[0004] Accordingly, there exists a need for allergen compositions that can prevent and/or treat allergies as well as reduce an allergic reaction upon accidental exposure to a food allergen, and methods for making allergen compositions to prevent and/or treat allergies.

SUMMARY

[0005] In one aspect, the present disclosure provides a method of making a sterile mixed allergen drug product ~~with known potency and identity~~ that is ~~substantially~~ free of replication viable organisms, the method comprising: separately irradiating each of 2 to 20 different raw complete food allergen substances, wherein irradiating comprises applying ionizing radiation to each individual raw complete food allergen substance, thereby producing 2 to 20 individual allergen drug substances each ~~substantially~~ free of replication viable organisms, and wherein each individual allergen drug substance retains ~~substantially~~ intact, allergenic proteins; and blending the 2 to 20 individual allergen drug substances together, thereby obtaining the mixed allergen drug product; wherein the ionizing radiation is beta radiation.

[0005a] This disclosure is directed, at least in part, to a method of making a sterile mixed allergen drug product substantially free of replication viable organisms with consistent identity and potency which can be used for oral immunotherapy. For example, in certain examples, the method comprises: separately irradiating each of 2 to 20 different raw complete food allergen substances, wherein irradiating comprises applying ionizing radiation to each individual raw complete food allergen substance, thereby producing 2 to 20 individual allergen drug substances each substantially free of replication viable organisms and wherein each individual allergen drug substance retains substantially intact, allergenic proteins; and blending the 2 to 20 individual allergen drug substances together, thereby obtaining the mixed allergen drug product.

[0006] In certain examples, the disclosure provides a method, wherein the individual raw complete food allergen substances are selected from the group consisting of hazelnut, cashew, pistachio, walnut, pecan, almond, peanut, sesame, soy, hen's egg, bovine milk, wheat, salmon, cod, and shrimp.

[0007] In another example, the disclosure provides a method, wherein blending further comprises blending the 2 to 20 individual allergen drug substances with one or more bulking agents and/or pharmaceutically acceptable excipients.

[0008] In certain examples, the method provides applying ionizing radiation, wherein the ionizing radiation is beta radiation, gamma radiation, alpha radiation, X radiation, or a combination thereof. In some examples, the ionizing radiation is applied in one or more doses of

[0014] In certain examples, the protein content/potency and/or identity of each raw complete food allergen substance is tested by ELISA.

[0015] In other examples, each individual allergen drug substance has a substantially similar allergen effect upon administration to a patient as administration of the substantially same protein amount of a corresponding raw complete food allergen substance, wherein allergen effect is measured by immune response in a patient.

[0016] In certain examples of the method of the present disclosure, the mixed allergen drug product comprises 6 to 20 individual allergen drug substances.

[0017] In certain examples, the method of the present disclosure provides a mixed allergen drug product comprising about 0.1 mg to about 500 mg, by protein mass, of each individual allergen drug substance. In some examples, the mixed allergen drug product comprises 15 or 16 individual allergen drug substances, wherein each individual allergen drug substance is present in about a 2:1 to about 1:2 ratio, by protein weight, with another individual allergen drug substance. In other examples, the mixed allergen drug product comprises substantially equal amounts of individual allergen drug substances by total protein weight.

[0018] In some examples of the present disclosure, the individual allergen drug substances are stable for at least 6 months. In further examples, the individual allergen drug substances are stable for at least one year. In other examples, the mixed allergen drug product is stable for at least 6 months. In still further examples, the mixed allergen drug product is stable for at least one year.

[0019] In another aspect, the present disclosure provides a method of making a sterile mixed allergen drug product free of replication viable organisms, the method comprising: providing 2 to 20 individual beta-irradiated allergen drug substances each free of replication viable organisms and wherein each individual allergen drug substance retains intact, allergenic proteins; and blending the 2 to 20 individual allergen drug substances together, thereby obtaining the mixed allergen drug product. In another ~~aspect~~example, the present disclosure provides a method of making a sterile mixed allergen drug product substantially free of replication viable organisms, the method comprising: providing 2 to 20 individual irradiated allergen drug substances each substantially free of replication viable organisms and wherein each individual allergen drug substance retains substantially intact, allergenic proteins; and blending the 2 to 20 individual allergen drug substances together, thereby obtaining the mixed allergen drug product. In another aspect, the present disclosure provides a method of making a mixed allergen drug product free of replication viable organisms, the method comprising: providing 6 to 20 different

raw complete food allergen substances; blending the 6 to 20 different raw complete food allergen substances to produce a bulk substance; and irradiating the bulk substance with beta radiation, thereby obtaining the mixed allergen drug product. In another ~~aspect~~example, the present disclosure provides a method of making a mixed allergen drug product substantially free of replication viable organisms, the method comprising: providing 6 to 20 different raw complete food allergen substances; blending the 6 to 20 different raw complete food allergen substances to produce a bulk substance; and irradiating the bulk substance with ionizing radiation, thereby obtaining the mixed allergen drug product.

[0020] Also disclosed ~~in another aspect~~ is a mixed allergen drug product that is substantially free of replication viable organisms prepared by any one of the methods disclosed herein. Also

contemplated is a mixed allergen drug product prepared by any one of the methods disclosed herein for oral immunotherapeutic treatment of food allergy in a child or adult. In another example, a mixed allergen drug product as disclosed herein is for mixture with a food to which the child or adult is not allergic.

[0021] In a further aspect, the present disclosure provides a method of making a sterile allergen drug product free of replication viable organisms, the method comprising: irradiating a raw complete food allergen substance, wherein irradiating comprises applying beta radiation to the raw complete food allergen substance, thereby producing an individual allergen drug substance free of replication viable organisms and wherein the allergen drug substance retains intact, allergenic proteins. In another ~~aspect~~example, the present disclosure provides a method of making a sterile allergen drug product substantially free of replication viable organisms, the method comprising: irradiating a raw complete food allergen substance, wherein irradiating comprises applying ionizing radiation to the raw complete food allergen substance, thereby producing an individual allergen drug substance substantially free of replication viable organisms, and wherein each allergen drug substance retains substantially intact, allergenic proteins. In a certain example, the raw complete food allergen substance is selected from the group consisting of hazelnut, cashew, pistachio, walnut, pecan , almond, peanut, sesame, soy, hen's egg, bovine milk, wheat, salmon, cod, and shrimp.

BRIEF DESCRIPTION OF THE DRAWINGS

[0022] **FIGURE 1A** shows an SDS-PAGE of non-irradiated and beta-radiated (E-beam irradiated) hazelnut powder. Lane 1 = protein standard ladder; lane 2 = E-beam irradiated hazelnut powder (7.5 kGy); lane 3 = non-irradiated hazelnut powder. **FIGURE 1B** shows optical densitometry of the SDS-PAGE of FIGURE 1A.

[0023] **FIGURE 2A** shows an SDS-PAGE of non-irradiated and beta-radiated (E-beam irradiated) cashew powder. Lane 1 = protein standard ladder; lane 2 = E-beam irradiated cashew powder (7.5 kGy); lane 3 = non-irradiated cashew powder. **FIGURE 2B** shows optical densitometry of the SDS-PAGE of FIGURE 2A.

[0024] **FIGURE 3A** shows an SDS-PAGE of non-irradiated and beta-radiated (E-beam irradiated) pistachio powder. Lanes 1 and 4 = protein standard ladder; lane 2 = E-beam irradiated pistachio powder (7.5 kGy); lane 3 = non-irradiated pistachio powder. **FIGURE 3B** shows optical densitometry of the SDS-PAGE of FIGURE 3A.

WHAT IS CLAIMED IS:

1. A method of making a sterile mixed allergen drug product ~~with known potency and identity~~ that is ~~substantially~~ free of replication viable organisms, the method comprising:

separately irradiating each of 2 to 20 different raw complete food allergen substances, wherein irradiating comprises applying ionizing radiation to each individual raw complete food allergen substance, thereby producing 2 to 20 individual allergen drug substances each ~~substantially~~ free of replication viable organisms, and wherein each individual allergen drug substance retains ~~substantially~~ intact, allergenic proteins; and

blending the 2 to 20 individual allergen drug substances together, thereby obtaining the mixed allergen drug product;

wherein the ionizing radiation is beta radiation.

2. The method of claim 1, wherein the individual raw complete food allergen substances are selected from the group consisting of hazelnut, cashew, pistachio, walnut, pecan , almond, peanut, sesame, soy, hen's egg, bovine milk, wheat, salmon, cod, and shrimp.

3. The method of claim 1 or 2, wherein blending further comprises blending the 2 to 20 individual allergen drug substances with one or more bulking agents and/or pharmaceutically acceptable excipients.

~~4. The method of any one of claims 1 to 3, wherein the applying ionizing radiation is applying beta radiation, gamma radiation, alpha radiation, X radiation, or a combination thereof.~~

~~5~~4. The method of any one of claims 1 to ~~4~~3, wherein the applying ionizing radiation is applying one or more doses of radiation of ~~about~~ 0.15 kilograys to ~~about~~ 30 kilograys.

~~6~~5. The method of any one of claims 1 to ~~5~~4, wherein applying ionizing radiation causes ~~about~~ a 0.25 to ~~about~~ 0.5ºC per kilogray dose increase in temperature in the raw complete food allergen substance.

~~7~~6. The method of any one of claims 1 to ~~6~~5, wherein the ionizing radiation is produced by a particle emitter having an energy of ~~about~~ 0.5 MeV to ~~about~~ 10 MeV.

~~8~~7. The method of any one of claims ~~4~~1 to ~~7~~6, wherein the beta radiation is single or double sided.

~~9. The method of any one of claims 4 to 7, wherein the gamma radiation is produced by cobalt-60 or cesium-137.~~

~~10. The method of any one of claims 4 to 7, wherein the X radiation is produced using tungsten or tantalum.~~

~~11~~8. The method of any one of claims 1 to ~~4~~3, wherein applying ionization radiation comprises applying a dose of beta radiation at 5.0 kilograys, 7.5 kilograys, 15 kilograys, or more.

~~12~~9. The method of claim ~~11~~8, wherein applying the dose of beta radiation occurs more than once.

~~13~~10. The method of any one of claims 1 to ~~12~~9, wherein the method further comprises milling the mixed allergen drug product to obtain a ~~substantially~~ consistent particle size.

~~14~~11. The method of any one of claims 1 to ~~13~~10, wherein the method further comprises milling one or more than one of the raw complete food allergen substances.

~~15~~12. The method of any one of claims 1 to ~~14~~11, wherein the method further comprises milling one or more than one of the individual allergen drug substances.

~~16~~13. The method of any one of claims 1 to ~~15~~12, further comprising independently packaging each of the 2 to 20 raw complete food allergen substances into separate irradiation compatible packaging before irradiating.

~~17~~14. The method of any one of claims 1 to ~~16~~13, wherein each of the 2 to 20 individual allergen drug substances has less than about 1000 CFU/g of aerobic bacterial organisms.

~~18~~15. The method of any one of claims 1 to ~~17~~14, wherein each of the 2 to 20 individual allergen drug substances has less than about 100 CFU/g of aerobic bacterial organisms.

~~19~~16. The method of any one of claims 1 to ~~18~~17, wherein each of the 2 to 20 individual allergen drug substances has less than about 10 CFU/g of aerobic bacterial organisms.

~~20~~17. The method of any one of claims 1 to ~~19~~16, wherein each of the 2 to 20 individual allergen drug substances has less than about 10 CFU/g of *Enterobacteriaceae*.

~~21~~18. The method of any one of claims 1 to ~~20~~17, wherein each of the 2 to 20 individual allergen drug substances has less than about 100 CFU/g of yeast.

~~22~~19. The method of any one of claims 1 to ~~21~~18, wherein each of the 2 to 20 individual allergen drug substances has less than about 10 CFU/g of yeast.

~~23~~20. The method of any one of claims 1 to ~~22~~19, wherein each of the 2 to 20 individual allergen drug substances has less than about 100 CFU/g of mold.

~~24~~21. The method of any one of claims 1 to ~~23~~20, wherein each of the 2 to 20 individual allergen drug substances has less than about 10 CFU/g of mold.

~~25~~22. The method of any one of claims 1 to ~~24~~21, wherein each of the 2 to 20 individual allergen drug substances has ~~about~~ 1% to ~~about~~ 10% moisture.

~~26~~23. The method of any one of claims 1 to ~~25~~22, wherein at least one of the 2 to 20 individual allergen drug substances has ~~about~~ 4% to ~~about~~ 7% moisture.

~~27~~24. The method of any one of claims 1 to ~~26~~23, wherein each of the 2 to 20 individual allergen drug substances has ~~about~~ 0.2 to ~~about~~ 0.6 water activity.

~~28~~25. The method of any one of claims 1 to ~~27~~24, wherein each individual allergen drug substance has ~~substantially~~ the same protein integrity as compared to a corresponding raw complete food allergen substance.

~~29~~26. The method of any one of claims 1 to ~~28~~25, wherein the protein integrity of each individual allergen drug substance is determined by SDS-PAGE.

~~30~~27. The method of any one of claims 1 to ~~29~~26, wherein the protein content/potency and/or identity of each individual allergen drug substance is tested by ELISA.

~~31~~28. The method of any one of claims 1 to ~~30~~27, wherein the protein content/potency and/or identity of each raw complete food allergen substance is tested by ELISA.

~~32~~29. The method of any one of claims 1 to ~~31~~28, wherein each individual allergen drug substance has a ~~substantially~~ similar allergen effect upon administration to a patient as administration of the ~~substantially~~ same protein amount of a corresponding raw complete food allergen substance.

~~33~~30. The method of claim ~~32~~29, wherein allergen effect is measured by immune response in the patient.

~~34~~31. The method of any one of claims 1 to ~~33~~30, wherein the mixed allergen drug product comprises 6 to 20 individual allergen drug substances.

~~35~~32. The method of any one of claims 1 to ~~34~~31, wherein the mixed allergen drug product comprises ~~about~~ 0.1 mg to ~~about~~ 500 mg, by protein mass, of each individual allergen drug substance.

~~36~~33. The method of any one of claims 1 to ~~35~~32, wherein the mixed allergen drug product comprises 15 or 16 individual allergen drug substances, wherein each individual allergen drug substance is present in ~~about~~ a 2:1 to ~~about~~ 1:2 ratio, by protein weight, with another individual allergen drug substance.

~~37~~34. The method of any one of claims 1 to ~~36~~33, wherein the mixed allergen drug product comprises ~~substantially~~ equal amounts of individual allergen drug substances by total protein weight.

~~38~~35. The method of any one of claims 1 to ~~37~~34, wherein the individual raw complete food allergen substances are selected from the group consisting of hazelnut flour, cashew flour, pistachio flour, walnut flour, pecan flour, almond flour, peanut flour, sesame flour, soy flour,

hen's egg powder, bovine milk powder, wheat flour, salmon powder, cod powder, and shrimp powder.

~~39~~36. The method of any one of claims 1 to ~~38~~35, wherein the individual allergen drug substances are stable for at least 6 months.

~~40~~37. The method of any one of claims 1 to ~~39~~36, wherein the individual allergen drug substances are stable for at least one year.

~~41~~38. The method of any one of claims 1 to ~~40~~37, wherein the mixed allergen drug product is stable for at least 6 months.

~~42~~39. The method of any one of claims 1 to ~~41~~38, wherein the mixed allergen drug product is stable for at least 1 year.

~~43~~40. A method of making a sterile mixed allergen drug product ~~substantially~~ free of replication viable organisms, the method comprising:

providing 2 to 20 individual beta-irradiated allergen drug substances each ~~substantially~~ free of replication viable organisms and wherein each individual allergen drug substance retains ~~substantially~~ intact, allergenic proteins; and

blending the 2 to 20 individual allergen drug substances together, thereby obtaining the mixed allergen drug product.

~~44~~41. A method of making a mixed allergen drug product ~~substantially~~ free of replication viable organisms, the method comprising:

providing 6 to 20 different raw complete food allergen substances;

blending the 6 to 20 different raw complete food allergen substances to produce a bulk substance; and

irradiating the bulk substance with ~~ionizing~~beta radiation,

thereby obtaining the mixed allergen drug product.

~~45. A mixed allergen drug product that is substantially free of replication viable organisms prepared by the method of any one of claims 1 to 44.~~

~~46. The mixed allergen drug product of claim 45, wherein the mixed allergen drug product is for oral immunotherapeutic treatment of food allergy in a child or adult.~~

~~47. The mixed allergen drug product of claim 46, wherein mixed allergen drug product is for mixture with a food to which the child or adult is not allergic~~

~~48~~42. A method of making a sterile allergen drug product ~~substantially~~ free of replication viable organisms, the method comprising:

irradiating a raw complete food allergen substance, wherein irradiating comprises applying ~~ionizing~~ beta radiation to the raw complete food allergen substance, thereby

producing an individual allergen drug substance ~~substantially~~ free of replication viable organisms and wherein the allergen drug substance retains ~~substantially~~ intact, allergenic proteins.

~~49~~43. The method of claim ~~48~~42, wherein the raw complete food allergen substance is selected from the group consisting of hazelnut, cashew, pistachio, walnut, pecan, almond, peanut, sesame, soy, hen's egg, bovine milk, wheat, salmon, cod, and shrimp.