CLAIMS

1. A method for manufacture of a squalene-containing oil-in-water emulsion vaccine adjuvant, comprising steps of:

   (i) formation of a first emulsion having a first average oil droplet size;

   (ii) microfluidization of the first emulsion to form a second emulsion having a second average oil droplet size which is less than the first average oil droplet size; and

   (iii) filtration of the second emulsion using a hydrophilic double-layer filter which has a first membrane layer with larger pores and a second membrane layer with smaller pores, thereby providing a vaccine adjuvant.

2. A method for the manufacture of a squalene-containing oil-in-water emulsion vaccine adjuvant, comprising steps of:

   (i) formation of a first emulsion having an average oil droplet size of 5000 nm or less;

   (ii) microfluidization of the first emulsion to form a second emulsion having an average oil droplet size which is 500nm or less; and

   (iii) filtration of the second emulsion using a hydrophilic membrane, thereby providing a vaccine adjuvant.

3. The method of claim 1 or claim 2, wherein the hydrophilic membrane is a hydrophilic polyethersulfone membrane.

4. A method for the manufacture of a squalene-containing oil-in-water emulsion vaccine adjuvant, comprising steps of:

   (i) formation of a first emulsion having a first average oil droplet size;

   (ii) microfluidization of the first emulsion to form a second emulsion having a second average oil droplet size which is less than the first average oil droplet size; and

   (iii) filtration of the second emulsion using a hydrophilic polyethersulfone membrane, thereby providing a vaccine adjuvant.

5. The method according to claim 1, 3 or 4, wherein the first average oil droplet size is 5000 nm or less.

6. The method according to any one of the preceding claims, wherein the number of oil droplets having a size of >1.2 μm in the first emulsion is 5×10^{11} /ml or less.

7. The method according to any one of the preceding claims, wherein the second average oil droplet size is 500 nm or less.

8. The method according to any one of the preceding claims, wherein the number of oil droplets having a size of >1.2 μm in the second emulsion is 5×10^{10} /ml or less.

9. A method for manufacture of a squalene-containing oil-in-water emulsion vaccine adjuvant, comprising steps of:

   (i) formation of a squalene-containing emulsion having an average oil droplet size of 500nm or less;

   (ii) filtration of the squalene-containing emulsion using a hydrophilic double-layer filter which has a first membrane layer with larger pores and a second membrane layer with smaller pores, thereby providing a vaccine adjuvant.

10. The method according to any one of the preceding claims, wherein the average oil droplet size after filtration is less than 220 nm.

11. The method according to any one of the preceding claims, wherein the number of oil droplets having a size of >1.2 μm after filtration is 5×10^{8} /ml or less.

12. The method according to any one of the preceding claims, wherein the second emulsion is prefiltered through a membrane prior to filtration.

13. The method of claim 12, wherein the prefiltration and filtration steps are carried out using a double-layer filter.

14. The method of claim 12 or claim 13, wherein the prefiltration membrane is asymmetric and/or porous.

15. The method of any one of the preceding claims, wherein the filtration membrane is asymmetric and/or porous.

16. The method of any one of the preceding claims, wherein the filtration membrane, and optionally the prefiltration membrane, comprises a polymeric support material.

17. The method of any one of the preceding claims, wherein (i) the first layer has a pore size ≥0.3μm, and/or (ii) the second layer has a pore size <0.3μm.

18. A method for preparing a vaccine composition, comprising preparing an emulsion adjuvant according to any one of claims 1 to 17 and combining the emulsion adjuvant with an antigen.

19. A method for preparing a vaccine kit comprising preparing an emulsion adjuvant according to any one of claims 1 to 17 and packaging the emulsion adjuvant into a kit as a kit component together with an antigen component.

20. The method of claim 19, wherein the kit components are in separate vials.

21. The method of claim 20, wherein the vials are made from borosilicate glass.

22. The method of any of claims 18 to 21, wherein the emulsion adjuvant is a bulk adjuvant and the method comprises extracting unit doses from the bulk adjuvant for packaging as kit components.

23. The method of any one of claims 18 to 22, wherein the antigen is an influenza virus antigen.

24. The method of claim 23, wherein the combination of the emulsion and the antigen forms a vaccine composition and wherein the vaccine composition includes about 15μg, about 10μg, about 7.5μg, about 5μg, about 3.8μg, about 3.75μg, about 1.9μg, or about 1.5μg of hemagglutinin per influenza virus strain.

25. The method of claim 23 or claim 24, wherein the combination of the emulsion and the antigen forms a vaccine composition and wherein the vaccine composition includes a thiomersal or 2-phenoxyethanol preservative.

26. Use of a hydrophilic double-layer filter which has a first membrane layer with larger pores and a second membrane layer with smaller pores for preparing an oil-in-water emulsion vaccine adjuvant.

27. Use according to claim 26, wherein the first and/or second membrane layer comprises hydrophilic polyethersulfone.

Claims

1. A method for manufacture of a squalene-containing oil-in-water emulsion vaccine adjuvant, comprising steps of:

(i) formation of a squalene-containing emulsion having an average oil droplet size of 500nm or less comprising the steps of

a. formation of a first emulsion having a first average oil droplet size;
b. microfluidization of the first emulsion to form a second emulsion having a second average oil droplet size of 500nm or less, which is less than the first average oil droplet size; and

(ii) filtration of the second emulsion using a hydrophilic double-layer polyethersulfone membrane with a first layer having a pore size of ≥0.3μm and a second layer having a pore size of <0.3μm, thereby providing a vaccine adjuvant.

2. The method of claim 1, wherein the first average oil droplet size is 5000 nm or less.

3. The method of claim 1 or claim 2, wherein the number of oil droplets having a size of >1.2 mm in the first emulsion is 5×10^{11} /ml or less.

4. The method of any of claims 1-3, wherein the number of oil droplets having a size of >1.2 mm in the second emulsion is 5×10^{10} /ml or less.

5. The method according to any one of the preceding claims, wherein the average oil droplet size after filtration is less than 220 nm.

6. The method according to any one of the preceding claims, wherein the number of oil droplets having a size of >1.2 μm after filtration is 5×10^{8} /ml or less.

7. The method according to any one of the preceding claims, wherein: (a) the first membrane layer is asymmetric and/or porous; and/or (b) the second membrane layer is asymmetric and/or porous.

8. The method of any one of the preceding claims, wherein the second membrane layer, and optionally the first membrane layer, comprise(s) a polymeric support material.

9. A method for preparing a vaccine composition, comprising preparing an emulsion adjuvant according to any one of claims 1 to 8 and combining the emulsion adjuvant with an antigen.

10. A method for preparing a vaccine kit comprising preparing an emulsion adjuvant according to any one of claims 1 to 8 and packaging the emulsion adjuvant into a kit as a kit component together with an antigen component.

11. The method of claim 10, wherein the kit components are in separate vials (for example, wherein the vials are made from borosilicate glass).

12. The method of any of claims 9 to 11, wherein the emulsion adjuvant is a bulk adjuvant and the method comprises extracting unit doses from the bulk adjuvant for packaging as kit components.

13. The method of any one of claims 9 to 12, wherein the antigen is an influenza virus antigen; for example, wherein the combination of the emulsion and the antigen forms a vaccine composition and wherein the vaccine composition includes about 15μg, about 10μg, about 7.5μg, about 5μg, about 3.8μg, about 3.75μg, about 1.9μg, or about 1.5μg of hemagglutinin per influenza virus strain.