CLAIMS

1. A method of manufacturing core-shell microparticles having a core comprising a hydrogel material and a shell comprising a hydrophobic polymer immiscible with the hydrogel material, the method comprising:-

   a) dissolving a hydrogel-forming agent in an aqueous solution comprising an osmolyte to form a first solution;

   b) dissolving a hydrophobic polymer in an organic solvent comprising a first surfactant to form a second solution;

   c) dispersing the first solution into the second solution to form a first emulsion;

   d) dispersing the first emulsion into an aqueous solution comprising a second surfactant and a reagent capable of effecting gelation of the hydrogel-forming agent to form a second emulsion; and

   e) extracting the organic solvent from the second emulsion by solvent evaporation, wherein concurrently, (i) the reagent capable of effecting gelation of the hydrogel-forming agent penetrates through the second solution and effects gelation of the hydrogel-forming agent to form hydrogel microparticles, and (ii) the hydrophobic polymer precipitates to form a shell around each of the hydrogel microparticles.

2. The method according to claim 1, wherein the hydrogel-forming agent comprises a physically cross-linkable polymer, a chemically cross-linkable polymer, or mixtures thereof.

3. The method according to claim 2, wherein the physically cross-linkable polymer is selected from the group consisting of alginate, pectin, furcellaran, carageenan, chitosan, derivatives thereof, copolymers thereof, and mixtures thereof.

4. The method according to claim 2, wherein the chemically cross-linkable polymer is selected from the group consisting of starch, gellan gum, dextran, hyaluronic acid,

poly(ethylene oxides), polyphosphazenes, derivatives thereof, copolymers thereof, and mixtures thereof.

5. The method according to any one of claims 1 to 4, wherein the hydrogel-forming agent comprises or consists essentially of sodium alginate.

6. The method according to any one of claims 1 to 5, wherein the osmolyte is selected from the group consisting of sodium chloride, potassium chloride, sodium bromide, sodium citrate, sodium lactate, sodium hydroxide, sodium iodide, sodium carbonate, sodium hydrogen carbonate, sodium nitrate, sodium fluoride, sodium sulfate, potassium carbonate, potassium citrate, potassium lactate, potassium hydrogen carbonate, potassium bromide, potassium hydroxide, potassium iodide, potassium nitrate, potassium sulfate, cesium chloride, rubidium chloride, lithium chloride, and mixtures thereof.

7. The method according to any one of claims 1 to 6, wherein the osmolyte comprises or consists essentially of sodium chloride.

8. The method according to any one of claims 1 to 7, wherein the amount of hydrogel-forming agent in the first solution is between about 1 % (w/v) to about 10 % (w/v).

9. The method according to any one of claims 1 to 8, wherein the amount of hydrogel-forming agent in the first solution is about 4.5 % (w/v).

10. The method according to any one of claims 1 to 9, wherein the concentration of osmolyte in the first solution is between about 0.5 M to about 2 M.

11. The method according to any one of claims 1 to 10, wherein the concentration of osmolyte in the first solution is about 1.35 M.

12. The method according to claim 1, wherein the hydrophobic polymer immiscible with the hydrogel-forming material is selected from the group consisting of poly-lactic-co-

glycolic acid (PLGA), poly-l-lactide (PLLA), poly-caprolactone (PCL), polyglycolide (PGA), derivatives thereof, copolymers thereof, and mixtures thereof.

13. The method according to any one of claims 1 to 12, wherein the hydrophobic polymer immiscible with the hydrogel-forming material is a biodegradable polymer or a biocompatible polymer.

14. The method according to any one of claims 1 to 13, wherein the organic solvent is selected from the group consisting of dichloromethane (DCM), dimethylformamide (DMF), tetrahydrofuran (THF), methyl ethyl ketone (MEK), chloroform, pentane, benzene, benzyl alcohol, carbon tetrachloride, ethyl acetate, acetone, acetonitrile, dimethyl sulfoxide, propylene carbonate, and mixtures thereof.

15. The method according to any one of claims 1 to 14, wherein the organic solvent comprises or consists essentially of dichloromethane.

16. The method according to any one of claims 1 to 15, wherein the first surfactant comprises or consists essentially of a hydrophobic surfactant.

17. The method according to claim 16, wherein the hydrophobic surfactant is selected from the group consisting of sorbitan ester, sorbitan monoester, sorbitan trioleate, sorbitan tristearate, sorbitan sesquioleate, sorbitan monolaurate, sorbitan monopalmitate, sorbitan monostearate, sorbitan monooleate, glycerol monooleate, glycerol monostearate, PEO/PPO copolymers, derivatives thereof, and mixtures thereof.

18. The method according to any one of claims 1 to 17, wherein the first surfactant comprises or consists essentially of sorbitan monooleate.

19. The method according to any one of claims 1 to 18, wherein the amount of hydrophobic polymer in the second solution is between about 1 % (w/v) to about 30 % (w/v).

20. The method according to any one of claims 1 to 19, wherein the amount of hydrophobic polymer in the second solution is about 10 % (w/v).

21. The method according to any one of claims 1 to 20, wherein the amount of first surfactant in the second solution is between about 0.1 % (w/v) to about 5 % (w/v).

22. The method according to any one of claims 1 to 21, wherein the amount of first surfactant in the second solution is about 1 % (w/v).

23. The method according to any one of claims 1 to 22, wherein dispersing the first solution into the second solution is carried out under continuous stirring.

24. The method according to any one of claims 1 to 23, wherein the second surfactant comprises or consists essentially of a hydrophilic surfactant.

25. The method according to claim 24, wherein the hydrophilic surfactant is selected from the group consisting of amphoteric surfactant, anionic surfactant, cationic surfactant, nonionic surfactant, and mixtures thereof.

26. The method according to claim 25, wherein the amphoteric surfactant is selected from the group consisting of dodecyl betaine, sodium 2,3-dimercaptopropanesulfonate monohydrate, dodecyl dimethylamine oxide, cocamidopropyl betaine, 3-[N,N-dimethyl(3-palmitoylaminopropyl)ammonio]-propanesulfonate, coco ampho glycinate, and mixtures thereof.

27. The method according to claim 25, wherein the anionic surfactant is selected from the group consisting of sodium dodecyl sulfate (SDS), sodium pentane sulfonate, dehydrocholic acid, glycolithocholic acid ethyl ester, ammonium lauryl sulfate and other alkyl sulfate salts, sodium laureth sulfate, alkyl benzene sulfonate, soaps, fatty acid salts, and mixtures thereof.

28. The method according to claim 25, wherein the cationic surfactant is selected from the group consisting of cetyl trimethylammonium bromide (CTAB), dodecylethyldimethylammonium bromide (D12EDMAB), didodecyl ammonium bromide (DMAB), cetylpyridinium chloride (CPC), polyethoxylated tallow amine (POEA), hexadecyltrimethylammonium p-toluenesulfonate, benzalkonium chloride (BAC), benzethonium chloride (BZT), and mixtures thereof.

29. The method according to claim 25, wherein the nonionic surfactant is selected from the group consisting of poloaxamers, alkyl poly(ethylene oxide), diethylene glycol monohexyl ether, polyvinyl alcohol (PVA), copolymers of poly(ethylene oxide) and poly(propylene oxide), hexaethylene glycol monohexadecyl ether, alkyl polyglucosides, digitonin, ethylene glycol monodecyl ether, cocamide MEA, cocamide DEA, cocamide TEA, fatty alcohols, and mixtures thereof.

30. The method according to any one of claims 1 to 29, wherein the second surfactant comprises or consists essentially of polyvinyl alcohol (PVA).

31. The method according to any one of claims 1 to 30, wherein the reagent capable of effecting gelation of the hydrogel-forming agent comprises or consists essentially of a salt.

32. The method according to claim 31, wherein the salt comprises a multivalent cation.

33. The method according to claim 32, wherein the multivalent cation is selected from the group consisting of calcium, magnesium, aluminum, barium, and strontium.

34. The method according to any one of claims 1 to 33, wherein the reagent capable of effecting gelation of the hydrogel-forming agent comprises or consists essentially of calcium (II) chloride.

35. The method according to any one of claims 1 to 34, wherein the aqueous solution in step (d) further comprises an osmolyte.

36. The method according to claim 35, wherein the osmolyte comprises or consists essentially of sodium chloride.

37. The method according to claim 35 or 36, wherein the concentration of osmolyte in the aqueous solution in step (d) is between about 0.2 M to about 2 M.

38. The method according to any one of claims 35 to 37, wherein the concentration of osmolyte in the aqueous solution in step (d) is about 0.6 M.

39. The method according to any one of claims 1 to 38, wherein the amount of second surfactant in the aqueous solution in step (d) is between about 0.01 % (w/v) to about 5 % (w/v).

40. The method according to any one of claims 1 to 39, wherein the amount of second surfactant in the aqueous solution in step (d) is about 0.5 % (w/v).

41. The method according to any one of claims 1 to 40, wherein the concentration of reagent capable of effecting gelation of the hydrogel-forming agent in the aqueous solution in step (d) is between about 10 mM to about 100 mM.

42. The method according to any one of claims 1 to 41, wherein the concentration of reagent capable of effecting gelation of the hydrogel-forming agent in the aqueous solution in step (d) is about 50 mM.

43. The method according to any one of claims 1 to 42, wherein dispersing the first emulsion into the aqueous solution is carried out under continuous stirring.

44. The method according to claim 43, wherein the continuous stirring is carried out at a speed of between about 300 rpm to about 2000 rpm.

45. The method according to claim 43 or 44, wherein the continuous stirring is carried out for a time period of between about 1 hour to about 12 hours.

46. The method according to any one of claims 43 to 45, wherein the continuous stirring is carried out for a time period of about 3 hours.

47. The method according to any one of claims 43 to 46, wherein gelation of the hydrogel-forming agent to form hydrogel microparticles is carried out via ionic gelation.

48. The method according to any one of claims 1 to 47, wherein the mean diameter of the hydrogel microparticles formed is between about 100 μm to about 800 μm.

49. The method according to any one of claims 1 to 48, wherein the hydrogel microparticles are essentially monodisperse.

50. The method according to any one of claims 1 to 49, further comprising adding a hydrophilic active compound to be encapsulated to the hydrogel-forming agent in step (a).

51. The method according to claim 50, wherein the hydrophilic active compound is selected from the group consisting of a drug, a protein, an enzyme, an antibody, a peptide, a growth factor, an organic molecule, a nucleic acid, a cell, a pesticide, a dye, a chemical indicator, and a fertilizer.

52. The method according to claim 51, wherein the hydrophilic active compound comprises or consists essentially of a drug.

53. The method according to claim 51 or 52, wherein the drug is selected from the group consisting of a vaccine, a protein, an inorganic molecule and mixtures thereof.

54. The method according to any one of claims 51 to 52, wherein the drug comprises or consists essentially of metoclopramide HCl.

55. The method according to any one of claims 1 to 54, further comprising at least one centrifugation and at least one washing step after extracting the organic solvent.

56. The method according to any one of claims 1 to 55, further comprising lyophilizing the core-shell microparticles formed in the method.

57. The method according to any one of claims 1 to 56, wherein the core-shell microparticles have a mean diameter of between about 150 μm to about 1000 μm.