CLAIMS

1. A method of producing a viral vaccine, the method comprising the steps:

    a. purifying viral particles from harvested cell culture;
    b. inactivating and splitting the viral particles to produce sub-virions; and
    c. purifying the sub-virions;

wherein inactivating and splitting the viral particles of step b comprises treating the viral particles with a reagent comprising at least one non-ionic surfactant and at least one ionic surfactant, and wherein the at least one non-ionic surfactant and the at least one ionic surfactant are present in an amount effective to reduce particle size of the viral particles.

2. The method of claim 1, wherein the reagent further comprises at least one salt, wherein the at least one salt is present in an amount effective to reduce particle size of the viral particles.

3. The method of claim 1, wherein the average hydrodynamic radius of the sub-virion ranges from 150 nm to 350 nm.

4. The method of claim 1, wherein the at least one non-ionic surfactant is polysorbate 80.

5. The method of claim 1, wherein the at least one non-ionic surfactant comprises at least about 1.0 g/L polysorbate 80.

6. The method of claim 1, wherein the at least one ionic surfactant comprises cetrimonium bromide (CTAB).

7. The method of claim 1, wherein the at least one ionic surfactant comprises about 1.25 g/L to 3.0 g/L CTAB.

8. The method of claim 2, wherein the at least one salt comprises sodium chloride (NaCl).

9. The method of claim 2, wherein the at least one salt comprises 0 - 200 mM NaCl.

10. The method of claim 1, wherein the at least one non-ionic surfactant comprises polysorbate 80, the at least one ionic surfactant comprises CTAB, and the at least one salt comprises sodium chloride NaCl.

11. The method of claim 1, wherein the particle size of the sub-virion is less than about 500 nm.

12. The method of claim 1, wherein the particle size of the sub-virion is the hydrodynamic radius.

13. The method of claim 1, wherein the viral particles are from influenza virus.

14. The method of claim 4, wherein the concentration of polysorbate 80 is 0.3 g/L prior to splitting.

15. The method of claim 4, wherein the concentration of polysorbate 80 increases in an amount that ranges from 0 - 2.2 g/L during splitting.

16. The method of claim 4, wherein the concentration of polysorbate 80 is 0.3 g/L, 1.4 g/L, or 2.5 g/L during splitting.

17. The method of claim 8, wherein a concentration of NaCl ranging from 0 - 25 mM is associated with increased filtration throughput.

18. A method of reducing viral particle size in a virus manufacturing process, the method comprising

a. purifying viral particles harvested from cell culture;
b. inactivating and splitting the viral particles to produce sub-virions; and
c. purifying the sub-virions;

wherein inactivating and splitting the viral particles of step b comprises treating the viral particles with a reagent comprising at least one non-ionic surfactant and at least one ionic surfactant, and wherein the at least one non-ionic surfactant and the at

least one ionic surfactant are present in an amount effective to reduce particle size of the viral particles.

19. A method of producing an influenza viral vaccine formulation comprising purified viral proteins, the method comprising the steps:

a. purifying viral particles from a harvested cell culture of MDCK cells;
b. inactivating and splitting the viral particles to produce sub-virions; and
c. purifying the sub-virions to produce purified viral proteins;

wherein inactivating and splitting the viral particles of step b comprises treating the viral particles with a reagent comprising at least one non-ionic surfactant and at least one salt, and wherein the at least one non-ionic surfactant and the at least one salt are present in an amount effective to reduce particle size of the viral particles.

20. A method of producing an influenza viral vaccine formulation comprising purified viral proteins, the method comprising the steps:

a. purifying viral particles from a harvested cell culture of MDCK cells;
b. inactivating and splitting the viral particles to produce sub-virions; and
c. purifying the sub-virions to produce purified influenza viral proteins;

wherein inactivating and splitting the viral particles of step b comprises treating the viral particles with a reagent comprising at least one ionic surfactant and at least one salt, and wherein the at least one ionic surfactant and the at least one salt are present in an amount effective to reduce particle size of the viral particles.

21. A method of producing an influenza viral vaccine formulation comprising purified viral proteins, the method comprising the steps:

a. purifying viral particles from a harvested cell culture of MDCK cells;
b. treating the purified viral particles with at least one alkylating agent to inactivate the viral particles;
c. treating the inactivated viral particle with at least one ionic surfactant to split the inactivated viral particles to produce subvirions; and
d. purifying the sub-virions to produce purified influenza viral proteins;

wherein inactivating and splitting the viral particles of step b and/or c further comprises treating the viral particles with a reagent comprising at least one non-ionic surfactant and at least one ionic surfactant, and wherein the at least one non-ionic

surfactant and the at least one ionic surfactant are present in an amount effective to reduce particle size of the viral particles.

22. The method of claim 1, wherein the viral vaccine is formulated in a sub-virion form.

23. The method of claim 1, wherein the particle size of the sub-virion ranges from greater than about 150 nm to less than about 500 nm.