suspension is subsequently dehydrated. The dehydration process may be carried out by freeze-drying or spray-drying. The application discloses several protocols for the freeze drying of said liposomal suspensions. After dehydration, the liposomal preparation can be rehydrated by the addition of water or an aqueous solution. The document does not provide comparative data on the in-use stability of liposomal preparations that were dehydrated by freeze-drying or by spray-drying prior to their rehydration.

In view of the described state of the art, the problem underlying the present invention was the preparation of liposomes, comprising at least one lipohilic active agent and/or cosmetic agent with a high agent to lipid ratio and with improved stability, especially regarding physical stability and release of the agent from the liposome. Especially the invention relates to the problem of providing a process for manufacturing said liposomal preparations that have an extended hold time during manufacturing and in-use stability, wherein the process involves a fast dehydration step.

Thus, the solution of the above problem is achieved according to the present invention by providing embodiments characterized in the claims and further depicted in the description of the invention.

SUMMARY OF THE DISCLOSUREINVENTION

The solution of the above problem is provided by liposome preparations where tensile stress on the liposome membranes is applied by osmotic forces and a process for preparing said liposomes.

Specifically, the solution is provided by a process for the preparation of a liposomal suspension in an aqueous phase with at least one active agent and/or cosmetic agent present in the liposomal membrane, wherein said suspension comprises at least one osmotically active substance in the aqueous phase, and wherein the osmolarity of the aqueous phase inside the liposomally encapsulated volume, O_{in}, is higher than the aqueous phase outside the liposomally encapsulated volume, O_{out}.

The liposomes are characterised by the presence of tensile stress on the liposome membranes (stressed liposomes). They can be obtained directly during liposome formation or at any processing step after liposome formation.

Stressed liposomes can be obtained by directly affecting the osmolarity of the aqueous phase inside and/or outside the liposomes or by changing membrane characteristics, such as molecular packing, of the liposome membrane where the liposomes are present in a medium of a given osmolarity.

Stressed liposomes can be prepared directly with the active agent and/or cosmetic agent present in the liposome membrane. Alternatively, stressed liposomes can be prepared without the agent, which is subsequently added to the liposomes.

An aspect of the disclosure~~invention~~ relates to a process for the manufacture of a liposomal preparation comprising:
a) providing a first liposomal preparation comprising a suspension of liposomes in an aqueous phase, wherein the liposomes comprise at least one membrane, wherein the membrane encloses a liposomally encapsulated volume of the aqueous phase and the aqueous phase comprises at least one osmotically active substance and has an initial overall osmolarity, O_1, b) thereafter generating an osmolar gradient in the aqueous phase of said preparation wherein the osmolarity of the aqueous phase outside the liposomally encapsulated volume, O_{out}, is lower than the osmolarity of the aqueous phase inside the liposomally encapsulated volume, O_{in}, to yield a second (stressed) liposomal preparation,
c) optionally dehydrating the second (stressed) liposomal preparation to obtain a dehydrated preparation, and
d) optionally rehydrating the dehydrated preparation.

The liposomal preparation of step a) preferably comprises at least one active agent or cosmetic agent in the liposomal membrane. Alternatively, the agent may be added at a later stage of the manufacturing process.

Step b) can be performed by reducing the initial overall osmolarity, O_1, of the liposomal suspension derived from step a) to yield a stressed liposomal preparation with an overall osmolarity, O_2, which is lower than the osmolarity O_1.

Step b) may be performed by diluting the liposomal suspension derived from step a) with an aqueous medium having an osmolarity which is lower than O_1, or by dialysing the suspension against an aqueous medium with an osmolarity which is lower than O_1. In the most simple way, the liposomal suspension is diluted with water.

According to the general concept of the disclosure~~invention~~ an osmolar gradient may be generated or altered at different stages during the manufacture of the liposome preparation. Also the osmolar gradient may be altered once or multiple times at several stages of the production process. This can possibly be achieved by the same or different procedures as described in the following. The production process of the liposomal preparation relates to all steps performed before the final application of the liposomal suspension.

Step b) of the inventive process may comprise the steps of:

b1) dehydrating the liposomal preparation in step a) to obtain a dehydrated liposomal preparation, and

b2) rehydrating said dehydrated liposomal preparation under conditions to yield a stressed liposomal preparation, preferably in an aqueous medium.

In one aspect, there is provided a process for the manufacture of a liposomal preparation comprising:

a) providing a first liposomal preparation comprising a suspension of liposomes in an aqueous phase, wherein the liposomes comprise at least one membrane, wherein the membrane encloses a liposomally encapsulated volume of the aqueous phase and the aqueous phase comprises at least one osmotically active substance and has an initial overall osmolarity, O_1, wherein the first liposomal preparation comprises at least one active agent or cosmetic agent in the liposomal membrane,

b) thereafter generating an osmolar gradient in the aqueous phase of said preparation wherein the osmolarity of the aqueous phase outside the liposomally encapsulated volume, O_{out}, is lower than the osmolarity of the aqueous phase inside the liposomally encapsulated volume, O_{in}, to yield a second liposomal preparation, and wherein at least one active agent or cosmetic agent is incorporated into the liposomal membrane of the second liposomal preparation,

c) optionally dehydrating the second liposomal preparation to obtain a dehydrated preparation, and

d) optionally rehydrating the dehydrated preparation;

wherein said active agent or cosmetic agent has a log P greater than 1.

Preferably the dehydration is performed by spray drying of the liposomal suspension.

The disclosure~~invention~~ also relates to compositions obtained or obtainable by the above processes.

Also the disclosure~~invention~~ relates to a liposomal preparation comprising at least one active agent or a cosmetic agent in the liposomal membrane, wherein the liposomal membrane is under tensile stress.

More particularly, the disclosure~~invention~~ relates to a liposomal preparation comprising at least one active agent or cosmetic agent in the liposomal membrane wherein the liposomes are present in a liquid phase with an osmolarity inside the liposomally encapsulated volume (O_{in}) which is higher than the osmolarity of the liquid phase outside of the liposomally encapsulated volume (O_{out}).

Surprisingly, the inventors have found that liposomal suspensions containing liposomes, whose liposomal membrane is under tensile stress, have an improved solubility for lipophilic compounds.

Thus the disclosure~~invention~~ also relates to a process for manufacturing a liposomal preparation comprising at least one lipophilic drug or cosmetic compound, comprising the steps of:

i) providing a stressed liposomal preparation, comprising a suspension of liposomes in an aqueous phase,

ii) incubating said stressed liposomal preparation with at least one lipophilic active agent or cosmetic agent, optionally in an unsolubilised form, and

iii) optionally separating unsolubilised agent from the liposome preparation, preferably by filtration or centrifugation,

iv) optionally dehydrating the incubated liposomal preparation, and

v) optionally rehydrating the dehydrated liposomal preparation.

In one aspect, there is provided a process for the manufacture of a liposomal preparation comprising at least one lipophilic active agent or cosmetic agent, comprising:

i) providing a stressed liposomal preparation,

ii) incubating said stressed liposomal preparation with at least one lipophilic active agent or cosmetic agent, optionally in an unsolubilised form, thereby obtaining a stressed liposomal preparation with at least one lipophilic active agent or cosmetic agent incorporated into the liposomal membrane, and

iii) optionally separating unsolubilised compound from the liposomal preparation, preferably by filtration or centrifugation;

wherein said active agent or cosmetic agent has a log P greater than 1.

Stressed liposomes can be obtained by any of the above mentioned procedures. Most preferably, at least one osmotically active substance is present in the aqueous phase of the liposome suspension, wherein O_{in} is higher than O_{out}.

The above mentioned active agent or cosmetic agent preferably has a low solubility in water.

The above mentioned active agent or cosmetic agent is lipophilic and preferably has a log P of greater than 1. More preferably the compound is a taxane, most preferably paclitaxel or a derivative thereof.

In one aspect, there is provided a liposomal preparation comprising a suspension of liposomes in an aqueous phase, wherein the liposomes comprise at least one membrane, wherein at least one active agent or cosmetic agent is present in the liposomal membrane and at least one osmotically active substance is present in the aqueous phase, wherein the osmolarity of the aqueous phase inside the liposomes, O_{in}, is higher than the osmolarity of the aqueous phase outside of the liposomes, O_{out}; wherein said active agent or cosmetic agent has a log P greater than 1.

In one aspect, there is provided a liposomal preparation comprising a suspension of liposomes in an aqueous phase, wherein the liposomes comprise at least one membrane, wherein at least one active agent or cosmetic agent is present in the liposomal membranes and at least one osmotically active substance is present in the aqueous phase, wherein the aqueous phase inside the liposomally encapsulated volume has a higher density than the aqueous phase outside the liposomally encapsulated volume; wherein said active agent or cosmetic agent has a log P greater than 1.

In one aspect, there is provided a liposomal preparation comprising a suspension of liposomes in an aqueous phase, wherein the liposomes comprise at least one membrane, wherein at least one active agent or cosmetic agent is present in the liposomal membranes and at least one osmotically active substance is present in the aqueous phase, wherein the liposomal membrane is under tensile stress; wherein said active agent or cosmetic agent has a log P greater than 1.

In one aspect, there is provided a liposomal preparation comprising a suspension of liposomes comprising at least one active agent of cosmetic agent in an aqueous solution obtained by rehydration of a dehydrated liposomal preparation, characterised by an average diameter ($Z_{average}$) which differs by less than a factor of 1.5 and a polydispersity index (PI) which differs by less than a factor of two from the liposomal preparation subjected to dehydration to obtain said dehydrated liposomal preparation; wherein said active agent or cosmetic agent has a log P greater than 1.

In one aspect, there is provided a liposomal preparation comprising a suspension of liposomes comprising at least one active agent or cosmetic agent in an aqueous phase obtained by rehydration of a dehydrated liposomal preparation, characterised by changes of the average diameter ($Z_{average}$) by not more than a factor of 1.5, and changes of the polydispersity index (PI) by not more that a factor of 2, over 24 hours at 25°C; wherein said active agent or cosmetic agent has a log P greater than 1.

In one aspect, there is provided a liposomal suspension comprising liposomes comprising DOTAP, DOPC, and paclitaxel at a total lipid concentration of 10 mM, and trehalose, suspended in an aqueous phase comprising about 10 mg/ml wherein said liposomes are characterised by an anhydrous density of at least 1.1 g/ml.

In one aspect, there is provided the liposomal suspension as defined herein, wherein DOTAP, DOPC, and paclitaxel are comprised in a molar ration of 50:47:3 and/or wherein the liposomal suspension comprises citric acid, and/or wherein said liposomes have a $Z_{average}$ of about 140nm.

It has been surprisingly found that the loading efficacy of lipophilic, poorly water soluble compounds, such as paclitaxel, to liposome membranes can be improved, and the release of such compounds from the liposome membranes can be reduced, if the liposomal membrane is stressed, particularly, if a water-soluble osmotically active compound is comprised in the liposomally encapsulated aqueous phase at a higher concentration than outside of the liposomally encapsulated phase. The higher loading efficacy of the lipophilic compound to these liposomes compared to liposomes without a concentration gradient enables to manufacture formulations with higher molar ratio of compound/lipid, and to improve the stability of given formulations because the tendency to release the compound from the liposome is reduced.

Liposomes comprising a lipophilic agent in the membrane compartment are less prone to release of the compound to the aqueous medium if said osmolar gradient is present. The equilibrium fraction of said lipophilic substance in the aqueous medium is reduced. Accordingly the risk that the concentration of the lipophilic compound in the aqueous phase exceeds the solubility limit and precipitates is also reduced.

Moreover it has been surprisingly found that empty liposomes comprising the above described gradient have a higher loading capacity for lipophilic compounds, i.e. a higher molar amount of lipophilic compound is solubilised by the same amount of liposomes (as defined by molar amount of lipid) in comparison to liposomes without such gradient. This can be realized, for example, by exposure of the lipophilic compound to empty liposomes.

It has also been surprisingly found, that liposomal preparations obtained by rehydration of previously dehydrated liposomes have a homogeneous size distribution, as indicated by a low polydispersity index (PI). With regard to quality control, it is always desirable to obtain a homogeneous product, especially for pharmaceutical uses. Furthermore the liposome suspensions of the present disclosure~~invention~~ exhibit a polydispersity index which remains substantially unchanged over a prolonged period of time. This indicates that the liposomes in the inventive suspensions do not form aggregates. Especially for intravenously administered liposomal suspensions, aggregates have to be avoided, because these aggregates may obstruct blood vessels and thus lead to embolies.

The present disclosure~~invention~~ substantially improves the state of the art by providing a process for stabilizing lipophilic agents in the liposomal membranes of a liposomal preparation, as well as maintaining size and polydispersity of a rehydrated liposomal preparation. As a consequence, the in-use stability of a final preparation comprising liposomes with a lipophilic compound can be prolonged. Also the stability of said liposomes during the processing of such formulations can be prolonged.

In many cases the time period for processing the liquid formulations during manufacturing (hold time) of liposome formulations is limited due to the risk of undesired release of the agent from the liposomes. The disclosure~~invention~~ reduces the risk of drug release, and therefore it enables continuous processing of liposomes during manufacturing for extended time scales and enables a more flexible design of the production process.

More specifically the disclosure~~invention~~ enables the preparation of the above mentioned formulations by spray-drying instead of freeze-drying. In freeze drying the liposomes are frozen and thus stabilized directly after manufacturing, therefore the risk of release during manufacturing is low. In spray drying the liquid formulations encounter extended hold times in the liquid phase, because spraying of a given batch may take several hours or days. Because the disclosure~~invention~~ enables to increase the stability of a given formulation, longer spraying sessions without interruption can be realised. Since

spray-drying has a higher overall throughput compared to freeze-drying, large scale production is facilitated and production costs can be reduced, while product quality is maintained.

Further the risk of drug release and crystallization in the period between reconstitution of the dehydrated liposomal composition and administration to a patient (in-use stability) is reduced. Crystallization may promote formation of subvisible particles which must not be present beyond certain limits in products for iv administration. In many cases, only an in-use stability of few hours is provided, which is an obstacle in clinical practice. Therefore, sufficient in-use stability is of great importance for practical application of such pharmaceutical or cosmetic products.

The preparation of liposomes frequently employs organic solvents, such as ethanol, which is usually found in dehydrated liposomal products, and accordingly in the rehydrated liposomal suspensions derived from it. This is especially the case for liposomal preparations which were dehydrated by freeze-drying (lyophilisation). However it is desirable for liposomal products used for application to humans to comprise as little organic solvent as possible. The present disclosure~~invention~~ enables dehydration by spray-drying, which facilitates the removal of most or all residual organic solvent, while obtaining liposomes with a high stability.

While providing the above mentioned advantages, the disclosure~~invention~~ can be practiced easily and is not cost intensive. It does neither require complicated technical devices, nor the addition of further ingredients to the above mentioned compositions. The osmotically active substances, which are used to practice the disclosure~~invention~~, are already known from liposomal compositions which are dehydrated as disclosed in US 4,880,635 or WO 2004/002468.

DEFINITIONS

"About" in the context of amount values refers to an average deviation of maximum +/- 20 %, preferably +/- 10 % based on the indicated value. For example, an amount of about 30 mol% cationic lipid refers to 30 mol% +/- 6 mol% and preferably 30 mol% +/- 3 mol% cationic lipid with respect to the total lipid/amphiphile molarity.

"Active compound" or "active agent" refers to a compound or mixture of compounds, having a particular biological or physical activity based on which it is useful as an agent for the diagnosis, prevention, or treatment of a human or animal disease or condition. Therapeutic agents such as drug substances and diagnostic agents are important examples of active agents according to the

CLAIMS

1. A process for the manufacture of a liposomal preparation comprising:

a) providing a first liposomal preparation comprising a suspension of liposomes in an aqueous phase, wherein the liposomes comprise at least one membrane, wherein the membrane encloses a liposomally encapsulated volume of the aqueous phase and the aqueous phase comprises at least one osmotically active substance and has an initial overall osmolarity, O_1, wherein the first liposomal preparation comprises at least one active agent or cosmetic agent in the liposomal membrane,

b) thereafter generating an osmolar gradient in the aqueous phase of said preparation wherein the osmolarity of the aqueous phase outside the liposomally encapsulated volume, O_{out}, is lower than the osmolarity of the aqueous phase inside the liposomally encapsulated volume, O_{in}, to yield a second liposomal preparation, and wherein at least one active agent or cosmetic agent is incorporated into the liposomal membrane of the second liposomal preparation,c) optionally dehydrating the second liposomal preparation to obtain a dehydrated preparation, and d) optionally rehydrating the dehydrated preparation,

wherein the active agent or cosmetic agent has a log P of greater than about 1.

2. The process according to claim 1, wherein step b) is performed by reducing the initial overall osmolarity, O_1, of the aqueous phase of the liposomal preparation in step a) to yield a stressed liposomal preparation with an overall osmolarity, O_2, which is lower than the osmolarity O_1.

3. The process according to claim 1 or 2, wherein step b) is performed by diluting the liposomal preparation in step a) with an aqueous medium having an osmolarity which is lower than O_1.

4. The process according to claim 1 or 2, wherein step b) is performed by dialysing the preparation in step a) against an aqueous medium with an osmolarity which is lower than O_1.

5. The process according to claim 1 or 2, wherein step b) is performed by:

b1) dehydrating the liposomal preparation in step a) to obtain a dehydrated liposomalpreparation, and

b2) rehydrating said dehydrated liposomal preparation under conditions to yield a stressed liposomal preparation, preferably in an aqueous medium.

6. The process according to claim 5, wherein the volume of aqueous medium used for rehydration is larger than the volume of liposomal preparation which has been dehydrated to obtain the respective amount of dehydrated liposomal composition.

7. The process according to any one of claims 2 to 6, wherein O_2 is at least 10 mOsm lower than O_1, more preferably O_2 is at least 50 mOsm lower than O_1, and even more preferably O_2 is at least 100 mOsm lower than O_1.

8. The process according to any one of claims 1 to 7, wherein the osmotic gradient between the aqueous phase outside the liposomally encapsulated volume and the aqueous phase inside the liposomally encapsulated volume is altered once or several times at different stages during the production process of the liposomal preparation.

9. The process according to any one of the foregoing claims, wherein dehydration is performed at a temperature above room temperature.

10. The process according to any one of claims 1-9, wherein dehydration is performed by spray drying.

11. A process for the manufacture of a liposomal preparation comprising at least one lipophilic active agent or cosmetic agent, comprising:
i) providing a stressed liposomal preparation, wherein an osmolar gradient is generated, wherein the osmolarity of an aqueous phase outside a liposomally encapsulated volume O_{out} is lower than that of an aqueous phase inside the liposomally encapsulated volume O_{in}, ii) incubating said stressed liposomal preparation with at least one lipophilic active agent or cosmetic agent, optionally in an unsolubilised form, thereby obtaining a stressed liposomal preparation with at least one lipophilic active agent or cosmetic agent incorporated into the liposomal membrane, wherein the active agent or cosmetic agent has a log P of greater than about 1, and
iii) optionally separating unsolubilised compound from the liposomal preparation, preferably by filtration or centrifugation.

12. The process according to claim 11, wherein step i) is performed by providing a liposomal preparation, wherein at least one osmotically active substance is comprised in the aqueous phase of the preparation to generate said osmolar gradient, wherein the aqueous phase has a higher osmolarity inside the liposomally encapsulated volume (O_{in}) than outside the liposomally encapsulated volume (O_{out}).

13. The process according to any one of the foregoing claims wherein the at least one

osmotically active substance is present inside and outside of the liposomes.

14. The process according to any one of the foregoing claims wherein the osmotically active substance is selected from the group consisting of organic and inorganic molecules such as saccharides, sugar alcohols, amino acids, peptides, proteins, water-soluble polymers, organic- or inorganic salts, ions and combinations thereof.

15. The process according to claim 14, wherein the saccharide is selected from mono-, di-, oligo- or poly–saccharides, preferably trehalose.

16. The process according to any one of the foregoing claims, wherein the active agent is a therapeutically or diagnostically active compound.

17. The process according to any one of the foregoing claims, wherein the active agent or cosmetic agent is a lipophilic compound.

18. The process according to any one of the foregoing claims, wherein the active agent or cosmetic agent has a log P of preferably greater than about 2, most preferably greater than about 3.

19. The process according to any one of the foregoing claims, wherein the active agent or cosmetic agent has solubility of lower than 0.1 mg/ml, more preferably lower than 0.01mg/ml and most preferably lower than 0.001 mg/ml in water at 25°C.

20. The process according to any one of the foregoing claims, wherein the active agent is a taxane, preferably paclitaxel, or a derivative thereof.

21. The process according to any one of the foregoing claims, wherein the active agent or cosmetic agent is substantially exclusively present in the membrane compartment of the liposomes.

22. A liposomal preparation obtained or obtainable by the process of any one of the forgoing claims.

23. The liposomal preparation according to claim 22, which is in dehydrated form or in form of an aqueous suspension.

24. The dehydrated liposomal preparation according claim 23, which is a pourable powder.

25. A liposomal preparation comprising a suspension of liposomes in an aqueous phase, wherein the liposomes comprise at least one membrane, wherein at least one active agent or cosmetic agent is present in the liposomal membrane and at least one osmotically active substance is present in the aqueous phase, wherein the osmolarity of the aqueous phase inside the liposomes, O_{in}, is higher than the osmolarity of the aqueous phase outside of the liposomes, $O_{out,}$ wherein the active agent or cosmetic agent has a log P of greater than about 1.

26. The liposomal preparation according to claim 25, wherein the difference between O_{in} and O_{out} is at least 10 mOsm, preferably at least 50 mOsm and up to 2000 mOsm.

27. A liposomal preparation comprising a suspension of liposomes in an aqueous phase, wherein the liposomes comprise at least one membrane, wherein at least one active agent or cosmetic agent is present in the liposomal membranes, wherein the active agent or cosmetic agent has a log P of greater than about 1, and at least one osmotically active substance is present in the aqueous phase, wherein the aqueous phase inside the liposomally encapsulated volume has a higher density than the aqueous phase outside the liposomally encapsulated volume, wherein the osmolarity of the aqueous phase inside the liposomes, O_{in}, is higher than the osmolarity of the aqueous phase outside of the liposomes, $O_{out,}$.

28. A liposomal preparation comprising a suspension of liposomes in an aqueous phase, wherein the liposomes comprise at least one membrane, wherein at least one active agent or cosmetic agent is present in the liposomal membranes and at least one osmotically active substance is present in the aqueous phase, wherein the liposomal membrane is under tensile stress, wherein the osmolarity of the aqueous phase inside the liposomes, O_{in}, is higher than the osmolarity of the aqueous phase outside of the liposomes, O_{out}.

29. The liposomal preparation according to any one of the claims 22 to 28, wherein the osmotically active substance is defined as in any of the claims 14 to 15.

30. The liposomal preparation according to any one of the claims 25 to 29, wherein the active agent or cosmetic agent is defined as in any of the claims 16 to 20.

31. The liposomal preparation according to any one of the claims 22 to 30 for use as a pharmaceutical, preferably for the treatment of cancer.

32. The liposomal preparation according to any one of the claims 22 to 30 for use as a cosmetic preparation.

33. The liposomal preparation according to any of the claims 22 to 30 for use as a diagnostic preparation.

34. A liposomal preparation comprising a suspension of liposomes in an aqueous solution obtained by rehydration of a dehydrated liposomal preparation, characterised by an average diameter ($Z_{average}$) which differs by less than a factor of 1.5 and a polydispersity index (PI) which differs by less than a factor of two from the liposomal preparation subjected to dehydration to obtain said dehydrated liposomal preparation, wherein the osmolarity of the aqueous phase inside the liposomes, O_{in}, is higher than the osmolarity of the aqueous phase outside of the liposomes, O_{out}.

35. The liposomal preparation according to claim 34, wherein the PI of 1 hour after reconstitution is preferably less than 0.4, more preferably less than 0.3, most preferably less than 0.25.

36. A liposomal preparation comprising a suspension of liposomes in an aqueous phase obtained by rehydration of a dehydrated liposomal preparation, characterised by changes of the average diameter ($Z_{average}$) by not more than a factor of about 1.5, preferably not more than 1.25, and changes of the polydispersity index (PI) by not more that a factor of about 2, preferably not more than about 1.5, most preferably not more than about 1.25 over 24 hours at 25°C, wherein the osmolarity of the aqueous phase inside the liposomes, O_{in}, is higher than the osmolarity of the aqueous phase outside of the liposomes, O_{out}.

37. The liposomal preparation according to any of the claims 34 to 36, wherein the liposomes comprise up to about 5 mole%, preferably up to about 3 mole% paclitaxel in the liposomal membranes.

38. The liposomal suspension according to any of the claims 34 to 37, wherein the liposomes comprise DOTAP, DOPC and paclitaxel, preferably in a molar ratio of about 50:47:3.

39. A liposomal suspension comprising liposomes comprising DOTAP, DOPC, and paclitaxel at a total lipid concentration of about 10 mM, and trehalose, suspended in an aqueous phase comprising about 10 mg/ml, especially 9.79 mg/ml trehalose, wherein said liposomes are characterised by an anhydrous density of at least about 1.1 g/ml, wherein the osmolarity of the aqueous phase inside the liposomes, O_{in}, is higher than the osmolarity of the aqueous phase outside of the liposomes, O_{out}.

40. The liposomal suspension of claim 39, wherein DOTAP, DOPC, and paclitaxel are comprised in a molar ration of 50:47:3.

41. The liposomal suspensions of claims 39 to 40, wherein the liposomal suspension

comprised citric acid.

42. The liposomal suspensions of claims 39 to 41, wherein said liposomes have a $z_{average}$ of about 140 nm.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A process for the manufacture of a liposomal preparation comprising:
   a) providing a first liposomal preparation comprising a suspension of liposomes in an aqueous phase, wherein the liposomes comprise at least one membrane, wherein the membrane encloses a liposomally encapsulated volume of the aqueous phase and the aqueous phase comprises at least one osmotically active substance and has an initial overall osmolarity, O_1, wherein the first liposomal preparation comprises at least one active agent or cosmetic agent in the liposomal membrane,
   b) thereafter generating an osmolar gradient in the aqueous phase of said preparation wherein the osmolarity of the aqueous phase outside the liposomally encapsulated volume, O_{out}, is lower than the osmolarity of the aqueous phase inside the liposomally encapsulated volume, O_{in}, to yield a second liposomal preparation, and wherein at least one active agent or cosmetic agent is incorporated into the liposomal membrane of the second liposomal preparation,
   c) optionally dehydrating the second liposomal preparation to obtain a dehydrated preparation, and
   d) optionally rehydrating the dehydrated preparation;
   wherein said active agent or cosmetic agent has a log P greater than 1.

2. The process according to claim 1, wherein step b) is performed by reducing the initial overall osmolarity, O_1, of the aqueous phase of the liposomal preparation in step a) to yield a stressed liposomal preparation with an overall osmolarity, O_2, which is lower than the osmolarity O_1.

3. The process according to claim 1 or 2, wherein step b) is performed by diluting the liposomal preparation in step a) with an aqueous medium having an osmolarity which is lower than O_1.

4. The process according to claim 1 or 2, wherein step b) is performed by dialysing the preparation in step a) against an aqueous medium with an osmolarity which is lower than O_1.

5. The process according to claim 1 or 2, wherein step b) is performed by:
   b1) dehydrating the liposomal preparation in step a) to obtain a dehydrated liposomal

preparation, and

b2) rehydrating said dehydrated liposomal preparation under conditions to yield a stressed liposomal preparation.

6. The process according to claim 5, wherein the volume of aqueous medium used for rehydration is larger than the volume of liposomal preparation which has been dehydrated to obtain the respective amount of dehydrated liposomal composition.

7. The process according to any one of claims 2 to 6, wherein O_2 is at least 10 mOsm lower than O_1.

8. The process according to any one of claims 1 to 7, wherein the osmotic gradient between the aqueous phase outside the liposomally encapsulated volume and the aqueous phase inside the liposomally encapsulated volume is altered once or several times at different stages during the production process of the liposomal preparation.

9. The process according to any one of the foregoing claims, wherein dehydration is performed at a temperature above room temperature.

10. The process according to any one of claims 1-9, wherein dehydration is performed by spray drying.

11. A process for the manufacture of a liposomal preparation comprising at least one lipophilic active agent or cosmetic agent, comprising:

i) providing a stressed liposomal preparation,

ii) incubating said stressed liposomal preparation with at least one lipophilic active agent or cosmetic agent, optionally in an unsolubilised form, thereby obtaining a stressed liposomal preparation with at least one lipophilic active agent or cosmetic agent incorporated into the liposomal membrane, and

iii) optionally separating unsolubilised compound from the liposomal preparation, preferably by filtration or centrifugation;

wherein said active agent or cosmetic agent has a log P greater than 1.

12. The process according to claim 11, wherein step i) is performed by providing a liposomal preparation, wherein at least one osmotically active substance is comprised

in the aqueous phase of the preparation and wherein the aqueous phase has a higher osmolarity inside the liposomally encapsulated volume than outside the liposomally encapsulated volume.

13. The process according to any one of the foregoing claims wherein the at least one osmotically active substance is present inside and outside of the liposomes and/orwherein the osmotically active substance is selected from the group consisting of saccharides, sugar alcohols, amino acids, peptides, proteins, water-soluble polymers, organic- or inorganic salts, ions and combinations thereof.

14. The process according to any one of the foregoing claims, wherein the active agent is a therapeutically or diagnostically active compound or cosmetic agent.

15. The process according to any one of the foregoing claims, wherein the active agent or cosmetic agent has a log P of greater than 2.

16. The process according to any one of the foregoing claims, wherein the active agent or cosmetic agent has solubility of lower than 0.1 mg/ml in water at 25°C.

17. The process according to any one of the foregoing claims, wherein the active agent is a taxane or a derivative thereof.

18. The process according to any one of the foregoing claims, wherein the active agent or cosmetic agent is substantially exclusively present in the membrane compartment of the liposomes.

19. A liposomal preparation obtained by the process of any one of the forgoing claims.

20. The liposomal preparation according to claim 19, which is in dehydrated form or in form of an aqueous suspension.

21. The dehydrated liposomal preparation according claim 20, which is a pourable powder.

22. A liposomal preparation comprising a suspension of liposomes in an aqueous phase,

wherein the liposomes comprise at least one membrane, wherein at least one active agent or cosmetic agent is present in the liposomal membrane and at least one osmotically active substance is present in the aqueous phase, wherein the osmolarity of the aqueous phase inside the liposomes, O_{in}, is higher than the osmolarity of the aqueous phase outside of the liposomes, O_{out}; wherein said active agent or cosmetic agent has a log P greater than 1.

23. The liposomal preparation according to claim 25, wherein the difference between O_{in} and O_{out} is at least 10 mOsm.

24. A liposomal preparation comprising a suspension of liposomes in an aqueous phase, wherein the liposomes comprise at least one membrane, wherein at least one active agent or cosmetic agent is present in the liposomal membranes and at least one osmotically active substance is present in the aqueous phase, wherein the aqueous phase inside the liposomally encapsulated volume has a higher density than the aqueous phase outside the liposomally encapsulated volume; wherein said active agent or cosmetic agent has a log P greater than 1.

25. A liposomal preparation comprising a suspension of liposomes in an aqueous phase, wherein the liposomes comprise at least one membrane, wherein at least one active agent or cosmetic agent is present in the liposomal membranes and at least one osmotically active substance is present in the aqueous phase, wherein the liposomal membrane is under tensile stress; wherein said active agent or cosmetic agent has a log P greater than 1.

26. The liposomal preparation according to any one of claims 19 to 25, wherein the osmotically active substance is defined as in claim 13.

27. The liposomal preparation according to any one of claims 22 to 26, wherein the active agent or cosmetic agent is defined as in any one of claims 14 to 17.

28. The liposomal preparation according to any one of claims 19 to 27 for use as a pharmaceutical, for use as a cosmetic preparation, or for use as a diagnostic preparation.

29. A liposomal preparation comprising a suspension of liposomes comprising at least one active agent of cosmetic agent in an aqueous solution obtained by rehydration of a dehydrated liposomal preparation, characterised by an average diameter ($Z_{average}$) which differs by less than a factor of 1.5 and a polydispersity index (PI) which differs by less than a factor of two from the liposomal preparation subjected to dehydration to obtain said dehydrated liposomal preparation; wherein said active agent or cosmetic agent has a log P greater than 1.

30. The liposomal preparation according to claim 29, wherein the PI of 1 hour after reconstitution is less than 0.4.

31. A liposomal preparation comprising a suspension of liposomes comprising at least one active agent or cosmetic agent in an aqueous phase obtained by rehydration of a dehydrated liposomal preparation, characterised by changes of the average diameter ($Z_{average}$) by not more than a factor of 1.5, and changes of the polydispersity index (PI) by not more that a factor of 2, over 24 hours at 25°C; wherein said active agent or cosmetic agent has a log P greater than 1.

32. The liposomal preparation according to any one of the claims 29 to 31, wherein the liposomes comprise up to about 5 mole%, and/or wherein the liposomes comprise DOTAP, DOPC and paclitaxel.

33. A liposomal suspension comprising liposomes comprising DOTAP, DOPC, and paclitaxel at a total lipid concentration of 10 mM, and trehalose, suspended in an aqueous phase comprising about 10 mg/ml wherein said liposomes are characterised by an anhydrous density of at least 1.1 g/ml.

34. The liposomal suspension of claim 33, wherein DOTAP, DOPC, and paclitaxel are comprised in a molar ration of 50:47:3 and/or wherein the liposomal suspension comprises citric acid, and/or wherein said liposomes have a $Z_{average}$ of about 140 nm.