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, ~~and~~ wherein the aqueous phase has a higher osmolarity ~~is present~~ 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 ~~greater than about 1,~~ 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.