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(21) International Application Number: PCT/EP98/00816 (22) International Filing Date: 12 February 1998 (12.02.98) (30) Priority Data: MI97A00363 20 February 1997 (20.02.97) IT (71) Applicant (for all designated States except US): ANGELINI RICERCHE S.P.A. SOCIETA' CONSORTILE [IT/IT]; Pizzalle della Stazione, I-00040 S. Palomba Pomezia (IT). (72) Inventors; and (75) Inventors/Applicants (for US only): CAVALLO, Giovanni [IT/IT]; Via delle Tartane, 45, I-00122 Ostia (IT). MARCHITTO, Leonardo [IT/IT]; Via S. Margherita, 2, I-63012 Cupra Marittima (IT). (74) Agents: MARCHI, Massimo et al.; Marchi & Partners s.r.l., Via Pirelli, 19, I-20124 Milano (IT). (71) Aziende chimiche Riunite Angelini Francesco A.C.R.F. SPA viale Amelia, 70 I-00181 Roma Italy		(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, 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 the receipt of amendments.
(54) Title: AQUEOUS PHARMACEUTICAL COMPOSITION COMPRISING AN ACTIVE INGREDIENT WHICH IS HIGHLY INSOLUBLE IN WATER		
(57) Abstract Aqueous pharmaceutical composition comprising an active ingredient which is highly insoluble in water, dispersed in liposomes and method of preparation thereof.		



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"Aqueous pharmaceutical composition comprising an active ingredient which is highly insoluble in water"

* * * * *

This invention relates to an aqueous pharmaceutical composition comprising an active ingredient which is highly insoluble in water. In particular, it relates to a pharmaceutical composition in which the active ingredient is dispersed in liposomes.

A great deal of research is being carried out to find new liposomal preparations in the pharmaceutical field. However, many difficulties have emerged particularly in relation to active ingredients which are highly insoluble in water. In particular, those with a solubility in water $\leq 0.01\%$ (w/v).

In fact, the technique currently used to produce liposomes comprising active ingredients of low water-solubility comprises:

- a) solubilizing of the active ingredient and the preselected phospholipids in a suitable organic solvent, for example, chloroform;
- b) evaporation of this solvent at reduced pressure to give an active ingredient/phospholipid film;
- c) addition of a second organic solvent, for example, tertbutylic alcohol;
- d) freezing of the solution obtained at the temperature of liquid nitrogen;
- e) lyophilisation of the frozen solution;
- f) hydration of the lyophilised solution with a buffer solution to give a suspension of multilamellar liposomes (MLV); and
- g) treatment of this suspension with ultrasound to give a suspension of smaller liposomes (SUV).

An example of this method is described by A. Sharma et al.

"Pharmaceutical Research", 2 (6), 889-896 (1994).

This technique, however, has the disadvantage of being very laborious and leads to the presence of traces of organic solvents in the liposomes.

However, the said authors refer to having investigated various techniques for the preparation of MLV liposomes such as the hydration of the dry lipid films (hand shaking), freeze thawing and various techniques such as extrusion and treatment with ultrasound to reduce then (postprocessing) the size of the liposomes (MLV → SUV) and conclude that the method described in detail above and comprising the said phases a) to g) was demonstrated to be the most acceptable (*loc. cit.* page 890, right column, lines 51-57). However, the said authors do not indicate how the said first techniques for the preparation of MLV liposomes and the said second techniques which can reduce the size of the liposomes were combined one another.

WO-A-96 40064, EP-A-0 578 629, DE-A-038 075 and DE-A-4 430 593 disclose pharmaceutical compositions where an active ingredient insoluble in water is dispersed in liposomes, such active ingredient is cyclosporin A, melatonin and, respectively, taxol.

However, none of the above mentioned documents describes a method for preparing an aqueous liposome composition which combines the freezing and thawing technique with extrusion.

Surprisingly, it has now been found that the freezing and thawing technique combined with extrusion allows the preparation of aqueous liposome compositions of active ingredients with a solubility in water $\leq 0.01\%$ (w/v) without the use of any organic solvent.

In this description, and the claims that follow, active ingredients with a solubility in water $\leq 0.01\%$ (w/v) are defined as "highly insoluble in water".

Therefore, it is a first object of this invention to provide a pharmaceutical composition according to an aqueous pharmaceutical composition including an active ingredient having a solubility in water of not higher than 0.01% (w/v) dispersed in liposomes, wherein the said



active ingredient is lonidamine or bindarit.

The following are typical examples of active ingredients which are highly insoluble in water:

lonidamine (solubility: 3×10^{-6} g/ml), melatonin

- 5 ["practically insoluble", G.S. Shida et al. "J. Pineal Res.", 16, 198-201, (1994)], cyclosporin-A ["insoluble in water", monograph on cyclosporin-A in "Analytical Profiles of Drug Substances", 16, 163, (1987)] and bindarit (solubility: 1×10^{-4} g/ml).

- 10 The liposomes of the compositions according to this invention are preferably made up of a component chosen from the group comprising phosphoglycerides, glycerides, diglycerides, triglycerides, phospholipids, galactosyl and glucosyl lipids, cholesterol and its
- 15 derivatives.



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sphingolipids and mixture thereof. More preferably, they are made up of phospholipids.

A typical example of the liposomal composition according to this invention comprises phosphatidylcholine, lysophosphatidylcholine, N-acyl-phosphatidylcholine, phosphatidyl ethanolamine, phosphatidylserine, sphingomyelin, non-polar lipids, triglycerides, free fatty acids, DL- α -tocopherol.

A preferred liposomal composition according to this invention comprises:

<u>Component</u>	<u>% (w/w)</u>
phosphatidylcholine	: 85 - 97
lysophosphatidylcholine	: 0 - 5
N-acyl-ethanolamine	: 0 - 4
phosphatidyl ethanolamine	: 0 - 10
triglycerides	: 0 - 4
free fatty acids	: 0 - 3
DL- α -tocopherol	: 0 - 1

A particularly preferred liposomal composition according to this invention comprises:

<u>Component</u>	<u>% (w/w)</u>
phosphatidylcholine	: 94
lysophosphatidylcholine	: 3
N-acyl-ethanolamine	: 1
phosphatidyl ethanolamine	: 0.1
triglycerides	: 1
free fatty acids	: 0.75
DL- α -tocopherol	: 0.15

Typically, the size of the liposomes according to this invention is less than 500 nm. Preferably, this is from 50-250 nm.

It is a second object of this invention to provide a method for the preparation of an aqueous pharmaceutical composition according to a method for the preparation of an aqueous pharmaceutical composition with an active ingredient having a solubility in water of not higher than 1.01% (w/v) dispersed in liposomes, further including the following phases:

- a) dispersion of the active ingredient in lipids at a temperature of between 20 and 30°C;
- b) suspension of the dispersion in an aqueous phase;
- c) resting of the suspension at ambient temperature for a period of between 0 and 48 hours;
- d) heating the suspension to 30-75°C for 10-40 minutes;
- e) freezing the suspension at -150/-200°C;
- f) repeating of phases d) and e) at least twice and not more than 8 times;
- g) filtering the suspension through a filtering membrane with pores of diameter 500-1000 nm;
- h) extruding through a membrane with pores of diameter 50-400 nm; and at the same time
- i) removing any active ingredient which is not trapped.

The duration of phase c) depends on the quantity of active ingredient highly insoluble in water to be trapped in the liposomes. The person skilled in the art does not therefore encounter any difficulties since a few simple routine experiments will determine the correct time for each type of active ingredient and liposomal composition.

The aqueous phase shall preferably be made up of an aqueous solution of sodium chloride at 0.05%-0.9% (w/v).

Typically, the quantity of lipid used is between 0.01-0.4 parts by weight for each part by weight of aqueous solution. In turn, the quantity of active ingredient is typically between 0.01 and 0.3 parts by weight for each part by weight of lipid.

Typically, the disperser is a homogeniser of the Ultraturrax™ type.



Typically, the extrusion is carried out using compressed air or an inert gas, chosen from the group comprising nitrogen, helium and argon, as the extrusion gas. The preferred inert gas is helium. In the extrusion phase, the pressure shall preferably be between 500 and 5500 kPa and the temperature shall preferably be between 20 and 75°C, and even more preferably between 40 and 65°C. Typical examples of suitable extruders are those of the Lipex Biomembranes Thermobarrel type or of the Emulsiflex CC Avestin type with filters with polycarbonate Costar™ membranes with pores of between 50 and 600 nm.

Typically phase h) is repeated at least twice and not more than 8 times. Preferably 6 times.

The following examples illustrate this invention without limiting it in any way.

EXAMPLE 1

100 mg of melatonin were dispersed in 1 g of phospholipid at 30°C for 10 minutes using an Ultraturrax™ type homogeniser. Immediately afterwards, this dispersion was suspended in 10 ml of aqueous solution of sodium chloride at 0.9% (w/v) using the said homogeniser and then heated in a water bath at 55°C for 20 minutes.

The suspension obtained in this way was subject to the following cycle of cooling and heating:

- cooling in liquid nitrogen for 1 minute,
- heating to 55°C until the phospholipids are completely fluid.

This cycle was repeated 6 times.

The suspension was passed twice through a 0.6 µm filter with the Lipex Biomembrane apparatus.

Thus, a "Multilamellar Large Vesicles" (MLV) suspension was obtained which was subjected to 6 cycles of continuous extrusion using a 10 ml extruder of the Lipex Biomembranes Extruder Thermobarrel type with 0.1

µm polycarbonate Costar™ filters at 55°C, using helium, as the extrusion gas, at a pressure of between 1000 and 4800 kPa.

Operating as described above three batches of the product (LM/186, LM/188 and LM/190) were prepared.

The following tests were carried out on the batches:

- * melatonin amount in the aqueous liposomal composition (HPLC analysis);
- * liposome size;
- * quantity of melatonin trapped in the liposomes.

The following table shows the parameters measured and their significance:

<i>Parameters</i>	<i>Significance</i>
liposome size	- stability in the formulation time; - measurement of the "fusion" of the vesicles;
melatonin amount	- concentration of melatonin in the aqueous liposomal composition; - stability in the formulation time;

The data obtained are given in Table 1 which shows:

- the concentration of melatonin obtained in the aqueous liposomal formulation was, expressed as an average value for the three batches, 8.05×10^{-3} g/ml;
- the average size of the liposomes for the three batches was 93 nm;
- the quantity trapped, expressed as an average value for the three batches, was 80.5 µg/mg
- the formulations showed no liposome aggregation phenomena.

TABLE 1

	HPLC amount (mg/ml)	average size (nm)	quantity trapped *µg/mg
LM/186	7.8	85	78
LM/188	8.46	97	84.6
LM/190	7.9	98	79



(*) expressed as γ of drug per mg of phospholipids used.

The following procedure was used for the HPLC analysis:

- fixed phase: column in inverse phase PKB-100 (250 x 4.6 mm; 5 μ m Supelco);
- mobile phase: water:acetonitrile 80:20 (v/v);
- detection: UV 254 nm.

Two pieces of apparatus are used for the analysis of the average size of the liposomes:

- 1) DELSA 440 Coulter,
- 2) NICOMP Submicron particle sizer model 370.

The procedure was as follows:

- a) for the tests carried out with apparatus 1), 1 ml of liposomal suspension was diluted with 10 ml of aqueous solution of sodium chloride at 0.9% (w/v);
- b) for the tests carried out with apparatus 2), 0,5 ml of solution a) was diluted to 10 ml with aqueous solution of sodium chloride at 0.9% (w/v).

EXAMPLE 2

Proceed as described in Example 1 above, using 2 g of phospholipid and 50 mg of lonidamine in place of 1 g of phospholipid and 100 mg of melatonin.

Thus three batches of the product (LM/195, GN/1L and GN/2L) are prepared. The data obtained are given in Table 2 which shows:

- the concentration of lonidamine in the aqueous composition went from the initial solubility value of 3×10^{-6} g/ml to an average value for the three batches of 3.83×10^{-3} g/ml;
- the average size of the liposomes for the three batches was 79.6 nm;
- the quantity trapped, expressed as an average value for the three batches, was 19.2 μ g/mg
- the formulations showed no liposome aggregation phenomena.



TABLE 2

batch	HPLC amount (mg/ml)	average size (nm)	quantity trapped * $\mu\text{g}/\text{mg}$
LM/195	3.66	103	18.3
GN/1L	3.31	53	16.5
GN/2L	4.54	76	22.7

(*) expressed as μg of drug per mg of phospholipids used.

EXAMPLE 3

Proceed as described in Example 1 above, using 2 g of phospholipid and 200 mg of melatonin in place of 1 g of phospholipid and 100 mg of melatonin.

Thus three batches of the product (GN/1M, GN/2M and GN/3M) were prepared. The data obtained are given in Table 3 which shows:

- the concentration of melatonin in the aqueous liposomal formulation, expressed as an average value for the three batches, was 13.5×10^{-3} g/ml;
- the average size of the liposomes for the three batches was 92.6 nm;
- the quantity trapped, expressed as an average value for the three batches, was $67.6 \mu\text{g}/\text{mg}$
- the formulations showed no liposome aggregation phenomena.

TABLE 3

batch	HPLC amount (mg/ml)	average size (nm)	quantity trapped * $\mu\text{g}/\text{mg}$
GN/1M	10.66	104	53.3
GN/2M	13.90	76	69.5
GN/3M	16.03	98	80.15

(*) expressed as μg of drug per mg of phospholipids used.

EXAMPLE 4



Proceed as described in Example 2 above, except that the extrusion is carried out through a polycarbonate membrane of 0.2 μm rather than 0.1 μm .

Thus three batches of the product (GN/3L, GN/4L and GN/5L) were prepared.

The data obtained are given in Table 4 which shows that, by increasing the lonidamine from 20 mg to 50 mg, the quantity of phospholipid for 1 to 2 g and extruding with a 0.2 μm instead of a 0.1 μm membrane, a significant increase in the concentration of lonidamine in the aqueous composition was obtained in example 2. In fact, an average value of 4.47×10^{-3} g/ml was obtained for the concentration of lonidamine.

TABLE 4

batch	HPLC amount (mg/ml)	average size (nm)	quantity trapped * $\mu\text{g}/\text{mg}$
GN/3L	4.23	134	21.15
GN/4L	4.44	129	22.20
GN/5L	4.75	109	23.75

(*) expressed as μg of drug per mg of phospholipids used.

EXAMPLE 5

20 mg of cyclosporin-A were dispersed in 1 g of phospholipid at 30°C for 10 minutes using an Ultraturrax™ type homogeniser. Immediately afterwards, this dispersion was suspended in an aqueous solution of sodium chloride at 0.9% (w/v) using the said homogeniser and then heated in a water-bath at 65°C for 20 minutes.

The suspension obtained in this way was subject to the following cycle of cooling and heating:

- cooling in liquid nitrogen for 1 minute,
- heating to 65°C until the phospholipids are completely fluid.

This cycle was repeated 6 times.



The suspension was passed twice through a 0.6 μm filter with the Lipex Biomembrane apparatus.

Thus a "Multilamellar Large Vesicles" (MLV) suspension was obtained which was subjected to 6 cycles of continuous extrusion using a 10 ml extruder of the Lipex Biomembrane Extruder Thermobarrel type with 0.1 μm polycarbonate Costar™ filters at 65°C, using helium as the extrusion gas at a pressure of between 1000 and 4800 kPa.

Thus three batches of the product (LM/416A, LM/416B and LM/416C) were prepared.

The data obtained are given in Table 5 which shows:

- the concentration of cyclosporin-A in the aqueous liposomal formulation, expressed as an average value for the three batches, was 0.96×10^{-3} g/ml;
- the average size of the liposomes for the three batches was 103 nm;
- the quantity trapped, expressed as an average value for the three batches, was 9.6 $\mu\text{g}/\text{mg}$
- the formulations showed no liposome aggregation phenomena.

TABLE 5

batch	HPLC amount (mg/ml)	average size (nm)	quantity trapped * $\mu\text{g}/\text{mg}$
LM/416A	0.96	103	9.6
LM/416B	0.94	99	9.4
LM/416C	0.98	107	9.8

(*) expressed as μg of drug per mg of phospholipids used.

EXAMPLE 6

Proceed as described in Example 1 above, using 2 g of phospholipids and 50 mg of bindarit in place of 1 g of phospholipids and 100 mg of melatonin.

Thus three batches of the product (LM/356, LM/357 and LM/358) were prepared.



The data obtained are given in Table 6 which shows:

- the concentration of bindarit in the aqueous liposomal composition went from the initial solubility value of 1×10^{-4} g/ml to an average value for the three batches of 4 mg/ml;
- the average size of the liposomes for the three batches was 108.3 nm;
- the quantity trapped, expressed as an average value for the three batches, was 20.2 $\mu\text{g}/\text{mg}$
- the formulations showed no liposome aggregation phenomena.

TABLE 6

batch	HPLC amount (mg/ml)	average size (nm)	quantity trapped * $\mu\text{g}/\text{mg}$
LM/356	4.1	109.4	20.5
LM/357	4	109.7	20
LM/358	4	106	20

(*) expressed as μg of drug per mg of phospholipids used.

EXAMPLE 7

30 mg of cyclosporin-A were dispersed in 2 g of phospholipid at 30°C for 10 minutes using an Ultraturrax™ type homogeniser. Immediately afterwards, this dispersion was suspended in an aqueous solution of sodium chloride at 0.9% (w/v) using the said homogeniser and left to rest at ambient temperature for 24 hours. Then the suspension obtained was heated in a water-bath at 65°C for 20 minutes.

The suspension obtained in this way was subject to the following cycle of cooling and heating:

- cooling in liquid nitrogen for 1 minute,
- heating to 65°C until the phospholipids are completely fluid.

This cycle was repeated 6 times.

The suspension was passed twice through a 0.6 μm filter with the Lipex Biomembrane apparatus.



Thus, a "Multilamellar Large Vesicles" (MLV) suspension was obtained which was subjected to 6 cycles of continuous extrusion using an extruder of the 10 ml Lipex Biomembrane Extruder Thermobarrel type with 0.1 μm polycarbonate Costar™ filters at 65°C, using helium as the extrusion gas at a pressure of between 1000 and 4800 kPa.

Thus three batches of the product (LM/422a, LM/422b and LM/422c) were prepared.

The data obtained are given in Table 7 which shows:

- the concentration of cyclosporin-A in the aqueous liposomal formulation, expressed as an average value for the three batches, was 3 mg/ml;
- the average size of the liposomes for the three batches was 119.5 nm;
- the quantity trapped, expressed as an average value for the three batches, was 15 $\mu\text{g}/\text{mg}$
- the formulations showed no liposome aggregation phenomena.

TABLE 7

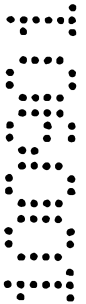
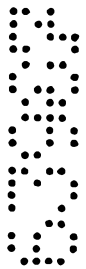
batch	HPLC amount (mg/ml)	average size (nm)	quantity trapped * $\mu\text{g}/\text{mg}$
LM/422a	3.2	121.5	16
LM/422b	3	117.9	15
LM/422c	2.8	119	14

(*) expressed as μg of drug per mg of phospholipids used.

It will be clearly understood that, although a number of prior art publications are referred to herein, this reference does not constitute an admission that any of these documents forms part of the common general knowledge in the art, in Australia or in any other country.



For the purposes of this specification it will be clearly understood that the word "comprising" means "including but not limited to", and that the words "comprise" and "comprises" have a corresponding meaning.



THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. An aqueous pharmaceutical composition including an active ingredient having a solubility in water of not higher than 0.01% (w/v) dispersed in liposomes, wherein said active ingredient is lonidamine or bindarit.
2. A composition according to claim 1, in which the liposomes include a component chosen from phosphoglycerides, glycerides, diglycerides, triglycerides, phospholipids, galactosyl and glucosyl lipids, cholesterol and its derivatives, sphingolipids or mixtures thereof.
3. A composition according to claim 1 or 2, in which the liposomes include a composition including phosphatidylcholine, lysophosphatidylcholine, N-acyl-phosphatidylcholine, phosphatidyl ethanolamine, phosphatidylserine, sphingomyelin, non-polar lipids, triglycerides, free fatty acids or DL- α -tocopherol.
4. A composition according to any one of claims 1 to 3, in which the quantity of liposomes of lipids is between 0.01 and 0.4 parts by weight for each part by weight of water.
5. A composition according to any of claims 1 to 4, in which the quantity of the active ingredient is between 0.01 and 0.3 parts by weight for each part by weight of lipids or liposomes.
6. A method for the preparation of an aqueous pharmaceutical composition with an active ingredient having a solubility in water of not higher than 0.01% (w/v) dispersed in liposomes, further including the following phases:
 - a) dispersion of the active ingredient in lipids at a temperature of between 20 and 30°C;
 - b) suspension of the dispersion in an aqueous phase;
 - c) resting of the suspension at ambient temperature for a period of between 0 and 48 hours;
 - d) heating the suspension to 30-75°C for 10-40 minutes;



- e) freezing the suspension at -150/-200°C;
- f) repeating of phases d) and e) at least twice and not more than 8 times;
- g) filtering the suspension through a filtering membrane
- 5 with pores of diameter 500-1000 nm;
- h) extruding through a membrane with pores of diameter 50-400 nm; and at the same time
- i) removing any active ingredient which is not trapped.

7. A method according to claim 6, in which the
10 aqueous phase includes an aqueous solution of sodium chloride at 0.05%-0.9% (w/v).

8. A method according to claim 6 or 7, in which the quantity of lipids used is between 0.01 and 0.4 parts by weight for each part by weight of water.

15 9. A method according to any one of claims 6 to 8, in which the quantity of the active ingredient used is between 0.01 and 0.3 parts by weight for each part by weight of lipids.

10 10. A method according to any one of claims 6 to 9, in which by the use of phase h) of the extrusion step involves the use of an extrusion gas, in which the gas includes air, nitrogen, helium or argon.

11. A method according to claim 10, in which the extrusion gas has a pressure of between 500 and 5500 kPa.

25 12. A method according to any one of claims 6 to 11, in which phase h) is carried out at a temperature of between 20 and 75°C.

13. A method according to claim 12, in which the temperature is between 40 and 65°C.

30 14. A method according to any one of claims 6 and 12, in which phase h) is repeated at least twice and not more than 8 times.

15. An aqueous pharmaceutical composition substantially as hereinbefore described with reference to
35 any one of the foregoing examples.

16. A method for the preparation of an aqueous pharmaceutical composition substantially as hereinbefore



described with reference to any one of the foregoing examples.

Dated this 10th day of September 2001

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