SUMMARY

Surprisingly, it has now been found that stable and highly drug-loaded nanocapsules can be prepared from, optionally alkoxylated, poly(alkyl cyanoacrylates) in the presence of a stabilizing agent selected from bile acids and/or bile salts.

In one aspect, the present invention refers to a nanocapsule comprising a) one or more than one polymer forming a polymeric shell, the polymer(s) comprising a main monomeric constituent selected from one or more than one of C_1-C_{10}-alkyl cyanoacrylates and C_1-C_6-alkoxy-C_1-C_{10}-alkyl cyanoacrylates; b) one or more than one pharmaceutically or cosmetically active agent comprised in a core encapsulated by said polymeric shell; and c) a nanoparticle stabilizing agent selected from one or more than one bile acid, one or more than one salt of a bile acid, and mixtures thereof, wherein the amount of the active agent(s) (b) is at least 50 wt-% relative to the total weight of shell-forming polymer(s) (a) and active agent(s) (b) of the nanocapsule.

In another aspect, the present invention refers to a plurality of nanocapsules, as disclosed herein, comprising a population of nanocapsules having a diameter of less than 500 nm, wherein the nanocapsules of the population comprise at least 50 wt-% of the active agent(s) (b) relative to the total weight of shell-forming polymer(s) (a) and active agent(s) (b) of the population.

In yet another aspect, the present invention refers to a method for preparing nanocapsules, the method comprising i) providing a hydrophobic liquid phase comprising one or more than one shell-forming polymer comprising a main monomeric constituent selected from one or more than one of C_1-C_{10}-alkyl cyanoacrylates and C_1-C_6-alkoxy-C_1-C_{10}-alkyl cyanoacrylates, and one or more than one pharmaceutically or cosmetically active agent dissolved in a non-water-miscible organic solvent or a mixture of two or more non-water-miscible organic solvents; ii) providing a hydrophilic liquid phase comprising a nanoparticle stabilizing agent selected from one or more than one bile acid, or one or more than one salt of a bile acid, or mixtures thereof dissolved in a hydrophilic solvent; iii) finely dispersing the hydrophobic liquid phase in the hydrophilic liquid phase so as to form an emulsion; and iv) removing at least part of the organic solvent(s) from the homogenized mixture so as to obtain a suspension of nanocapsules in the hydrophilic solvent. In a further aspect, the present invention refers to a nanocapsule obtainable by the method as disclosed herein. In another aspect, the present invention refers to a pharmaceutical composition comprising a plurality of nanocapsules as disclosed herein, and a pharmaceutically acceptable carrier.

Thus, in one example, there is described a nanocapsule comprising:

a) one or more than one polymer forming a polymeric shell, the polymer(s) comprising a main monomeric constituent selected from one or more than one of C_1-C_{10}-alkyl cyanoacrylates and C_1-C_6-alkoxy-C_1-C_{10}-alkyl cyanoacrylates;

b) one or more than one pharmaceutically or cosmetically active agent comprised in a core encapsulated by said polymeric shell; and

c) a nanoparticle stabilizing agent selected from one or more than one bile acid, one or more than one bile salt, and mixtures thereof.

In a further example, there is described a plurality of nanocapsules as described herein comprising a population of nanocapsules having a diameter of less than 500 nm, wherein the nanocapsules of the population comprise at least 50 wt-%, in particular at least 60 wt-%, at least 70 wt-%, preferably at least 80 wt-%, more preferably at least 90 wt-%, at least 95 wt-% and most preferably at least 99 wt-% or at least 99.9 wt-%, of the active agent(s) (b) relative to the total weight of shell-forming polymer(s) (a) and active agent(s) (b) of the population.

Also, in another example, there is described a method for preparing nanocapsules, the method comprising:

i) providing a hydrophobic liquid phase comprising:

- one or more than one shell-forming polymer comprising a main monomeric constituent selected from one or more than one of C_1-C_{10}-alkyl cyanoacrylates and C_1-C_6-alkoxy-C_1-C_{10}-alkyl cyanoacrylates, and
- one or more than one pharmaceutically or cosmetically active agent

dissolved in a non-water-miscible organic solvent or a mixture of two or more non-water-miscible organic solvents, and

- optionally, one or more than one sorbitan fatty acid ester, and

- optionally, one or more than one amphiphilic lipid carrying a detectable moiety, a targeting moiety or a linker moiety;

ii) providing a hydrophilic liquid phase comprising:

- a nanoparticle stabilizing agent selected from one or more than one bile acid, one or more than one bile salt, and mixtures thereof

dissolved in a hydrophilic solvent, and

- optionally, one or more than one uptake mediator selected from polyoxyethylene sorbitan fatty acid esters;

iii) finely dispersing the hydrophobic liquid phase in the hydrophilic liquid phase so as to form an emulsion; and

iv) removing at least part of the organic solvent(s) from the homogenized mixture so as to obtain a suspension of nanocapsules in the hydrophilic solvent.

In another example, there is described a pharmaceutical composition comprising a plurality of nanocapsules as described herein and a pharmaceutically acceptable carrier.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows suspensions of PBCA nanoparticles prepared from different polymer-drug ratios as described in example 3 (samples 3#1 to 3#9) as well as the average particles sizes (Z-average diameters, columns) and polydispersities (PDI, curve) of these nanoparticles which were determined using a Zetasizer device.

Figure 2 shows the zeta potentials (ZP) of PBCA nanoparticles prepared from different polymer-drug ratios as described in example 3 (samples 3#1 to 3#9) which were determined using a Zetasizer device and indicate a switch between two systems, highly-drug loaded nanocapsules and nanospheres, between polymer-drug ratios of 50:50 and 90:10.

Figure 3 shows transmission election microscopy (TEM) images of PBCA nanoparticles prepared from different polymer-drug ratios as described in example 3 (samples 3#1 to 3#9). The reference bars indicate a length of 100 nm.

Figure 4 shows the encapsulation efficiency (EE) of PBCA nanoparticles prepared from different polymer-drug ratios as described in example 3 (samples 3#1 to 3#9).

CLAIMS

1. A nanocapsule comprising:
   a) one or more than one polymer forming a polymeric shell, the polymer(s) comprising a main monomeric constituent selected from one or more than one of C_1-C_{10}-alkyl cyanoacrylates and C_1-C_6-alkoxy-C_1-C_{10}-alkyl cyanoacrylates;
   b) one or more than one pharmaceutically or cosmetically active agent comprised in a core encapsulated by said polymeric shell; and
   c) a nanoparticle stabilizing agent selected from one or more than one bile acid, one or more than one salt of a bile acid, and mixtures thereof

   wherein the amount of the active agent(s) (b) is at least 50 wt-% relative to the total weight of shell-forming polymer(s) (a) and active agent(s) (b) of the nanocapsule.
2. The nanocapsule of claim 1, wherein the one or more than one active agent (b) is a water-insoluble or poorly water-soluble compound.
3. The nanocapsule of claim 2, wherein the solubility of the one or more than one active agent (b) in water at 25°C and at pH 7.0 is 0.1 g/100 ml or less.
4. The nanocapsule of any one of claims 1-3, wherein the one or more than one active agent (b) has a molecular weight in the range of less than 2000 g/mol.
5. The nanocapsule of any one of claims 1-4, wherein at least 50% of the one or more than one active agent (b) is present in an undissolved solid form.
6. The nanocapsule of any one of claims 1-4, wherein at least 50% of the one or more than one active agent (b) is present in a crystalline state.
7. The nanocapsule of any one of claims 1-4, wherein at least 50% of the one or more than one active agent (b) is present in an amorphous state.
8. The nanocapsule of any one of claims 1-4, wherein at least 50% of the one or more than one active agent (b) is present in a semi-crystalline state.
9. The nanocapsule of any one of claims 1-8, wherein the main monomeric constituent of the shell-forming polymer(s) (a) is selected from one or more than one of methyl 2-cyanoacrylate, 2-methoxyethyl 2-cyanoacrylate, ethyl 2-cyanoacrylate, n-butyl 2-cyanoacrylate, 2-octyl 2-cyanoacrylate and isobutyl 2-cyanoacrylate.

10. The nanocapsule of claim 9, wherein the one or more than one shell-forming polymer (a) is selected from poly(n-butyl 2-cyanoacrylate), poly(ethyl 2-cyanoacrylate), and mixtures thereof.

11. The nanocapsule of any one of claims 1-10, wherein the nanoparticle stabilizing agent (c) is a bile acid selected from cholic acid, taurocholic acid, glycocholic acid, deoxycholic acid, lithocholic acid, chenodeoxycholic acid, dehydrocholic acid, ursodeoxycholic acid, hyodeoxycholic acid and hyocholic acid, or a salt of said bile acids, or a mixture of more than one of said bile acids and/or more than one of said bile salts.

12. The nanocapsule of claim 11, wherein the nanoparticle stabilizing agent (c) is selected from one or more than one of cholic acid, salts of cholic acid, and mixtures thereof.

13. The nanocapsule of claim 12, wherein the nanoparticle stabilizing agent (c) is sodium cholate.

14. The nanocapsule of any one of claims 1-13, wherein the amount of the nanoparticle stabilizing agent (c) is from 3 to 36 wt-% relative to the total weight of shell-forming polymer(s) (a) and active agent(s) (b) of the nanocapsule.

15. The nanocapsule of any one of claims 1-14, wherein the nanocapsule is basically free of any monomers of the shell-forming polymer(s).

16. The nanocapsule of any one of claims 1-15, wherein the diameter of the nanocapsule is less than 500 nm.

17. The nanocapsule of claim 16, wherein the diameter of the nanocapsule is in the range of from 50-200 nm.

18. The nanocapsule of any one of claims 1-17, wherein the amount of the active agent(s) (b) is at least 80 wt-% relative to the total weight of shell-forming polymer(s) (a) and active agent(s) (b) of the nanocapsule.

19. The nanocapsule of any one of claims 1-18, further comprising one or more than one uptake mediator selected from polyoxyethylene sorbitan fatty acid esters.

20. The nanocapsule of claim 19, wherein the uptake mediator is polyoxyethylene (20) sorbitan monooleate.

21. The nanocapsule of any one of claims 1-20, further comprising one or more than one sorbitan fatty acid ester.

22. The nanocapsule of claim 21, wherein the sorbitan fatty acid ester is sorbitan monooleate.

23. The nanocapsule of any one of claims 1-22, further comprising one or more than one amphiphilic lipids.

24. The nanocapsule of claim 23, wherein the amphiphilic lipid is selected from the group consisting of naturally occurring or synthetic phospholipids, cholesterols, lysolipids, sphingomyelins, tocopherols, glucolipids, stearylamines and cardiolipins.

25. A plurality of nanocapsules of any one of claims 1-24 comprising a population of nanocapsules having a diameter of less than 500 nm, wherein the nanocapsules of the population comprise at least 50 wt-% of the active agent(s) (b) relative to the total weight of shell-forming polymer(s) (a) and active agent(s) (b) of the population.

26. The plurality of nanocapsules of claim 25, wherein the population of nanocapsules having a diameter of less than 500 nm accounts for more than 90 wt-% of the plurality of nanocapsules.

27. The plurality of nanocapsules of claim 25 or claim 26 comprising a sub-population of nanocapsules having a diameter in the range of from 50-200 nm, wherein the nanocapsules of the sub-population comprise at least 50 wt-% of the active agent(s) (b) relative to the total weight of shell-forming polymer(s) (a) and active agent(s) (b) of the sub-population.

28. The plurality of nanocapsules of claim 27, wherein the nanocapsules of the subpopulation comprise at least 80 wt-% of the active agent(s) (b) relative to the total weight of shell-forming polymer(s) (a) and active agent(s) (b) of the sub-population.

29. The plurality of nanocapsules of claim 27 or 28, wherein the sub-population of nanocapsules having a diameter in the range of from 50-200 nm accounts for more than 90 wt-% of the plurality of nanocapsules.

30. A method for preparing nanocapsules, the method comprising:

i) providing a hydrophobic liquid phase comprising:

- one or more than one shell-forming polymer comprising a main monomeric constituent selected from one or more than one of C_1-C_{10}-alkyl cyanoacrylates and C_1-C_6-alkoxy-C_1-C_{10}-alkyl cyanoacrylates, and
- one or more than one pharmaceutically or cosmetically active agent

dissolved in a non-water-miscible organic solvent or a mixture of two or more non-water-miscible organic solvents;

ii) providing a hydrophilic liquid phase comprising:

- a nanoparticle stabilizing agent selected from one or more than one bile acid, or one or more than one salt of a bile acid, or mixtures thereof

dissolved in a hydrophilic solvent;

iii) finely dispersing the hydrophobic liquid phase in the hydrophilic liquid phase so as to form an emulsion; and

iv) removing at least part of the organic solvent(s) from the homogenized mixture so as to obtain a suspension of nanocapsules in the hydrophilic solvent.

31. The method of claim 30, wherein the concentration of the nanoparticle stabilizing agent in the hydrophilic liquid phase provided in step (ii) is in the range of from 50-150% of its critical micelle concentration.

32. The method of claim 30 or 31, wherein the hydrophilic liquid phase provided in step (ii) further comprises one or more than one uptake mediator selected from polyoxyethylene sorbitan fatty acid esters.

33. The method of any one of claims 30-32, wherein the hydrophobic liquid phase provided in step (i) further comprises one or more than one sorbitan fatty acid ester.

34. The method of any one of claims 30-33, wherein the shell-forming polymer(s), the active agent(s), the nanoparticle stabilizing agent, the uptake mediator and the sorbitan fatty acid ester, respectively, are as defined in any one of claims 2-15, 17, 20 and 22.

35. The method of any one of claims 30-34, wherein step (iii) is carried out by homogenization under pressure and/or ultrasonically.

36. The method of any one of claims 30-35, wherein in step (iv) the organic solvent(s) is/are evaporated.

37. A nanocapsule obtainable by the method of any one of claims 30-36.

38. A pharmaceutical composition comprising a plurality of nanocapsules according to any one of claims 1-29, and a pharmaceutically acceptable carrier.