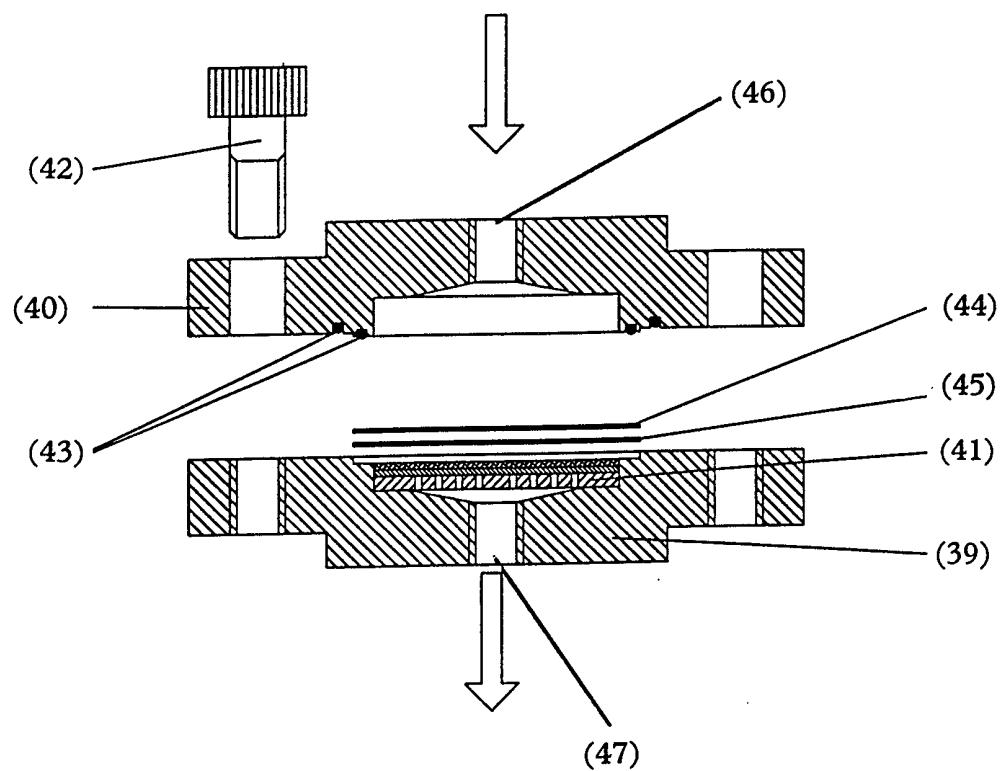


FIG 4

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/02741

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 B01F5/06 B01F7/00

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 C25D

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y, P	WO 99 08782 A (NYCOMED IMAGING AS, J.COCKBAIN) 25 February 1999 (1999-02-25) the whole document ---	1-17
Y	PATENT ABSTRACTS OF JAPAN vol. 12, no. 479 (C-552), 14 December 1988 (1988-12-14) & JP 63 195291 A (KANSAI PLANT KOGYO KK), 12 August 1988 (1988-08-12) abstract ---	1-17
Y	US 3 854 083 A (G.N.HULDERMANN) 10 December 1974 (1974-12-10) abstract ---	1-17



Further documents are listed in the continuation of box C.



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
25 October 1999	02/11/1999
Name and mailing address of the ISA 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	Authorized officer Cordero Alvarez, M

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/02741

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PATENT ABSTRACTS OF JAPAN vol. 7, no. 181 (C-180), 10 August 1983 (1983-08-10) & JP 58 087296 A (MASAMI KOBAYASHI), 25 May 1983 (1983-05-25) abstract ---	1-17
A	DE 32 07 422 A (LICENTIA PATENT-VERWALTUNGS-GMBH) 8 September 1983 (1983-09-08) claim 1 -----	1-17

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 99/02741

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9908782	A 25-02-1999	AU	8814898 A	08-03-1999
JP 63195291	A 12-08-1988	JP	1922549 C	07-04-1995
		JP	6031469 B	27-04-1994
		JP	3193895 A	23-08-1991
		JP	6031463 B	27-04-1994
US 3854083	A 10-12-1974	NONE		
JP 58087296	A 25-05-1983	JP	1320414 C	29-05-1986
		JP	60047913 B	24-10-1985
DE 3207422	A 08-09-1983	NONE		