

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:	:	Confirmation No.: 6465
Yiming Zhao et al.	:	
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Application No.: 18/215,698	:	Art Unit: 1619
	:	
Filed: June 28, 2023	:	Examiner: T. M. Wheeler
For: SUSTAINED RELEASE FORMULATIONS USING NON-AQUEOUS EMULSIONS		

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Commissioner for Patents
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RESPONSE TO FINAL OFFICE ACTION UNDER 37 C.F.R. § 1.116

In response to the Office Action dated 2 December 2025 having a three-month shortened statutory period for response set to expire 2 March 2026, Applicant respectfully requests reconsideration of the above-identified application in view of the following:

Amendments to the Claims begin on page 2 of this paper.

Remarks begin on page 9 of this paper.

AMENDMENT TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

1. (Currently amended) A method of producing encapsulated protein microparticles comprising:

combining spray-dried protein powder and a polymer into a hydrocarbon solvent to form a non-aqueous first solution;

adding the first solution to a second solution, wherein the second solution comprises a fluorocarbon liquid and a fluorosurfactant;

agitating the combined solutions to form a non-aqueous emulsion comprising multiple emulsion hydrocarbon droplets in the fluorocarbon liquid;

removing the hydrocarbon solvent; and

removing the fluorocarbon liquid to isolate the encapsulated protein microparticles, wherein the encapsulated protein microparticles comprise protein encapsulated within a matrix of polymer, wherein the encapsulated protein microparticles are sustained release encapsulated protein microparticles, and wherein the encapsulated protein microparticles comprise a polymer cortex devoid of pores or channels.

2. (Withdrawn) The method of claim 1, wherein the encapsulated protein microparticles comprise a single core-shell structure.

3. (Previously presented) The method of claim 1, wherein at least one of the encapsulated protein microparticles comprise multiple cores dispersed within the polymer.

4. (Previously presented) The method of claim 1, wherein the encapsulated protein microparticles comprise microparticles comprising a combination of a single core-structures encapsulated by a polymer and microparticles comprising multi-core structures encapsulated by a polymer.

5. (Original) The method of claim 1, wherein the fluorocarbon liquid comprises a perfluoro C5-C18 compound.

6. (Currently amended) The method of claim 1, wherein the hydrocarbon solvent is selected from the group consisting of dichloromethane, chloroform, toluene, ethyl acetate, tetrahydrofuran, or a combination thereof.

7. (Currently amended) The method of claim 1, wherein the fluorocarbon liquid comprises 1,1,2,2,3,3,4,4,4-nonafluoro-N,N-bis(1,1,2,2,3,3,4,4,4-nonafluorobutyl)butan-1-amine.

8. (Original) The method of claim 1, wherein the hydrocarbon solvent comprises dichloromethane, ethyl acetate, or a combination thereof.

9. (Currently amended) The method of claim 1, wherein the fluorocarbon liquid comprises hydrofluoroether.

10. (Original) The method of claim 1, wherein the fluorosurfactant comprises Perfluoropolyether-b-Polyethylene glycol-b- Perfluoropolyether.

11. (Original) The method of claim 1, wherein the polymer comprises polyorthoester (POE).

12. (Original) The method of claim 1, wherein the polymer is selected from the group consisting of polylactic acid and poly(lactic-co-glycolic acid).

13. (Currently amended) The method of claim 1, wherein the protein is an antibody or antigen binding fragment thereof, a fusion protein, or a recombinant protein.

14. (Currently amended) The method of claim 1, wherein the protein is a VEGF Trap protein.
15. (Withdrawn) The method of claim 14, wherein the protein is a truncated form of VEGF Trap protein.
16. (Previously presented) The method of claim 1, wherein the encapsulated protein microparticles have a diameter of 1 to 200 μm .
17. (Original) The method of claim 1, wherein the protein powder comprises particles comprising a diameter of 0.5 to 20 μm of micronized protein.
18. (Original) The method of claim 1, wherein protein powder is micronized by spray-drying, electrospray drying, reversible precipitation, spray freezing, microtemplating, or a combination thereof.
19. (Original) The method of claim 1, wherein the emulsion is formed using homogenization, vortexing, sonication, cavitation, agitation, or a combination thereof.
20. (Original) The method claim 1, wherein removing the hydrocarbon solvent while stirring the combined solutions.
21. (Previously presented) The method of claim 20, wherein the hydrocarbon solvent is removed under vacuum to harden the encapsulated protein microparticles.
22. (Original) The method of claim 1, wherein the hydrocarbon solvent is removed by evaporation.
23. (Withdrawn) The method of claim 1, wherein the fluorocarbon liquid is removed by filtration optionally under vacuum.

24. (Original) The method of claim 22, wherein a hydrofluoroether is used as a cosolvent to extract the hydrocarbon.

25.- 27. (Cancelled).

28. (Currently amended) A method for producing encapsulated protein microspheres comprising:

combining

(1) a dispersed phase comprising 1.0 to 30.0% w/w of total solid spray dried-protein suspended in a hydrocarbon solution, wherein the hydrocarbon solution comprises 5.0 to 35% w/v POE, into

(2) a continuous phase to form emulsion droplets of the dispersed phase, wherein the continuous phase comprises a fluorocarbon solution comprising 0.1 to 5.0% w/v fluorosurfactant;

hardening the emulsion droplets by removing the hydrocarbon liquids to form hardened encapsulated protein microspheres, wherein the encapsulated protein microspheres are sustained release encapsulated protein microspheres, wherein the encapsulated protein microspheres comprise a polymer cortex devoid of pores or channels.

29. (Original) The method of claim 28, wherein the non-aqueous emulsion is stirred, and the hydrocarbon solution is removed by evaporation under ambient atmospheric pressure or under vacuum while stirred.

30. (Previously presented) The method of claim 29, wherein the hardened encapsulated protein microspheres are harvested by vacuum filtration.

31. (Currently amended) A method for producing encapsulated protein microparticles, comprising:

combining a hydrocarbon solution comprising dissolved polymer and spray-dried protein powder to produce a dispersed phase;

combining the dispersed phase with a continuous phase to produce emulsion droplets of the dispersed phase in the continuous phase, wherein the continuous phase comprises a fluorocarbon liquid and 0.1 to 5.0% w/v of a fluorosurfactant; and

harvesting the encapsulated protein microparticles, wherein the encapsulated protein microparticles are sustained release encapsulated protein microparticles, wherein the encapsulated protein microparticles comprise a polymer cortex devoid of pores or channels.

32. (Previously presented) The method of claim 31, wherein the spray-dried protein is an antibody, recombinant protein, fusion protein, or a fragment of the spray-dried protein thereof.

33. (Currently amended) The method of claim 31, wherein the spray-dried protein is a VEGF Trap protein or a truncated VEGF Trap protein.

34. (Original) The method of claim 31, wherein the hydrocarbon solution is selected from the group consisting of dichloromethane, chloroform, toluene, ethyl acetate, tetrahydrofuran, or a combination thereof.

35. (Original) The method of claim 31, wherein the fluorocarbon liquid comprises trifluoromethyl)bis(1,1,2,2,3,3,4,4,4-nonafluorobutyl)amine.

36. (Currently amended) The method of claim 31, wherein the encapsulated protein microparticles are hardened by removing the hydrocarbon solution while stirring by evaporation or under vacuum.

37. (Previously presented) The method of claim 36, further comprises harvesting the hardened encapsulated protein microparticles.

38. -43. (Cancelled).

44. (Original) The method of claim 9, wherein the hydrofluoroether comprises 4-Ethoxy-1,1,1,2,2,3,3,4,5,6,6,6-didecafluoro-5-(trifluoromethyl)hexane.

45. (Previously presented) A method for producing encapsulated protein microparticles comprising:

- combining a first solution comprising a spray-dried protein powder and a polymer in a hydrocarbon solvent with a second solution comprising a fluorocarbon solvent and a fluorosurfactant;
- agitating the combined solutions to produce an emulsion;
- removing the hydrocarbon solvent under vacuum while stirring the combined solutions to harden the encapsulated protein microparticles;
- harvesting the encapsulated protein microparticles;
- optionally washing the encapsulated protein microparticles;
- and drying the encapsulated protein microparticles, wherein the encapsulated protein microparticles comprises a polymer cortex devoid of pores or channels.

46. (Original) The method of claim 45, wherein the hydrocarbon solvent is selected from the group consisting of dichloromethane, chloroform, toluene, ethyl acetate, tetrahydrofuran, acetonitrile, ethanol, methanol, propanol, dimethylformamide, dimethyl sulfoxide or a combination thereof.

47. (Original) The method of any one of claim 45, wherein the fluorocarbon solvent comprises trifluoromethylbis(1,1,2,2,3,3,4,4,4-nonafluorobutyl)amine.

48. (Original) The method of claim 45, wherein the polymer comprises POE, polylactic acid, poly(lactic-co-glycolic acid), or a combination thereof.

49. (Previously presented) The method of claim 45, wherein the encapsulated protein microparticles comprise a polymer cortex and a hollow core.

50. (Cancelled).

51. (Currently amended) The method of claim 45, wherein [[the]] a diameter of the encapsulated protein microparticles is tuned to a desired diameter by changing the hydrocarbon solvent, agitation speed, polymer concentration, or a combination thereof.

52. (Cancelled).

REMARKS

After entry of the foregoing, claims 1-24, 28-37, 43-49 and 51 are pending in the application. Claims 25-27, 38-42, 50 and 52 were previously canceled and claims 2, 15, and 23 were withdrawn from consideration.

Claims 1, 6, 7, 9, 13, 14, 28, 31, 33, 36 and 51 are amended to address informalities. No new matter is added by these amendments. Accordingly, entry of the amendments and reconsideration of the application are respectfully requested.

The arguments and contentions presented in the Office Action should not be construed as any acquiescence or agreement by Applicant with the stated reasoning therein regardless of whether or not the following remarks specifically address any particular argument or contention from the Office Action. Furthermore, although certain distinctions between the claims of the present application and the cited references are addressed below, these distinctions are not necessarily exhaustive.

Allowable Subject Matter

Applicant appreciates the indication that claims 3-12, 16-22, 24, 29-32, 34-37 and 43-49 are allowed and that claims 1, 28, 31 contain allowable subject matter. As explained below, amendments to certain claims were made to expedite prosecution and place the application in condition for immediate allowance.

Claim Objections

Claims 1, 28 and 31 stand objected to based on informalities. As recommended by the Office on pages 3-4 of the Office Action, claims 1, 28 and 31 were amended to address the informalities. Accordingly, reconsideration and withdrawal of the objections to these claims are solicited.

Claim Rejection Under 35 U.S.C. § 112

Claims 13, 14, 33 and 50 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite. Claims 13, 14, 33 and 50 were amended to clarify the subject matter therein. Accordingly, reconsideration and withdrawal of the rejections of these claims are solicited.

Rejoinder of Withdrawn Claims

Claims 2, 15, and 23 stand withdrawn. As each of these claims depend, directly or indirectly, on independent claim 1, and since claim 1 should be in condition for allowance, it is respectfully requested that claims 2, 15, and 23 be rejoined and allowed in the application.

Conclusion

In view of the foregoing, Applicant submits that this application should be allowed and the case passed to issue. If there are any questions or issues raised by this paper or the application in general, a telephone call to the undersigned would be appreciated to expedite prosecution of the application.

To the extent necessary, a petition for an extension of time under 37 C.F.R. § 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 50-2036 and please credit any excess fees to such deposit account.

Respectfully submitted,

Dated: ___, 2025

/Draft/

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