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 comprising polysaccharide; a second polymer grafted to the first polymer wherein the second polymer is a polymer comprising a vinyl, or an acrylic polymer; and a polyethoxylated sorbitan-based 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~~ polyethoxylated sorbitan ester 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; and a polyethoxylated sorbitan-based moiety covalent bound to the second polymer .

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

(a) solubilising a polymer comprising a polysaccharide 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 polyethoxylated sorbitan-based molecules having a functional group reactive with the forming chains, wherein:

step (c) is conducted in the presence of the polyethoxylated sorbitan-based molecules to covalently link the polethoxylated sorbitan-based 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 comprising a polysaccharide 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; and

(e) covalently linking polethoxylated sorbitan-based molecules with the polymeric chains during graft polymerization of the monomer .

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 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 (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 comprising a polysaccharide;
- a second polymer grafted to the first polymer wherein the second polymer is a polymer comprising a vinyl, or an acrylic polymer; and
- a polyethoxylated sorbitan-based 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 sorbitan-based moiety is a polyethoxylated sorbitan ester having a R(C9-C31)-C(O)O-group wherein the polyethoxylated sorbitan ester 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 one 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~~ polyethoxylated sorbitan ester 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~~ polyethoxylated sorbitan ester 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~~polyethoxylated sorbitan ester 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; and
- a polyethoxylated sorbitan-based moiety covalently bound to the second polymer.

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

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 comprising a polysaccharide 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 polyethoxylated sorbitan-based molecules having a functional group reactive with the forming chains, wherein:

step (c) is conducted in the presence of the polyethoxylated sorbitan-based molecules to covalently link the polyethoxylated sorbitan-based 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 polyethoxylated sorbitan-based molecules are a polyethoxylated sorbitan ester having a R(C9-C31)-C(O)O-group wherein the polyethoxylated sorbitan ester 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 comprising a polysaccharide 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; and

(e) covalently linking polyethyoxylated sorbitan-based molecules with the polymeric chains during the graft polymerization of the monomer.

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

26. The method of claim ~~25~~24, wherein the monomer is diethylaminoethyl ~~methacrylic acid~~methacrylate.

27. The method of claim ~~25~~24, wherein the monomer is methacrylic acid.