CLAIMS

1. Method for changing the phase of a composition, in particular pharmaceutical compositions, comprising:

storing a quantity of the composition in a vial;

changing the phase of the composition in the vial by applying thermal gas to the vial; and

wherein changing the phase of the composition comprises freezing or thawing the composition, and wherein the thermal gas is respectively a cooling gas or a heating gas;

wherein changing the phase of the composition is characterized by performing at least one of (A), (B) (C), wherein (A) is an initial temperature change control scheme performed before entering a phase wherein the crystallization amount of the composition changes; (B) is a crystallization change control scheme during a phase wherein the crystallization amount of the composition changes; (C) is a final temperature change control scheme performed until the composition reaches its final temperature;

obtaining the composition after the change in phase is complete;

wherein the initial temperature change control scheme (A) comprises:

(I) performing an initial measurement on the vial and/or the composition to determine whether the phase wherein the crystallization amount of the composition changes has started;

(II) controlling the temperature and/or flow rate of the thermal gas such that the temperature of the vial and/or the composition is in accordance with a pre-determined initial temperature evolution over time; and

repeating steps (I) and (II) until the initial measurement determines that the phase wherein the crystallization amount of the composition changes has started;

wherein the crystallization change control scheme (B) comprises:

(I) performing a crystallization-change measurement on the vial and/or the composition to determine whether there is no longer a change in the crystallization amount in the composition;

(II) controlling the temperature and/or flowrate of the thermal gas such that the

temperature of the vial and/or the composition is in accordance with a pre-determined crystallization-change temperature evolution over time;

repeating steps (I) and (II) until there is no longer a change in the crystallization amount in the composition; and

wherein the final temperature change control scheme (C) comprises:

(I) controlling the temperature and/or flow rate of the thermal gas such that the

temperature of the vial and/or the composition is in accordance with a pre-determined final temperature evolution over time;

(II) performing a final temperature measurement on the vial and/or the composition to determine whether the vial and/or the composition has reached its pre- determined final temperature; and

repeating steps (I) and (II) until the final temperature measurement determines that the vial and/or the composition has reached its pre-determined final temperature.

2. The method for changing the phase of a composition according to claim 1, wherein in at least one of (A), (B) and (C) before repeating steps (I) and (II), the control scheme can wait a pre-determined amount of time.

3. The method for freezing injectable compositions according to claim 1 or 2, wherein the initial measurement, the crystallization-change measurement, and/or the final temperature measurement are performed using a thermal sensor for capturing thermal information and/or a sensor for capturing spectroscopy information,

preferably wherein the spectroscopy information of the vial is converted into structure information of the composition using an image processing module,

preferably wherein the thermal information and/or the structure information is used together with a mathematical model to determine in real-time properties of the composition.

4. Method according to any one of the preceding claims, wherein changing the phase of

the composition is freezing the composition;

wherein the composition is injectable and stored in the vial as a quantity of a dispersion of the injectable composition in an aqueous dispersion medium;

wherein the initial temperature change control scheme is an initial cooling control scheme (X) before nucleation has occurred in the dispersion layer, wherein the crystallization change control scheme is a crystallization control scheme (Y) during crystallization of the dispersion layer, and wherein the final temperature change control scheme is a final cooling control scheme (Z) after the dispersion layer has crystallized;

wherein in the initial cooling control scheme (X) the initial measurement is a nucleation measurement to determine whether nucleation has occurred in the dispersion, wherein the initial temperature evolution over time is an initial cooling temperature evolution over time, and wherein steps (I) and (II) are repeated until the nucleation measurement determines that nucleation has occurred in the dispersion;

wherein in the crystallization control scheme (Y) the crystallization-change measurement determines whether crystallization has finished in the dispersion, wherein the crystallization-change temperature evolution over time is a crystallization temperature evolution over time, and wherein steps (I) and (II) are repeated until the crystallization measurement determines that crystallization has finished in the dispersion; and

wherein in the final cooling control scheme (Z) the final temperature evolution over time is a final cooling temperature evolution over time.

5. The method for freezing injectable compositions according to claim 4, wherein (X) and (Y), (Y) and (Z), (X) and (Z), or (X), (Y) and (Z) are performed.

6. The method for freezing injectable compositions according to claim 4 or 5, wherein the initial cooling control scheme (X) further comprises inducing condensation nuclei in the distribution, and/or inducing artificial density gradients in the composition by acoustic waves or pressure waves, and/or inducing thermal shocks in the distribution, preferably wherein the acoustic waves or pressure waves are produced by inducing rotation variations, and preferably wherein the thermal shocks are induced by variations in the temperature or flow rate of the cooling gas.

7. The method for freezing injectable compositions according to claims 4-6, wherein the method further comprises:

rotating the vial at least for a period of time to form a dispersion layer at an inner surface of a circumferential wall of the vial;

cooling the vial by applying cooling gas to the rotating vial.

8. The method for freezing injectable compositions according to claims 4-7,

wherein the method is a method for freeze-drying injectable compositions, by additionally performing a drying step while applying a vacuum and supplying heat.

9. Method according to claims 1-3, wherein changing the phase of the composition is thawing the composition;

wherein the composition is frozen, preferably wherein the frozen composition is a dispersion of an injectable composition in an aqueous dispersion medium, more preferably wherein the frozen composition is a frozen dispersion layer at an inner surface of a circumferential wall of the vial, more preferably wherein the frozen composition is obtained by a method according to any one of claims 4-8;

wherein the initial temperature change control scheme is an initial heating control scheme (V) during a heating phase before a eutectic point is reached in the composition and/or a secondary heating control scheme (X) during a heating phase before a melting point of water in the composition is reached, wherein the crystallization change control scheme is a de- crystallization control scheme (W) during an excipient de-crystallization phase and/or a melting control scheme (Y) during a melting of ice phase, and wherein the final temperature change control scheme is a final heating control scheme (Z) to reach a use temperature of the composition;

wherein in the initial heating control scheme (V) the initial measurement is a eutectic point measurement to determine whether the composition has reached the eutectic point, wherein the initial temperature evolution over time is an initial heating temperature evolution over time, and wherein steps (I) and (II) are repeated until the eutectic point measurement determines that the composition has reached the eutectic point;

wherein in the de-crystallization control scheme (W) the crystallization-change

measurement is a de-crystallization measurement to determine whether de-crystallization has finished in the composition, wherein the crystallization-change temperature evolution over time is a de-crystallization temperature evolution over time and wherein steps (I) and (II) are repeated until the de-crystallization measurement determines that de-crystallization has finished in the composition;

wherein in the secondary heating control scheme (X) the initial measurement is a melting point measurement to determine whether the composition has reached the melting point of ice comprised in the composition, wherein the initial temperature evolution over time is a secondary heating temperature evolution over time and wherein steps (I) and (II) are repeated until the melting point measurement determines that the composition has reached the melting point;

wherein in the melting control scheme (Y) the crystallization-change measurement is a melting measurement to determine whether melting of ice has finished in the composition, wherein the crystallization-change temperature evolution over time is a melting temperature evolution over time and wherein steps (I) and (II) are repeated until the melting measurement determines that melting has finished in the composition; and

wherein in the final heating control scheme (Z) the final temperature evolution over time is a final heating temperature evolution over time.

10. The method for thawing frozen compositions according to claim 9, wherein (V) and (W); (V) and (X), (V) and (Y); (V) and (Z); (W) and (X); (W) and (Y); (W) and (Z); (X) and (Y); (X) and (Z); (Y) and (Z); (V), (W) and (X); (V), (W) and (Y); (V), (W) and (Z); (V), (X) and (Y); (V), (X) and (Z); (V), (Y) and (Z); (W), (X) and (Y); (W), (X) and (Z); (W), (Y) and (Z), (X), (Y) and (Z); (V), (W), (X) and (Y); (V), (W), (X) and (Z); (V), (W), (Y) and (Z); (V), (X), (Y) and (Z); (W), (X), (Y) and (Z); or (V), (W), (X), (Y) and (Z) are performed.

11. The method for thawing frozen compositions according to claims 9-10, wherein the method further comprises rotating the vial at least for a period of time and heating the vial by applying heating gas to the rotating vial.

12. A freezing apparatus for freezing injectable compositions, in particular pharmaceutical

compositions, wherein the freezing apparatus comprises:

a freezing chamber for cooling therein one or more vials, the one or more vials comprising a quantity of a dispersion of an injectable composition in an aqueous dispersion medium, and comprising a cooling gas system for applying cooling gas to the vial such that the vial is cooled;

wherein the freezing apparatus further comprises:

control means, for controlling the freezing process according to any one of claims 4-8; means for measuring the temperature of the vial during at least a certain time of the freezing process,

a control mechanism for influencing the flow rate and/or temperature of the cooling gas, to adjust the cooling rate during at least a part of the freezing process.

13. A freezing apparatus according to claim 12, wherein the freezing apparatus further comprises:

rotation means for the one or more vials, wherein the one or more vials can be rotated at least for a period of time to form a dispersion layer at an inner surface of a circumferential wall of the vial, such that the cooling gas system applies cooling gas to the rotating vial such that the vial is cooled.

14. A freeze-drying system for freeze-drying injectable compositions, in particular pharmaceutical compositions, wherein the freeze-drying system comprises:

a freezing apparatus according to claim 12;

an annealing apparatus and/or a sublimation apparatus,

wherein the annealing apparatus and/or the sublimation apparatus comprise a respective annealing chamber and a sublimation chamber,

wherein the annealing apparatus and/or the sublimation apparatus comprise a respective annealing chamber heat exchange element and a sublimation chamber heat exchange element

in thermal contact with the annealing chamber and the sublimation chamber

respectively, wherein the annealing/sublimation chamber heat exchange element cools the annealing

chamber and/or the sublimation chamber by using the used cooling gas from the freezing chamber or by using another cold liquid or gas.