and clinical development as a drug (in particular against cancer), while improving patient compliance and reducing the frequency of dosing double-stranded polyribonucleotide molecules with well-defined safety margin and therapeutic effects.

SUMMARY

The present disclosure relates to a composition comprising particles wherein

(i) each of said particles comprises a complex of at least one double-stranded polyribonucleotide, or a salt or solvate thereof, and at least one polyalkyleneimine, or a salt and/or solvate thereof;

(ii) at least 95%, or at least 90%, of said particles has a diameter of less than or equal to 600 nm, preferably, less than or equal to 300 nm (for example, between 140 and 250 nm); and

(iii) said particles have a z-average diameter of less than or equal to 200 nm, preferably less than or equal to 150 nm, in particular, as measured according to ISO 22412.

In a preferred embodiment, the present disclosure relates to an aqueous composition comprising particles wherein

(i) each of said particles comprises a complex of at least one double-stranded polyribonucleotide, or a salt or solvate thereof, and at least one linear polyalkyleneimine, or a salt and/or solvate thereof, wherein said double-stranded polyribonucleotide is polyinosinic-polycytidylic acid [poly(I:C)] and the average molecular weight of said linear polyalkyleneimine is between 17 and 23 kDa;

(ii) at least 90% of said particles has a mono-modal diameter distribution below 300 nm;

(iii) said particles have a z-average diameter of less than or equal to 150 nm, as measured according to ISO 22412; and

(iv) said composition has a zeta potential equal or superior to 30 mV, according to ISO 13099.

The present disclosure also relates to an aqueous composition comprising particles as described herein wherein:

(i) each of said particles is formed by making a complex of at least one double-stranded polyribonucleotide, or a salt or solvate thereof, and at least one linear polyalkyleneimine, or a salt and/or solvate thereof, wherein said double-stranded polyribonucleotide is polyinosinic-polycytidylic acid [poly(I:C)] and the average molecular weight of said linear polyalkyleneimine is between 17 and 23 kDa;

(ii) at least 90% of said particles has a mono-modal diameter below 300 nm;

(iii) said particles have a z-average diameter of less than or equal to 150 nm, as measured according to ISO 22412; and

(iv) said composition has a zeta potential equal or superior to 30 mV, according to ISO 13099;

wherein said particles are formed at the ratio of the number of moles of nitrogen of said polyalkyleneimine to the number of moles of phosphorus of said double-stranded polyribonucleotide in said composition being equal to or greater than 2.5.

In a first aspect, there is provided an aqueous composition comprising particles, wherein

(a) each particle comprises a complex of at least one double-stranded polyribonucleotide, or a salt or solvate thereof, and at least one polyalkyleneimine, or a salt and/or solvate thereof, wherein

(i) the double-stranded polyribonucleotide is polyinosinic-polycytidylic acid [poly(I:C)], wherein at least 60% of the double-stranded polyribonucleotides have at least 850 base pairs, at least 70% of the double-stranded polyribonucleotides have between 400 and 5000 base pairs, and between 20% and 45% of the double-stranded polyribonucleotides have between 400 and 850 base pairs; and

(ii) the polyalkyleneimine comprises at least 95% polyethyleneimines, wherein the average molecular weight of the polyalkyleneimine is between 17 and 23 kDa and the polydispersity index is < 1.5, and

wherein the ratio of the number of moles of nitrogen of the polyalkyleneimine to the number of moles of phosphorus of the double-stranded polyribonucleotide in the composition is around 3; and

(b) the particles have a z-average diameter measured according to ISO 22412:2008 of between 30 nm and 150 nm, and

(c) wherein at least 99% of the particles have a diameter distribution below 600 nm.

In a second aspect, there is provided a composition obtained by lyophilisation of the aqueous composition as described herein.

In addition, the present disclosure relates to a composition, as described herein, for use as a medicament.

In a third aspect, there is provided a composition as described herein for use as a medicament, optionally wherein the composition further comprises an immune-modulating agent targeting one or more of PD-1, PD-L1, and PD-L2, preferably wherein the immune-modulating agent is a PD-1 inhibitor, such as an anti-PD-1 antibody.

Moreover, the present disclosure relates to a composition, as described herein, for use in treatment of a cell growth disorder characterized by abnormal growth of human or animal cells.

In a fourth aspect, there is provided a composition as described herein for use in treatment of a cell growth disorder characterized by an abnormal growth of human or animal cells, wherein the cell growth disorder is cancer or a gynecological disorder characterized by an abnormal growth of cells of the female mammalian reproductive organs.

In a fifth aspect, there is provided use of a composition as described herein in the manufacture of a medicament for the treatment of a cell growth disorder characterized by an abnormal growth of human or animal cells, wherein the cell growth disorder is cancer or a gynecological disorder characterized by an abnormal growth of cells of the female mammalian reproductive organs.

Furthermore, the present disclosure relates to a process to manufacture the composition, as described herein, which comprises:

(i) preparing an aqueous solution of at least one double-stranded polyribonucleotide, or a salt or solvate thereof, and an aqueous solution of at least one polyalkyleneimine, or a salt or solvate thereof, wherein either or both solutions optionally further comprise a pharmaceutically acceptable carrier, organic solvent, excipient and/or adjuvant;

(ii) independently filtering each solution through a filter having a pore diameter of less than or equal to 500 nm to form sterilized solutions;

(iii) mixing the resulting sterilized solutions in a mixing chamber to form an aqueous composition by addition of one of said solutions into the other solution in said mixing chamber, optionally by injection, at a rate of greater than or equal to 1 mL/min, or by simultaneous addition of each of said solutions into said mixing chamber, optionally by injection, at a rate of greater than or equal to 1 mL/min; and optionally

(iv) filtering the resulting aqueous composition through a filter having a pore diameter of less than or equal to 600 nm to form a filtrate, or centrifuging the resulting aqueous composition at greater than or equal to 22480 m/s^2 to form a supernatant; and/or

(v) lyophilising the resulting aqueous composition, filtrate or supernatant.

In a sixth aspect, there is provided a process for manufacturing the composition as described herein, comprising:

(a) providing (i) an aqueous solution of at least one double-stranded polyribonucleotide, or a salt or solvate thereof, and (ii) an aqueous solution of at least one polyalkyleneimine, or a salt or solvate thereof, wherein either or both solutions optionally further comprise a pharmaceutically acceptable carrier, organic solvent, excipient and/or adjuvant;

(b) filtering each respective aqueous solution of step (a) independently through a filter having a pore diameter of less than or equal to 500 nm to form a respective sterilized solution;
and

(c) mixing each respective resulting sterilized solution in a mixing chamber to form an aqueous composition by simultaneous addition of each respective sterilized solution into the mixing chamber, optionally by injection, at a rate of greater than or equal to 1 mL/min, or by sequential addition of one sterilized solution into the other sterilized solution in the mixing chamber, optionally by injection, at a rate of greater than or equal to 1 mL/min; and
optionally

(d) filtering the resulting aqueous composition of step (c) through a filter having a pore diameter of less than or equal to 600 nm to form a filtrate, or centrifuging the resulting aqueous composition at greater than or equal to 22480 m/s^2 to form a supernatant.

Preferably, the present disclosure also relates to a composition comprising particles wherein:

(i) each of said particles comprises a complex of at least one double-stranded polyribonucleotide, or a salt or solvate thereof, and at least one polyalkyleneimine, or a salt and/or solvate thereof, wherein

(a) said double-stranded polyribonucleotide is polyinosinic-polycytidylic acid [poly(I:C)] or polyadenylic-polyuridylic acid [poly(A:U)], wherein at least 60% of said double-stranded polyribonucleotides have at least 850 base pairs, at least 70% of said double-stranded polyribonucleotides have between 400 and 5000 base pairs, and between 20% and 45% of said double-stranded polyribonucleotides have between 400 and 850 base pairs; and

(b) said polyalkyleneimine comprises at least 95% polyethyleneimines, wherein the weight average molecular weight of said polyalkyleneimine is between 17 and 23 kDa and the polydispersity index is < 1.5, and wherein the ratio of the number of moles of nitrogen of said polyalkyleneimine to the number of moles of phosphorus of said double-stranded polyribonucleotide in said composition is between 2.5 and 5.5;

(ii) at least 99% of said particles has a diameter of less than or equal to 600 nm; and

(iii) said particles have a z-average diameter of between 30 nm and 150 nm.

More preferably, the present disclosure also relates to an aqueous composition which comprises particles wherein:

(i) each of said particles comprises a complex of at least one double-stranded polyribonucleotide, or a salt or solvate thereof, and at least one polyalkyleneimine, or a salt and/or solvate thereof, wherein

(a) said double-stranded polyribonucleotide is polyinosinic-polycytidylic acid [poly(I:C)], wherein at least 60% of said poly(I:C) has at least 850 base pairs, at least 70% of said poly(I:C)

CLAIMS

1. An aqueous composition comprising particles, wherein

(a) each particle comprises a complex of at least one double-stranded polyribonucleotide, or a salt or solvate thereof, and at least one polyalkyleneimine, or a salt and/or solvate thereof, wherein

(i) the double-stranded polyribonucleotide is polyinosinic-polycytidylic acid [poly(I:C)],

wherein at least 60% of the double-stranded polyribonucleotides have at least 850 base pairs, at least 70% of the double-stranded polyribonucleotides have between 400 and 5000 base pairs, and between 20% and 45% of the double-stranded polyribonucleotides have between 400 and 850 base pairs; and

(ii) the polyalkyleneimine comprises at least 95% polyethyleneimines,

wherein the average molecular weight of the polyalkyleneimine is between 17 and 23 kDa and the polydispersity index is < 1.5, and

wherein the ratio of the number of moles of nitrogen of the polyalkyleneimine to the number of moles of phosphorus of the double-stranded polyribonucleotide in the composition is around 3; and

(b) the particles have a z-average diameter measured according to ISO 22412:2008 of between 30 nm and 150 nm, and

(c) wherein at least 99% of the particles have a diameter distribution below 600 nm.

2. The composition according to claim 1, wherein at least 95% of the particles have a diameter of less than or equal to 400 nm, and/or wherein the diameter distribution is mono-modal.

3. The composition according to claim 1, wherein the composition has a zeta potential of between 35 and 50 mV, measured according to ISO 13099-2:2012.

4. The composition according to any of claims 1 to 3, wherein the polyalkyleneimine is a linear polyalkyleneimine which is a water-soluble homo-polyalkyleneimine or a hetero-polyalkyleneimine.

5. The composition according to any preceding claim, wherein the polyribonucleotide composition contains polyinosinic-polycytidylic acid [poly(I:C)] at a concentration of at least 0.5 mg/ml.

6. The composition according to any preceding claim, wherein the composition further comprises

(a) at least one pharmaceutically acceptable carrier, organic solvent, excipient and/or adjuvant; and/or

(b) at least one compound selected from an organic compound, an inorganic compound, a nucleic acid, an aptamer, a peptide and a protein.

7. The composition according to claim 1, wherein the composition further comprises glucose or mannitol at a concentration of between 1 and 10% weight/volume of the composition.

8. The composition according to claim 3, wherein the composition further has:

(a) a pH of between 2 and 4; and/or

(b) an osmolality of between 200 and 600 mOsm/kg.

9. The composition according to any preceding claim, wherein the composition is formed by making the complex from at least 0.5 mg of polyinosinic-polycytidylic acid [poly(I:C)] per ml of the total volume of the composition.

10. The composition according to any preceding claim, wherein the composition is formed by additionally adding glucose or mannitol in a concentration of between 1 and 10% weight/volume of the composition.

11. A composition obtained by lyophilisation of the aqueous composition according to any preceding claim.

12. A composition according to any preceding claim for use as a medicament, optionally wherein the composition further comprises an immune-modulating agent targeting one or more of PD-1, PD-L1, and PD-L2, preferably wherein the immune-modulating agent is a PD-1 inhibitor, such as an anti-PD-1 antibody.

13. The composition for use according to claim 12, wherein the medicament is an injectable, aqueous composition, optionally further comprising a pharmaceutically acceptable carrier, excipient and/or adjuvant.

14. A composition according to any of claims 1 to 11 or a composition for use according to any of claims 12 and 13 for use in treatment of a cell growth disorder characterized by an abnormal growth of human or animal cells, wherein the cell growth disorder is cancer or a gynecological disorder characterized by an abnormal growth of cells of the female mammalian reproductive organs.

15. The composition for use according to claim 14, wherein the composition is administered by intratumoral or peritumoral injection, or by injection at the level of skin or of an internal organ or tissue.

16. A process for manufacturing the composition according to any of claims 1 to 11, comprising:

(a) providing (i) an aqueous solution of at least one double-stranded polyribonucleotide, or a salt or solvate thereof, and (ii) an aqueous solution of at least one polyalkyleneimine, or a salt or solvate thereof, wherein either or both solutions optionally further comprise a pharmaceutically acceptable carrier, organic solvent, excipient and/or adjuvant;

(b) filtering each respective aqueous solution of step (a) independently through a filter having a pore diameter of less than or equal to 500 nm to form a respective sterilized solution; and

(c) mixing each respective resulting sterilized solution in a mixing chamber to form an aqueous composition by simultaneous addition of each respective sterilized solution into the mixing chamber, optionally by injection, at a rate of greater than or equal to 1 ml/min, or by sequential addition of one sterilized solution into the other sterilized solution in the mixing chamber, optionally by injection, at a rate of greater than or equal to 1 ml/min; and optionally

(d) filtering the resulting aqueous composition of step (c) through a filter having a pore diameter of less than or equal to 600 nm to form a filtrate, or centrifuging the resulting aqueous composition at greater than or equal to 22480 m/s^2 to form a supernatant.

17. The process of claim 16, further comprising:

(e) lyophilising the resulting aqueous composition, filtrate or supernatant.

18. Use of a composition according to any of claims 1 to 11 in the manufacture of a medicament for the treatment of a cell growth disorder characterized by an abnormal growth of human or animal cells, wherein the cell growth disorder is cancer or a gynecological disorder characterized by an abnormal growth of cells of the female mammalian reproductive organs.

19. The use according to claim 18, wherein the composition further comprises an immune-modulating agent targeting one or more of PD-1, PD-L1, and PD-L2, preferably wherein the immune-modulating agent is a PD-1 inhibitor, such as an anti-PD-1 antibody.

20. The use according to claim 18 or 19, wherein the medicament is an injectable, aqueous composition, optionally further comprising a pharmaceutically acceptable carrier, excipient and/or adjuvant.

21. The use according to any one of claims 18 to 20, wherein the composition is to be administered by intratumoral or peritumoral injection, or by injection at the level of skin or of an internal organ or tissue.