WO 2005/066333 describes a viral composition comprising urea, a sugar, a salt, a buffer, a dispersing agent and a mixture of essential and non-essential amino acids.

WO 2007/056847 discloses a virus-containing formulation comprising sucrose, sorbitol, a polyvinyl pyrrolidone, urea, a TRIS buffer, monosodium glutamate and another amino acid such as arginine, alanine, serine or glycine.

WO2008/114021 and WO2011/121306 describe viral compositions comprising polyethyleneimine compounds, optionally in combination with one or more sugar(s).

Nevertheless, there remains a need for new formulations allowing stabilization of biological materials, and particularly virus-based materials, allowing industrial applications, storage without affecting biological activity of the product, and more particularly to avoid virus titer loss.

The present Invention provides formulation containing virus-based materials, more particularly aqueous formulation, suitable for freeze-drying. According to preferred embodiment, the formulation of the Invention are stable over long-term stability tests as defined hereinafter and more particularly during storage at temperatures above 0°C, particularly between about 4°C and about 30°C, preferably between about 4°C and about 25°C, more preferably between about 2°C and about 8°C, and even more preferably between about 4°C and about 5°C (e.g. refrigerated temperature).

Disclosure of the invention

In one aspect, there is provided a formulation comprising (i) at least one poxvirus-based material, (ii) at least one polymer selected in the group of polyvinylpyrrolidone and derivatives thereof selected from copovidone and cross-linked polyvinylpyrrolidone, (iii) at least one sugar, (iv) at least two different amino acids, (v) at least two pharmaceutical acceptable salts, wherein at least one of said salts is a phosphate salt and, optionally (vi) a pharmaceutical acceptable buffer.

In another aspect, there is provided a method for the preparation of a freeze-dried formulation, wherein said method comprises the step of freeze-drying the aqueous formulation as described herein.

In a further aspect, there is provided a freeze-dried formulation obtained by the method as described herein.

In yet another aspect, there is provided a reconstituted formulation obtained by the addition of suitable amount of pharmaceutically acceptable solvent to the freeze-dried formulation as described herein.

In another aspect, there is provided the use of the formulation or the reconstituted formulation as described herein in the manufacture of a medicament for use as a vaccine.

In a further aspect, there is provided the use of the formulation or the reconstituted formulation as described herein in the manufacture of a medicament for the treatment and/or the prevention of disease or conditions chosen among cancers, infectious diseases and/or autoimmune disorders.

FORMULATION

According to a first embodiment, the present invention concerns a formulation comprising (i) at least one virus-based material, (ii) at least one polymer selected in the group of polyvinylpyrrolidone and derivatives thereof, (iii) at least one sugar, (iv) at least two different amino acids, (v) at least two pharmaceutical acceptable salts, wherein at least one of said salts is a phosphate salt and, optionally (vi) a pharmaceutical acceptable buffer.

Unless otherwise stated, the following terms as used throughout the entire application, have the following meaning.

Claims

1. A formulation comprising (i) at least one poxvirus-based material, (ii) at least one polymer selected in the group of polyvinylpyrrolidone and derivatives thereof selected from copovidone and cross-linked polyvinylpyrrolidone, (iii) at least one sugar, (iv) at least two different amino acids, (v) at least two pharmaceutical acceptable salts, wherein at least one of said salts is a phosphate salt and, optionally (vi) a pharmaceutical acceptable buffer.

2. The formulation of claim 1, wherein it is an aqueous formulation.

~~3. The formulation of claim 1, wherein it is a freeze-drying formulation.~~

43. The formulation of claim 1 or 2, wherein said (ii) at least one polymer is selected in the group of polyvinylpyrrolidone, ~~and~~ derivatives thereof selected from copovidone and cross-linked polyvinylpyrrolidone, and mixture thereof.

~~5~~4. The formulation of claim 43, wherein said polyvinylpyrrolidone or derivatives thereof selected from copovidone and cross-linked polyvinylpyrrolidone have a molecular weight comprised between 10 kDa and 40 kDa, preferably between 15 kDa and 30 kDa and more preferably of 25 kDa.

~~6~~5. The formulation of claim 43 or ~~5~~4, wherein said formulation comprises between 10g/L and 50g/L, preferably between 15g/L and 40g/L, and more preferably between 20g/L and 35g/L of polyvinylpyrrolidone or derivatives selected from copovidone and cross-linked polyvinylpyrrolidone or mixture thereof.

~~7~~6. The formulation of any of the preceding claims, wherein said (iii) at least one sugar is chosen among monosaccharide, disaccharide, trisaccharide and tetrasaccharide ~~and derivatives thereof~~.

~~8~~7. The formulation of claim ~~7~~6, wherein said formulation comprises at least one disaccharide selected from the group consisting in sucrose, lactulose, lactose, maltose, trehalose, cellobiose, isomaltose and maltulose.

~~9~~8. The formulation of claim ~~7~~6 or ~~8~~7, wherein said formulation comprises between 20g/L and 80g/L, preferably between 30g/L and 70g/L and more preferably between 40g/L and 60g/L of sugar.

~~10~~9. The formulation of claim ~~9~~8, wherein said formulation comprises 50g/L of sucrose.

~~11~~10. The formulation of any of the preceding claims, wherein said (iv) at least two different amino acids are chosen among alanine, arginine, asparagine, aspartate, cysteine, glutamine, glutamate, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, pyrrolysine, selenocysteine, serine, threonine, tryptophane, tyrosine and valine ~~and derivatives thereof~~, including both stereoisomers.

~~12~~11. The formulation of claim ~~11~~10, wherein said formulation comprises between 5g/L and 100g/L and preferably between 5g/L and 80g/L of arginine.

~~13~~12. The formulation of claim ~~11~~10 or ~~12~~11, wherein said formulation comprises between 1g/L and 10g/L and preferably between 1g/L and 5g/L of glutamate.

~~14~~13. The formulation of any of the preceding claims, wherein at least one of said salts is a phosphate salt and is selected in the group consisting of sodium and potassium salts, and combination thereof.

~~15~~14. The formulation of claim ~~14~~13, wherein said phosphate salt is selected in the group consisting of monobasic phosphate salts, dibasic phosphate salts and tribasic phosphate salts.

~~16~~15. The formulation of claim ~~14~~13 or ~~15~~14, wherein it further comprises an additional pharmaceutically acceptable monovalent salt.

~~17~~16. The formulation of claim ~~16~~15, wherein said additional pharmaceutically acceptable salt is selected in the group consisting of NaCl and KCl, and is preferably NaCl.

~~18~~17. The formulation of claim ~~16~~15 or ~~17~~16, wherein said formulation comprises between 1g/L and 5g/L of said additional pharmaceutical acceptable salt.

~~19~~18. The formulation of any of the preceding claims, wherein said (i) poxvirus-based material is a wild type, attenuated or recombinant poxvirus or poxviral particle.

~~2019~~19. The formulation of claim ~~1918~~18, wherein said virus-based material is a virus or viral particle selected from the group consisting of Vaccinia Virus (VV) and modified Vaccinia Virus Ankara (MVA).

~~2120~~20. The formulation of claim ~~2019~~19, wherein said poxvirus-based material is a recombinant MVA selected from the group consisting in a MVA expressing HCV NS3, NS4 and NS5B antigens; a MVA expressing the MUC-1 antigen and IL-2 and a MVA expressing non oncogenic E6 and E7 antigens of HPV-16 and IL-2.

~~2221~~21. The formulation of claim ~~2019~~19, wherein said poxvirus-based material is a recombinant Vaccinia Virus selected from the group consisting in a thymidine kinase (TK)-inactivated vaccinia virus expressing an immune-stimulating cytokine which is a granulocyte macrophage colony stimulating factor and a doubly thymidine kinase (TK-) and ribonucleotide reductase (I4L-) inactivated vaccinia virus expressing a suicide gene.

~~2322~~22. The formulation of any one of claims ~~1918~~18 to ~~2221~~21, wherein the poxvirus titer in said formulation is comprised between 1.10^6 Pfu/mL and 1.10^{10} Pfu/mL.

23. A method for the preparation of a freeze-dried formulation, wherein said method comprises the step of freeze-drying the aqueous formulation of any one of claims 2-22.

24. A freeze-dried formulation obtained by the method of claim 23.

25. A reconstituted formulation obtained by the addition of suitable amount of pharmaceutically acceptable solvent to the freeze-dried formulation of claim 24.

26. Use of the formulation according to any one of claims 1 to 22 or the reconstituted formulation according to claim 25 in the manufacture of a medicament for use as a vaccine.

27. Use of the formulation according to any one of claims 1 to 22 or the reconstituted formulation according to claim 25 in the manufacture of a medicament for the treatment and/or the prevention of disease or conditions chosen among cancers, infectious diseases and/or autoimmune disorders.