et al. have also described the grafting of the polymethacrylic acid onto chitosan nanoparticles as delivery systems for paclitaxel [24(a)]. Hirosue et al. have described in international patent publication WO 2010/084060 a polymer having a starch backbone onto which methylacrylate monomer was grafted by atom transfer radical polymerization (ATRP) subsequent to modification of backbone hydroxyl groups by a linker such as 2-bromo isobutyryl bromide. Nanoparticles were formulated with the starch polymer by an emulsion diffusion method.

Summary

In one aspect, there is provided a nanoparticle comprising: a first polymer; a second polymer grafted to the first polymer; and a polyethoxylated moiety covalently bound to the second polymer.

Another aspect provides a composition comprising a plurality of nanoparticles as disclosed herein, and further comprising a pharmaceutically active agent.

A further aspect relates to a composition comprising a plurality of nanoparticles as disclosed herein, and further comprising a signal molecule, a biological agent, or a pharmaceutically active agent.

Another aspect relates to a nanoparticle comprising: a first polymer comprising a polysaccharide; a second crosslinked polymer comprising poly(methacrylic acid) grafted to the first polymer; and a polysorbate comprising a (C9-C31)R-C(O)O- group covalently bound to the second polymer by a C-C bond between the carbon backbone of the second polymer and the R group.

Yet a further aspect relates a nanoparticle comprising: a first polymer comprising a polysaccharide; and a second crosslinked polymer comprising an alkylaminoalkyl ester of methacrylic acid, or a monomer comprising a vinyl group and one carboxyl group, grafted to the first polymer, wherein the second polymer is crosslinked.

In another aspect, there is provided a method of producing a nanoparticle, the method comprising the steps of:

(a) solubilising a polymer in a liquid solution;

(b) providing a polymerizable monomer comprising a carboxylic acid side group or an alkylaminoalkyl ester side group;

(c) graft polymerizing the monomer to form polymeric chains on the solubilised polymer,

(d) providing ethoxylated molecules having a functional group reactive with the forming chains, wherein:

step (c) is conducted in the presence of the ethoxylated molecules to covalently link the ethoxylated molecules to the polymeric chains.

Another aspect provides a method of producing a nanoparticle for delivery of a biological agent, comprising the method as disclosed above, wherein the agent is covalently linked to the polymer of step (a).

Still another aspect relates to a method of producing nanoparticles for delivery of a biological agent, comprising dispersing the agent and nanoparticles obtained by the method disclosed above in a liquid medium to incorporate the agent into the nanoparticles.

Yet another aspect provides a method of producing a nanoparticle, the method comprising the steps of:

(a) solubilising a polymer in a liquid solution;

(b) providing a polymerizable monomer comprising an alkylaminoalkyl ester side group or a monomer comprising a vinyl group and one carboxyl group;

(c) providing a crosslinker; and

(d) graft polymerizing the monomer to form polymeric chains on the solubilised polymer to form the nanoparticle.

Description of the Invention

The invention described herein includes a method for the synthesis of nanoparticles.

Nanoparticles of the invention include a polymer backbone having grafted thereto polymeric chains containing carboxyl groups or amino groups. Covalently linked as part of the nanoparticle are polyethoxylate moieties that present on the exterior surface of the nanoparticles.

Nanoparticles of the invention are especially useful as carriers for e.g., therapeutics and/or signal molecules.

Preferably, nanoparticles of the invention are formed in aqueous solution in a "one-pot" synthetic procedure in which a monomer graft polymerizes onto a backbone polymer and polyethoxylate moieties participate in the polymerization to become covalently incorporated as part of the nanoparticle.

In disclosed embodiments, the polymer backbone is provided by starch, the monomer is methacrylic acid (MAA), diethylaminoethyl methacrylate (DEAEM), and the polyethoxylated moieties are provided by polysorbate 80 (Tween® 80).

Nanoparticles of the invention are particularly useful as a carrier nanoparticle. The cargo or payload of the carrier can be a therapeutic agent such as a drug, a signal molecule such as a
6 fluorophore e.g., fluoresceinamine, gadolinium, etc.

A therapeutic can be loaded to the nanoparticle after its formation. Alternatively, and especially where the particle cargo includes a signal or other molecule that is not intended to be dislodged from the carrier particle while present in a patient, the polymer can be functionalized with the molecule by covalent attachment thereto before nanoparticle production. In disclosed examples, an organic chelator, diethylenetriaminepentaacetic dianhydride
12 (DTPA bisanhydride), was covalently linked to nanoparticles. In one example, DTPA was covalently attached to a polysaccharide polymer backbone prior to production of the nano-

CLAIMS

1. A nanoparticle comprising:

- a first polymer;
- a second polymer grafted to the first polymer; and
- a polyethoxylated moiety covalently bound to the second polymer.

2. The nanoparticle of claim 1, wherein the second polymer comprises polymerized vinyl groups having about one carboxyl group per two carbons of the backbone of the second polymer.

3. The nanoparticle of claim 2, wherein the second polymer is poly(methacrylic acid).

4. The nanoparticle of any one of claims 1 to 3, wherein the polyethoxylated moiety is a sorbitan having a R(C9-C31)-C(O)O-group wherein the sorbitan is linked to the second polymer through a C-C covalent bond of the R-group.

5. The nanoparticle of claim 4, wherein the first polymer comprises starch.

6. The nanoparticle of claim 5, wherein the second polymer is crosslinked.

7. A composition comprising a plurality of nanoparticles of any one of claims 1 to 6, further comprising a pharmaceutically active agent.

8. A composition comprising a plurality of nanoparticles of any of claims 1 to 6, further comprising a signal molecule, a biological agent, or a pharmaceutically active agent.

9. The composition of claim 8, further comprising a pharmaceutically active agent.

10. A nanoparticle comprising:

- a first polymer comprising a polysaccharide;
- a second crosslinked polymer comprising poly(methacrylic acid) grafted to the first polymer; and
- a polysorbate comprising a (C9-C31)R-C(O)O- group covalently bound to the second polymer by a C-C bond between the carbon backbone of the second polymer and the R group.

11. The nanoparticle of claim 10, wherein the polysorbate comprises the groups $-O(CH_2CH_2O)_w-C(O)(C17)R$, $HO(CH_2CH_2O)_x-$, [[-]] $HO(CH_2CH_2O)_y-$, [[-]] $HO(CH_2CH_2O)_z-$, wherein $w+x+y+z = 20$.

12. The nanoparticle of claim 10 or 11, wherein the first polymer comprises starch.

13. The nanoparticle of any one of claims 10 to 12, wherein the molar ratio of the monomeric unit of the polysaccharide to the monomeric methacrylate units of the poly(methacrylic acid) is between 0.2 and 8.0.

14. The nanoparticle of any one of claims 10 to 13, wherein the molar ratio of the polysorbate and the monomeric methacrylate units of the poly(methacrylic acid) is between 0.002 and 0.03.

15. A nanoparticle comprising:

- a first polymer comprising a polysaccharide; and
- a second crosslinked polymer comprising an alkylaminoalkyl ester of methacrylic acid, or a monomer comprising a vinyl group and one carboxyl group, grafted to the first polymer, wherein the second polymer is crosslinked.

16. The nanoparticle of claim 15, wherein the second polymer is polymerized diethylaminoethyl methacrylic acid.

17. The nanoparticle of claim 15, wherein second polymer comprises polymerized methacrylic acid.

18. A method of producing a nanoparticle, the method comprising the steps of:

(a) solubilising a polymer in a liquid solution;

(b) providing a polymerizable monomer comprising a carboxylic acid side group or an alkylaminoalkyl ester side group;

(c) graft polymerizing the monomer to form polymeric chains on the solubilised polymer,

(d) providing ethoxylated molecules having a functional group reactive with the forming chains, wherein:

step (c) is conducted in the presence of the ethoxylated molecules to covalently link the ethoxylated molecules to the polymeric chains.

19. The method of claim 18, wherein the liquid solution comprises a hydroxylic solvent.

20. The method of claim 18, wherein the polymer of step (a) comprises starch.

21. The method of claim 18, wherein the ethoxylated molecules are a polyethoxylated sorbitan having a R(C9-C31)-C(O)O-group wherein the sorbitan is linked to the second polymer through a C-C covalent bond of the R(C9-C31)-C(O)O-group during the step of polymerizing.

22. A method of producing a nanoparticle for delivery of a biological agent, comprising the method of any one of claims 18 to 21, wherein the agent is covalently linked to the polymer of step (a).

23. A method of producing nanoparticles for delivery of a biological agent, comprising dispersing the agent and nanoparticles obtained by the method of any one of claims 18 to 22 in a liquid medium to incorporate the agent into the nanoparticles.

24. A method of producing a nanoparticle, the method comprising the steps of:

(a) solubilising a polymer in a liquid solution;

(b) providing a polymerizable monomer comprising an alkylaminoalkyl ester side group or a monomer comprising a vinyl group and one carboxyl group;

(c) providing a crosslinker; and

(d) graft polymerizing the monomer to form polymeric chains on the solubilised polymer to form the nanoparticle.

25. The method of claim 24, wherein the polymer of step (a) comprises starch.

26. The method of claim 25, wherein the monomer is diethylaminoethyl methacrylic acid.

27. The method of claim 25, wherein the monomer is methacrylic acid.

CLAIMS

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

(a) solubilising a polymer in a liquid solution;

(b) providing a polymerizable monomer comprising a carboxylic acid side group;

(c) graft polymerizing the monomer to form polymeric chains on the solubilised polymer,

(d) providing ethoxylated molecules having a functional group reactive with the forming chains, wherein:

step (c) is conducted in the presence of the ethoxylated molecules to covalently link the ethoxylated molecules to the polymeric chains.

2. The method of claim 1, wherein the liquid solution comprises a hydroxylic solvent.

3. The method of claim 2, wherein the hydroxylic solvent comprises water.

4. The method of claim 1, 2 or 3, wherein the polymer is a polyhydroxyl polymer having a degree of substitution between 0.05 and 3 per unit of the polymer, the monomer includes an alkenyl group, and the graft polymerizing step is conducted in the presence of a cross-linking agent.

5. The method of claim 4, wherein the polyhydroxyl polymer has a degree of substitution between 0.5 and 3.

6. The method of claim 4, wherein the polyhydroxyl polymer has a degree of substitution between 2 and 3.

7. The method of claim 4, wherein the polyhydroxyl polymer comprises a polysaccharide having a degree of substitution between 0.5 and 3.

8. The method of claim 7, wherein the polyhydroxyl polymer comprises glucose.

9. The method of claim 7, wherein the polysaccharide comprises starch.

10. The method of claim 4, 5 or 6, wherein the monomer of step (c) is present in an amount between 1 and 20 times the amount of the cross-linking agent (mol/mol).

11. The method of claim 10, wherein the monomer of step (c) is present in an amount between 3 and 6 times the amount of the cross-linking agent.

12. The method of any one of claims 4 to 11, wherein the step of polymerizing is a free radical graft polymerizing conducted in the presence of a free radical initiator.

13. The method of any one of claims 4 to 12, wherein the initiator is substantially free of transition metals.

14. The method of any one of claims 4 to 12, wherein the initiator is persulfate or functional equivalent thereof.

15. The method of any one of claims 1 to 14, wherein the ethoxylate groups of the ethoxylated molecules terminate in free hydroxyl groups.

16. The method of any one of claims 1 to 15, wherein the ethoxylated molecules include an alkenyl group which chemically reacts to covalently link the surfactant molecules to the polymeric chains.

17. The method of claim 16, wherein the ethoxylated molecules are a polyethoxylated sorbitan having a R(C9-C31)-C(O)O-group wherein the sorbitan is linked to the second polymer through a C-C covalent bond of the R(C9-C31)-C(O)O-group during the step of polymerizing.

18. The method of claim 17, wherein the sorbitan is a polysorbate in which the total number of oxyethylene units is at least 10.

19. The method of claim 15, wherein the total number of oxyethylene units is 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30 or 32.

20. The method of claim 17, 18 or 19, wherein said R(C9-C31)-C(O)O-group contains at least one C-C unsaturation which reacts to form the C-C covalent bond in the step of polymerizing.

21. The method of claim 20, wherein the polyethoxylated molecule is polysorbate 80.

22. The method of any one of claims 1 to 21, wherein the amount of polymer and the amount of monomer of step (c) are selected to produce a nanoparticle in which the molar ratio of monomeric units in the polymeric chains to monomeric units of the polymer is between 0.1 and 10.

23. The method of claim 22, wherein the amount of polymer and the amount of monomer of step (c) are selected to produce a nanoparticle in which the molar ratio of monomeric units in the polymeric chains to monomeric units of the polymer is between 0.3 and 7.0.

24. The method of claim 22, wherein the amount of polymer and the amount of monomer of step (c) are selected to produce a nanoparticle in which the molar ratio of monomeric units in the polymeric chains to monomeric units of the polymer is between 1 and 5.0.

25. The method of any one of claims 1 to 24, wherein the amount of ethoxylate molecule and the amount of monomer in step (c) are selected to produce a nanoparticle in which the molar ratio of ethoxylate molecules to monomeric units is between 0.0005 and 1.

26. The method of claim 25, wherein the amount of ethoxylate molecule and the amount of monomer in step (c) are selected to produce a nanoparticle in which the molar ratio of ethoxylate molecules to monomeric units is between 0.003 and 0.01.

27. The method of any one of claims 1 to 26, wherein the polymerizing step is conducted in the presence of a surfactant.

28. The method of claim 27, wherein the surfactant is an anionic surfactant.

29. A method of producing a nanoparticle for delivery of a biological agent, comprising the method of any one of claims 1 to 28, wherein the agent is covalently linked to the polymer of step (a).

30. The method of claim 29, wherein the polymer is a polyyhroxylated polymer and the agent is covalently linked to the polymer by substitution of a hydroxyl hydrogen atom thereof.

31. The method of claim 29, wherein the agent comprises an organic moiety capable of complexing a metal.

32. The method of claim 31, further comprising forming the metal-organic moiety complex.

33. The method of claim 31 or 32, wherein the metal is selected to provide a signal in magnetic resonance imaging.

34. The method of claim 33, wherein the metal is Gd^{+3}.

35. The method of any one of claims 1 to 34, wherein the amount of monomer of step (c) is sufficiently high that the absolute value of the zeta potential, measured at pH 7.4 and an ionic strength of 10 mM, of an aqueous solution of the nanoparticles produced is at least 15 mV.

36. A method of producing nanoparticles for delivery of a biological agent, comprising dispersing the agent and nanoparticles obtained by the method of any one of claims 1 to 35 in a liquid medium to incorporate the agent into the nanoparticles.

37. A method of producing nanoparticles for delivery of a biological agent, comprising covalently linking to nanoparticles produced by the method of any one of claims 1 to 35 and the agent to said carboxylic acid groups of the polymeric chains of the nanoparticles.

38. A method of producing a carrier nanoparticle comprising the steps of:

(i) solubilising a polymer in an aqueous solution;

(ii) providing a polymerizable monomer comprising a carboxylic acid side group;

(iii) graft polymerizing the monomer to form polymeric chains on the solubilised polymer,

(iv) providing polyethoxylated molecules having a functional group reactive with the forming chains, wherein:

polymerizing step (ii) is conducted in the presence of the polyethoxylated molecules to covalently link the polyethoxylated molecules to the forming chains and the polymerized product forms into the nanoparticle with polyethoxylated moieties on the exterior of the nanoparticle.

39. A nanoparticle comprising:

- a first polymer;
- a second polymer grafted to the first polymer; and
- a polyethoxylated moiety covalently bound to the second polymer.

40. The nanoparticle of claim 39, wherein the second polymer comprises polymerized vinyl groups having about one carboxyl group per two carbons of the backbone of the second polymer.

41. The nanoparticle of claim 39, wherein the second polymer is a polyalkenyl polymer.

42. The nanoparticle of claim 41, wherein the polyalkenyl polymer is a polyacrylic acid.

43. The nanoparticle of claim 42, wherein the polyacrylic acid is poly(methacrylic acid).

44. The nanoparticle of any one of claims 39 to 43, wherein the polyethoxylated moiety is a sorbitan having a R(C9-C31)-C(O)O-group wherein the sorbitan is linked to the second polymer through a C-C covalent bond of the R-group.

45. The nanoparticle of any one of claims 39 to 44, wherein the first polymer comprises a polyhydroxyl polymer.

6 46. The nanoparticle of claim 45, wherein the polyhydroxyl polymer comprises a polysaccharide having a degree of substitution between 0.05 and 3.

47. The nanoparticle of claim 46, wherein the polysaccharide comprises starch.

48. The nanoparticle of claim 47, wherein the second polymer is crosslinked.

49. A composition comprising a plurality of nanoparticles of any one of claims 39 to 48, further comprising a pharmaceutically active agent.

12 50. The composition of claim 49, wherein the agent is adsorbed to the nanoparticles.

51. A composition comprising a plurality of nanoparticles of any of claims 39 to 48, further comprising a signal molecule.

52. The composition of claim 51, wherein the signal molecule is a metal chelated by an organic moiety, wherein the moiety is covalently bound to the nanoparticles.

53. The composition of claim 52, wherein the organic moiety is covalently bound to the first
18 polymer.

54. The composition of claim 51, wherein the signal molecule is covalently bound to the nanoparticles, preferably covalently linked to a carboxylic acid side group.

55. The composition of claim 51 or 54, wherein the signal molecule is a fluorophore.

56. The composition of any one of claims 51 to 54, further comprising a pharmaceutically active agent.

24 57. A nanoparticle comprising:

- a first polymer comprising a polysaccharide;
- a second crosslinked polymer comprising poly(methacrylic acid) grafted to the first polymer; and

- a polysorbate comprising a (C9-C31)R-C(O)O- group covalently bound to the second polymer by a C-C bond between the carbon backbone of the second polymer and the R group.

58. The nanoparticle of claim 57, wherein the (C9-C31)R-C(O)O-group is -(C17)R-C(O)O- wherein R is straight chain alkyl.

59. The nanoparticle of claim 58, wherein the polysorbate comprises the groups $-O(CH_2CH_2O)_w-C(O)(C17)R$, $HO(CH_2CH_2O)_x-$, $-HO(CH_2CH_2O)_y-$, $-HO(CH_2CH_2O)_z-$, wherein $w+x+y+z = 20$.

60. The nanoparticle of claim 57, 58 or 59, wherein the molecular weight of the polysaccharide is between 2,600 and 4,500Da.

61. The nanoparticle of claim 57, 58 or 59, wherein the first polymer comprises starch.

62. The nanoparticle of any one of claims 57 to 61, wherein the molar ratio of the monomeric unit of the polysaccharide to the monomeric methacrylate units of the poly(methacrylic acid) is between 0.2 and 8.0.

63. The nanoparticle of any one of claims 57 to 62, wherein the molar ratio of the polysorbate and the monomeric methacrylate units of the poly(methacrylic acid) is between 0.002 and 0.03.

64. A method of producing a nanoparticle, the method comprising the steps of:

(a) solubilising a polymer in a liquid solution;

(b) providing a polymerizable monomer comprising an alkylaminoalkyl ester side group;

(c) providing a crosslinker; and

(d) graft polymerizing the monomer to form polymeric chains on the solubilised polymer to form the nanoparticle.

65. The method of claim 64, wherein the polymer is a polyhydroxyl polymer having a degree of substitution between 0.05 and 3 per unit of the polymer, the monomer includes an alkenyl group, and the graft polymerizing step is conducted in the presence of a cross-linking agent.

66. The method of claim 65, wherein the polyhydroxyl polymer has a degree of substitution between 1 and 3 per unit of the polymer.

67. The method of claim 65, wherein the polyhydroxyl polymer comprises a polysaccharide having a degree of substitution between 0.5 and 3.

68. The method of claim 67, wherein the polyhydroxyl polymer comprises glucose.

69. The method of claim 67, wherein the polysaccharide comprises starch.

70. The method of any one of claims 64 to 69 wherein the liquid solution comprises a hydroxylic solvent.

71. The method of claim 70, wherein the hydroxylic solvent comprises water and/or an alcohol.

72. The method of claim 71, wherein the hydroxylic solvent comprises water and ethanol.

73. The method of any one of claims 64 to 72, wherein the polymerizable monomer is an alkylaminoalkyl ester of methacrylic acid.

74. The method of claim 73, wherein the monomer is diethylaminoethyl methacrylic acid.

75. The method of any one of claims 64 to 74, wherein the step of polymerizing is a free radical graft polymerizing conducted in the presence of a free radical initiator.

76. The method of claim 75 wherein the initiator is substantially free of transition metals.

77. The method of claim 75 or 76 wherein the initiator is the initiator is persulfate or functional equivalent thereof.

78. The method of any one of claims 64 to 77, wherein the crosslinker is ethylene glycol dimethacrylate.

79. The method of any one of claim 64 to 78, wherein the monomer of step (d) is present in an amount between 1 and 200 times the amount of the cross-linking agent (mol/mol).

80. The method of claim 79, wherein the monomer of step (d) is present in an amount between 3 and 50 times the amount of the cross-linking agent (mol/mol).

81. The method of any one of claims 64 to 80, wherein the amount of polymer and the amount of monomer of step (c) are selected to produce a nanoparticle in which the molar ratio of monomeric units in the polymeric chains to monomeric units of the polymer is between 0.05 and 20.

82. The method of claim 81, wherein the amount of polymer and the amount of monomer of step (c) are selected to produce a nanoparticle in which the molar ratio of monomeric units in the polymeric chains to monomeric units of the polymer is between 2 and 4.

83. The method of any of claims 64 to 82, wherein a polysorbate is present in step (d).

84. The method of claim 83, wherein the R-group of the polysorbate is a hydrocarbyl group containing an unsaturation.

85. The method of claim 84, wherein the polysorbate is polysorbate 80.

86. The method of claim 83, 84 or 85, wherein the polymerizable monomer is present in an amount of between 5 and 50 times the amount of the polysorbate (mol/mol).

87. The method of claim 86, wherein the polymerizable monomer is present in an amount of between 20 and 30 times the amount of the polysorbate (mol/mol)..

88. The method of any one of claim 64 to 87, wherein a non-ionic stabilizer is present in step (d).

89. The method of claim 88, wherein the stabilizer is polyvinylpyrollidone.

90. A method of producing a nanoparticle for delivery of a biological agent, comprising the method of any one of claims 64 to 89 wherein the agent is covalently linked to the polymer of step (a).

91. The method of claim 90, wherein the agent comprises an organic moiety capable of complexing a metal.

92. The method of claim 91, further comprising forming the metal-organic moiety complex.

93. The method of claim 92, wherein the organic moiety is DTPA.

94. The method of claim 92 or 93, wherein the metal is selected to provide a signal in magnetic resonance imaging.

95. The method of claim 94, wherein the metal is Gd^{+3}.

96. A method of producing nanoparticles for delivery of a biological agent, comprising dispersing the agent and nanoparticles obtained by the method of any of claims 64 to 95 in a liquid medium to incorporate the agent into the nanoparticles.

97. A nanoparticle comprising:

- a first polymer comprising a polysaccharide; and
- a second crosslinked polymer comprising an alkylaminoalkyl ester of methacrylic acid grafted to the first polymer, wherein the second polymer is crosslinked.

98. The nanoparticle of claim 97, wherein the second polymer is polymerized diethylaminoethyl methacrylic acid.

99. The nanoparticle of claim 97, wherein second polymer comprises polymerized vinyl groups having about one carboxyl group per two carbons of the backbone of the second polymer.

100. The nanoparticle of claim 97, 98 or 99, wherein the polysaccharide is starch.

101. A composition comprising a solution of nanoparticles of any one of claims 97 to 100, wherein the nanoparticles exhibit an increased volume change of between 500 and 1500 fold when the pH of their ambient solution is changed from about 4 to about 7.4.

102. A composition of claim 101, wherein the nanoparticles exhibit an increased volume change of between 700 and 1100 fold when the pH of their ambient solution is changed from about 4 to about 7.4.

103. A composition comprising a plurality of nanoparticles of any one of claims 97 to 100, further comprising a signal molecule.

104. The composition of claim 101 or 102, further comprising a signal molecule.

105. The composition of claim 103 or 104, wherein the signal molecule is a metal chelated by an organic moiety, wherein the moiety is covalently bound to the nanoparticles.

106. The composition of claim 105, wherein the organic moiety is covalently bound to the first polymer.

107. The composition of claim 106, wherein the metal is selected to provide a signal in magnetic resonance imaging, and the molar ratio of the alkylaminoalkyl ester of methacrylic acid to the monomeric unit of the polysaccharide is between 0.5 and 5.

108. The composition of claim 107, wherein the molar ratio of the alkylaminoalkyl ester of methacrylic acid to the monomeric unit of the polysaccharide is between between 0.5 and 2.

109. A composition comprising a plurality of nanoparticles of any one of claims 97 to 100, further comprising a pharmaceutically active agent.

110. The composition of claim 109, wherein the agent is adsorbed to the nanoparticles.