CLAIMS

1. A method of determining the trapped volume (Vt) and the trapped aqueous volume (Vtaq) of a plurality of liposomes in a liposomal composition, the method comprising the steps of:
   (i) obtaining a liposomal composition comprising a plurality of liposomes at a predetermined concentration of lipids which are suspended or dispersed in a fluid medium;
   (ii) adding a marker to said liposomal composition, wherein the marker is liposome impermeable and has a molecular weight equal to or higher than 1 kDa;
   (iii) measuring a signal induced by the marker in said liposomal composition thereby determining the total volume of the liposomal composition;
   (iv) separating the fluid medium from the plurality of liposomes thereby obtaining a fluid medium and a precipitate comprising a plurality of liposomes and an interstitial medium between the liposomes;
   (v) measuring a signal induced by the marker in the separated fluid medium of step (iv) thereby determining the volume of the fluid medium and the interstitial medium;
   (vi) optionally measuring a signal induced by the marker in the precipitate comprising a plurality of liposomes and an interstitial medium between the liposomes of step (iv) thereby determining the interstitial volume between the liposomes in the precipitate; and
   (vii) calculating the trapped volume (Vt) and the trapped aqueous volume (Vtaq) of the plurality of liposomes based on the volumes determined in steps (iii) and (v) or in steps (iii), (v), and (vi) and the predetermined concentration of step (i).

2. The method of claim 1, wherein determining the trapped volume (Vt) of a plurality of liposomes in a liposomal composition comprises determining the specific trapped volume; or wherein determining the trapped aqueous volume of a plurality of liposomes in a liposomal composition comprises determining the specific trapped aqueous volume.

3. The method of claim 1, wherein step (vi) is performed and step (vii) comprises calculating the trapped volume (Vt) and the trapped aqueous volume (Vtaq) of the plurality of liposomes based on the volumes determined in steps (iii), (v), (vi), and the predetermined concentration of step (i).

4. The method of claim 1, wherein step (vi) is not performed and step (vii) comprises calculating the trapped volume (Vt) and the trapped aqueous volume (Vtaq) of the plurality of liposomes based on the volumes determined in steps (iii), (v), and the predetermined concentration of step (i), preferably wherein step (vii) comprises calculating the ratio between the signal induced by the marker in the fluid medium following step (iv) and the signal induced by the marker in the liposomal composition prior to step (iv).

5. The method of any one of claims 1 to 4, wherein the marker is water soluble; and/or wherein the marker has a molecular weight of at least about 2 kDa; and/or wherein the marker is a radioactive marker, preferably wherein the marker is ^{14}C-carboxy inulin.

6. The method of any one of claims 1 to 5, wherein the liposomal composition comprises a plurality of liposomes selected from the group consisting of unilamellar vesicles (SUV), large unilamellar vesicles (LUV), giant unilamellar vesicles (GUV), oligolamellar vesicles (OLV), multilamellar vesicles (MLV), multivesicular liposomes (MVL), and a mixture or combination thereof; and/or wherein the liposomal composition comprises a plurality of liposomes in sizes ranging from about 0.3 μm to about 50 μm; and/or wherein the liposomal composition comprises a plurality of liposomes at a lipid concentration of about 50 mM to about 300 mM; and/or wherein the liposomal composition comprises a plurality of empty liposomes essentially free of an active pharmaceutical agent; or wherein the liposomal composition comprises a plurality of liposomes encapsulating an active pharmaceutical ingredient, preferably wherein the method further comprises determining the concentration of the active pharmaceutical ingredient encapsulated by the plurality of liposomes.

7. The method of any one of claims 1 to 6, wherein step (iv) provides a fluid medium which is substantially devoid of liposomes; and/or wherein step (iv) is performed by centrifugation, filtration, or decantation.

8. The method of claim 7, wherein step (iv) is performed by centrifugation, preferably wherein step (iv) is performed at a relative centrifugal force of about 10,000 to about 30,000 (×g); and/or wherein step (iv) is performed at a temperature of about 2°C to about 25°C; and/or wherein step (iv) is performed for a time period in the range of about 10 minutes to about 100 minutes.

9. A method for controlling the quality of a liposomal composition, the method comprising:

(i) determining the trapped volume (Vt) and the trapped aqueous volume (Vtaq) of a plurality of liposomes in a liposomal composition according to any one of claims 1 to 8;

(ii) comparing the determined trapped volume (Vt) and trapped aqueous volume (Vtaq) with reference trapped volume (Vt) and trapped aqueous volume (Vtaq) values; and

(iii) rejecting said liposomal composition if the determined trapped volume (Vt) and trapped aqueous volume (Vtaq) differ from the reference values by more than plus or minus 10%.

10. A method for controlling the quality of a liposomal composition comprising an active pharmaceutical ingredient encapsulated within a plurality of liposomes, the method comprising:

(i) determining the concentration of the active pharmaceutical ingredient encapsulated within a plurality of liposomes in a liposomal composition by determining the trapped volume (Vt) and the trapped aqueous volume (Vtaq) of a plurality of liposomes in a liposomal composition according to any one of claims 1 to 8;

(ii) comparing the determined active pharmaceutical ingredient concentration with a reference active pharmaceutical ingredient concentration; and

(iii) rejecting said liposomal composition if the determined active pharmaceutical ingredient concentration differs from the reference active pharmaceutical ingredient concentration by more than plus or minus 10%.

11. A liposomal composition formulated for intra-articular administration comprising a fluid medium; a polyol tonicity agent; and a plurality of liposomes consisting essentially of 1,2-Dimyristoyl-sn-Glycero-3-Phosphocholine (DMPC), and 1,2-Dipalmitoyl-sn-Glycero-3-Phosphocholine (DPPC) at a ratio of about 45:55, wherein the composition is essentially free of an active pharmaceutical agent, and wherein the plurality of liposomes are characterized by a specific trapped aqueous volume in the range of about 1 to about 4 μl/mg lipid as determined by a method comprising the steps of:

(i) adding a marker to said liposomal composition, wherein the marker is liposome impermeable and has a molecular weight equal to or higher than 1 kDa;

(ii) measuring a signal induced by the marker in said liposomal composition thereby determining the total volume of the liposomal composition;

(iii) determining the volume of the fluid medium and the interstitial medium between liposomes obtained by separating the fluid medium from the plurality of liposomes and measuring a signal induced by the marker in the fluid medium following separation; and

(iv) calculating the trapped volume (Vt) and trapped aqueous volume (Vtaq) of the plurality of liposomes based on the volumes determined in steps (ii) and (iii) and the concentration of the lipids forming the liposomes.

12. The liposomal composition of claim 11, wherein step (iii) further comprises determining the interstitial volume between liposomes in a precipitate by measuring a signal induced by the marker in the precipitate following separation; and/or wherein the marker has a molecular weight of at least about 2 kDa; and/or wherein the marker is water soluble; and/or wherein the marker is a radioactive marker, preferably wherein the marker

is ^{14}C-carboxy inulin; and/or wherein separating the fluid medium from the plurality of liposomes is performed by centrifugation.

13. The liposomal composition of any one of claims 11 to 12, wherein the plurality of liposomes are selected from the group consisting of unilamellar vesicles (SUV), large unilamellar vesicles (LUV), giant unilamellar vesicles (GUV), oligolamellar vesicles (OLV), multilamellar vesicles (MLV), multivesicular liposomes (MVL), and a mixture or combination thereof, preferably wherein the plurality of liposomes are multilamellar vesicles (MLV); and/or wherein the plurality of liposomes have sizes ranging from about 0.3 μm to about 50 μm; and/or wherein the concentration of the lipids forming the liposomes is in the range of about 50 mM to about 300 mM; and/or wherein the composition has a pH of about 5 to about 8.

14. The liposomal composition of any one of claims 11 to 13, wherein the fluid medium is a histidine buffer; and/or wherein the polyol is a linear polyol; and/or wherein the polyol is selected from the group consisting of mannitol, dextrose, lactose, trehalose and combinations thereof, preferably wherein the polyol is mannitol; and/or wherein DMPC is present in the composition in a weight percent ranging from about 1% (w/w) to about 10% (w/w), and DPPC is present in the composition in a weight percent ranging from about 2% (w/w) to about 12% (w/w).

15. The liposomal composition of any one of claims 11 to 14, wherein the specific trapped aqueous volume is in the range of about 1.5 to about 3.5 μl/mg lipid, preferably wherein the specific trapped aqueous volume is in the range of about 2 to about 3 μl/mg lipid; and/or wherein the trapped aqueous volume is in the range of about 10% to about 35%, preferably wherein the trapped aqueous volume is in the range of about 20% to about 30%.