There is therefore a need to provide a drug delivery system that overcomes or at least ameliorates, one or more of the disadvantages described above. There is also need to provide a method of forming such a drug delivery system.

Summary

According to a first aspect, there is provided a micellar nanocomplex comprising a micelle and an agent encapsulated within the micelle, the micelle comprising a polymer-flavonoid conjugate, wherein the polymer is bonded to the B ring of the flavonoid.

Advantageously, the micellar nanocomplexes can be used as drug delivery systems. Micellar nanocomplexes have a small size and high drug loading capacity favourable for tumor-targeted drug delivery. Further advantageously, sustained release of the agent may be achieved using micellar nanocomplexes in physiological conditions. More advantageously, the nanocomplexes may be promising delivery vehicles for a variety of water-insoluble anticancer agents. Further advantageously, the micellar nanocomplex may suppress tumor growth significantly, with reduced toxicity associated with agent administration. More advantageously, the micellar nanocomplexes may represent a unique and effective drug delivery system with synergistic therapeutic effects from the drug delivery system or the micelle carrier and the agent.

The agent may be doxorubicin. Advantageously, micellar nanocomplexes encapsulating doxorubicin may exhibit sustained drug release. This sustained drug release may be due to the strong interaction between EGCG and doxorubicin within the micellar nanocomplexes. Further advantageously, in some embodiments, only a marginal burst release was observed at the initial stage, suggesting that doxorubicin molecules were stably encapsulated in the micellar nanocomplexes. Such low drug leakage may be essential to ensure maximal therapeutic efficacy with minimal side effects, as the drug molecules encapsulated in the nanocomplexes maynot leak prematurely during circulation in the blood stream. Even further advantageously, the micellar nanocomplexes may be applied for systemic administration of doxorubicin for cancer treatment.

The agent may be Sunitinib (SU) and the flavonoid may be epigallalocatechin-3-gallate (EGCG). Advantageously, the micellar nanocomplexes may exhibit a sustained release of SU. Further advantageously, in some embodiments, hardly any burst release was observed, suggesting that SU molecules were stably encapsulated in the micellar nanocomplexes.

In an embodiment, the flavonoid may be a monomeric flavonoid. In another embodiment, the flavonoid may be a dimeric flavonoid. Advantageously, micellar nanocomplex comprising the monomeric flavoid may show faster and more SU release as compared to micellar nanocomplexes comprising the dimeric flavonoid. Advantageously, there may be a stronger interaction between SU and dimeric flavonoid.

Advantageously, micellar nanocomplexes may minimise the adverse side-effects of agents such as SU by stably encapsulating the agent in their interior, and delivering them to the target site. The micellar nanocomplex may therefore provide beneficial synergistic effects between SU and EGCG.

Further advantageously, the micellar nanocomplex comprising SU may have enhanced tumor effects in vivo when compared to free SU. More advantageously, the micellar nanocomplex comprising SU may have less adverse effects in vivo when compared to free SU. Further advantageously, less dosage of the micellar nanocomplex comprising SU may be required compared to free SU to achieve the same effects. More advantageously, the inhibitory effect of the micellar nanocomplex comprising SU may be maintained for a substantial period even when the therapy is halted.

Further advantageously, the micellar nanocomplex comprising SU may lead to reduced plasma concentrations of free SU, resulting in less adverse effects of SU. Further advantageously, this reduction in plasma concentration may be due to the interaction between the flavonoid and the SU, as well as the enhanced permeability and retention (EPR) effect offered by micellar nanoparticles.

According to a second aspect, there is provided a method for forming a micellar nanocomplex comprising a micelle and an agent encapsulated within the micelle, the method comprising the steps of: (a) adding the agent in a suitable solvent to a polymer-flavonoid conjugate, wherein the polymer is bonded to the B ring of the flavonoid; and (b) allowing the self-assembly of a micelle comprising the polymer-flavonoid conjugate and encapsulation of the agent within the micelle to thereby form the micellar nanocomplex.

Advantageously, the nanocomplex is self-assembled in the presence of the polymer-flavonoid conjugate and the agent. Further advantageously, the formation of the nanocomplex was achieved by utilizing the binding property of the flavonoid with the agents.

According to a third aspect, there is provided a polymer-flavonoid conjugate comprising a polymer bonded to the B ring of a flavonoid.

Advantageously, a flavonoid is conjugated to a polymer. In an embodiment, the polymer may be polyethylene glycol (PEG). Advantageously, the polymer-based nanoparticles avoid both renal clearance and entrapment by the reticuloendothelial system (RES), allowing subsequent accumulation within tumor tissues by the EPR effect. More advantageously, PEG-stabilized micelles exhibit a prolonged plasma half-life than unmodified micelles because the PEG surface chains prevent recognition and clearance by the RES in the body. Further advantageously, PEG can be used to modify the surface of polymeric micelles and nanoparticles to produce anti-fouling surfaces.

According to the disclosure, there is provided a method for forming the polymer-flavonoid conjugate as defined above comprising the step of conjugating the flavonoid with the polymer via nucleophilic addition under basic conditions, wherein the polymer has a free nucleophilic group.

According to a fourth aspect, there is provided a method for forming the polymer-flavonoid conjugate as defined above comprising the step of conjugating the flavonoid with the polymer via nucleophilic addition under basic conditions, wherein the polymer has a free nucleophilic group and the nucleophilic group is selected from the group consisting of a thiol, an amine, a diazoalkane and an azide.

Advantageously, the polymer-flavonoid conjugates may be synthesized by nucleophilic addition at basic pH. Advantageously, the conjugation may be accomplished by nucleophilic addition of a nucleophilic group such as a thiol group of the polymer such as PEG at the C2' position of the B ring of the flavonoid under controlled pH conditions.

In an embodiment, the polymer is polyethylene glycol (PEG) and the free nucleophilic group is thiol. Advantageously, the electron-deficient ortho-quinone of the flavonoid such as EGCG may react with a nucleophilic group such as thiol groups. Thiol groups are present in a diverse range of biomolecules including cysteine, glutathione, and proteins. EGCG may bind covalently to cysteine residues in human erythrocyte membrane proteins and glyceraldehyde-3-phosphate dehydrogenase (GAPDH). In addition, covalent adducts of EGCG may form when oxidized in the presence of cysteine and glutathione. Further advantageously, the resulting cysteine conjugates of EGCG may exhibit higher pro-oxidant activities than EGCG, while retaining its growth inhibitory and anti-inflammatory activities. More advantageously, N-acetlycysteine-conjugated EGCG may enhance the growth inhibitory and apoptosis-inducing effects of the EGCG against murine and human lung cancer cells.

According to the disclosure, there is provided the use of a micellar nanocomplex comprising a micelle and an agent encapsulated within the micelle as a drug delivery vehicle, wherein the micelle comprises a polymer-flavonoid conjugate, and wherein the polymer is bonded to the B ring of the flavonoid.

According to a fifth aspect, there is provided the use of a micellar nanocomplex comprising a micelle and an agent encapsulated within the micelle as a drug delivery vehicle, wherein the micelle comprises a polymer-flavonoid conjugate, and wherein the polymer is bonded to the B ring of the flavonoid or optionally wherein the micellar nanocomplex delivers the encapsulated agent to a targeted tumor site in vivo,

According to the disclosure, there is provided a method of treating a tumor comprising the step of administering the micellar nanocomplex as defined above to a cancer agent.

Advantageously, the micellar nanocomplex may have a greater anticancer effect as compared to free agent. Further advantageously, micellar nanocomplexes may minimise the adverse side-effects of agents such as Suhitinib (SU) by stabling encapsulating the agent in their interior, and delivering them to the target site. Such delivery systems may also provide beneficial synergistic effects.

According to the disclosure, there is provided the micellar nanocomplex as defined above for treating a tumor.

According to a sixth aspect, there is provided the micellar nanocomplex as defined above for use in treating a tumor.

According to a seventh aspect, there is provided the use of the micellar nanocomplex as defined above in the manufacture of a medicament for the treatment of a tumor.

Definitions

The following words and terms used herein shall have the meaning indicated:

The "B ring" of a flavonoid refers to an optionally substituted phenyl that is bonded to a bicyclic structure (the bicyclic structure made up of a benzene ring (A) condensed with a six membered ring (C)). The optionally substituted phenyl is bonded to the 2-position of the C ring. For the purposes of this disclosure, the rings are labelled as follows:
[Chem. 1]

Claims

1. A micellar nanocomplex comprising a micelle and an agent encapsulated within said micelle, said micelle comprising a polymer-flavonoid conjugate, wherein said polymer is bonded to the B ring of said flavonoid.

2. The micellar nanocomplex of claim 1, wherein at least one flavonoid is bonded to said polymer.

3. The micellar nanocomplex of claim 1 or 2, wherein said polymer is bonded to said flavonoid via a linker, or optionally

wherein said linker is selected from the group consisting of a thioether, imine, amine, azo and 1,2,3-triazole group, or more optionally

wherein said flavonoid is a monomeric flavonoid or a dimeric flavonoid.

4. The micellar nanocomplex of any one of claims 2 to 3, wherein when more than one flavonoid is present in said conjugate, at least one of the flavonoid is bonded to said polymer via the B ring, or optionally

wherein the other of said at least one flavonoid is bonded to said polymer via the A ring.

5. The micellar nanocomplex of any one of the preceding claims, wherein said polymer is a hydrophilic polymer and said hydrophilic polymer is selected from the group consisting of polyacrylamide, poly(N-isopropylacrylamide), poly(oxazoline), polyethylenimine, poly(acrylic acid), polymethacrylate, poly(ethylene glycol), poly(ethylene oxide), poly(vinyl alcohol), poly(vinylpyrrolidinone), polyethers, poly(allylamine), polyanhydrides, poly(*β*-amino ester), poly(butylene succinate), polycaprolactone, polycarbonate, polydioxanone, poly(glycerol), polyglycolic acid, poly(3-hydroxypropionic acid), poly(2-hydroxyethyl methacrylate), poly(*N*-(2-hydroxypropyl)methacrylamide), polylactic acid, poly(lactic-*co*-glycolic acid), poly(ortho esters), poly(2-oxazoline), poly(sebacic acid), poly(terephthalate-*co*-phosphate) and copolymers thereof, or optionally

wherein said hydrophilic polymer comprises monomers selected from the group consisting of acrylamides, alkyls, oxazolines, alkenyls, imines, acrylic acids, methacrylates, diols, oxiranes, alcohols, amines, anhydrides, esters, lactones, carbonates, carboxylic acids, acrylates, hydroxyls, phosphates, terephthalate, amides and ethers.

6. The micellar nanocomplex of claim 5, wherein said hydrophilic polymer is a polysaccharide

selected from the group consisting of hyaluronic acid, dextran, pullulan, chitosan, cellulose, amylose, starch, gelatin, carrageenan, cyclodextrin, dextran sulfate, Ficoll, gellan, guar gum, pectin, polysucrose, pullulan, scleroglucan, xanthan, xyloglucan and alginate.

7. The micellar nanocomplex of any one of the preceding claims, wherein said flavonoid is selected from the group consisting of flavones, isoflavones, flavans, proanthocyanidins and anthocyanidins, or optionally

said flavans is selected from the group consisting of (-)-epicatechin, (+)-epicatechin, (-)-catechin, (+)-catechin, epicatechin gallate, epigallocatechin, epigallocatechin gallate, Fisetinidol, Gallocatechin, Gallocatechin gallate, Mesquitol and Robinetinidol, ellagitannin, gallotannin, oolongtheanin, phlorotannin, tannin, theacitrin, theadibenzotropolone, theaflavin, theanaphthoquinone, thearubigins, theasinensin and mixtures thereof.

8. The micellar nanocomplex of any one of the preceding claims, wherein said agent is a therapeutic agent and

said therapeutic agent is a chemotherapeutic agent selected from the group consisting of alkylating agents, anthracyclines, cytoskeletal disruptors, epothilones, histone deacetylase inhibitors, topoisomerase I inhibitors, topoisomerase II inhibitors, kinase inhibitors, monoclonal antibodies, antibody-drug conjugates, nucleotide analogs, precursor analogs, peptide antibiotics, platinum-based agents, retinoids, vinca alkaloids , cytokines , anti-metabolites, and vinca alkaloids derivatives, and other cytotoxics, or optionally

wherein said chemotherapeutic agent is selected from the group consisting of Actinomycin, Afatinib, All-trans retinoic acid, Axitinib, Azacitidine, Azathioprine, Bevacizumab, Bleomycin, Bosutinib, Bortezomib, Carboplatin, Capecitabine, Cetuximab, Cisplatin, Chlorambucil, Crizotinib, Cyclophosphamide, Cytarabine, Dasatinib, Daunorubicin, Docetaxel, Doxifluridine, Doxorubicin, Epirubicin, Epothilone A ($C_{26}H_{39}NO_6S$), Epothilone B ($C_{27}H_{41}NO_6S$), Epothilone C ($C_{26}H_{39}NO_5S$), Epothilone D ($C_{27}H_{41}NO_5S$), Epothilone E ($C_{26}H_{39}NO_7S$), Epothilone F ($C_{27}H_{41}NO_7S$), Erlotinib, Etoposide, Fluorouracil, Fostamatinib, Gefitinib, Gemcitabine, Hydroxyurea, Idarubicin, Imatinib, Irinotecan, Lapatinib, Lenvatinib, Mechlorethamine, Mercaptopurine, Methotrexate, Mitoxantrone, Nilotinib, Oxaliplatin, Paclitaxel, Panitumumab, Pazopanib, Pegaptanib, Pemetrexed, Ranibizumab, Regorafenib, Ruxolitinib, Sorafenib, Sunitinib, Trastuzumab, Teniposide, Tioguanine, Tofacitinib, Topotecan, Valrubicin, Vemurafenib, Vinblastine, Vincristine, Vindesine, Vinorelbine.

9. The micellar nanocomplex of any one of the preceding claims, wherein said micellar nanocomplex has a size in the range of 30 to 300 nm, 50 to 300 nm, 100 to 300 nm, 30 to 50 nm, 30 to 100 nm, 30 to 150 nm, 150 to 300 nm, 200 to 300 nm, 250 to 300 nm, 100 to 150 nm, 100 to 200 nm, 100 to 250 nm, 130 to 180 nm, or 130 to 250 nm.

10. The micellar nanocomplex of any one of the preceding claims, wherein the loading efficiency of said agent present within said micelle is more than 30%, more than 35%, more

than 40%, more than 45%, more than 50%, more than 55%, more than 60%, more than 65%, more than 70%, more than 75%, or 80%, or

wherein the loading content of said agent present within said micelle is in the range of 1 to 10 w/w%, 5 to 25 w/w%, 20 to 45 w/w%, 30 to 50 w/w%, 35 to 50 w/w%, 40 to 50 w/w%, 45 to 50 w/w%, 30 to 35 w/w%, 30 to 40 w/w% or 30 to 45 w/w%.

11. A method for forming a micellar nanocomplex comprising a micelle and an agent encapsulated within said micelle, the method comprising the steps of:
a. adding said agent in a suitable solvent to a polymer-flavonoid conjugate, wherein said polymer is bonded to the B ring of said flavonoid; and
b. allowing the self-assembly of a micelle comprising said polymer-flavonoid conjugate and encapsulation of said agent within said micelle to thereby form said micellar nanocomplex, or optionally

wherein step (a) further comprises the steps of:
a. removing said solvent to form a dry film of said agent and said polymer-flavonoid conjugate; and
b. hydrating said dry film with an aqueous solvent, or

further comprising the step of isolating the formed micellar nanocomplex by filtration, or optionally

wherein step (a) further comprises the step of dialysing the agent in a suitable solvent.

12. A polymer-flavonoid conjugate comprising a polymer bonded to the B ring of a flavonoid.

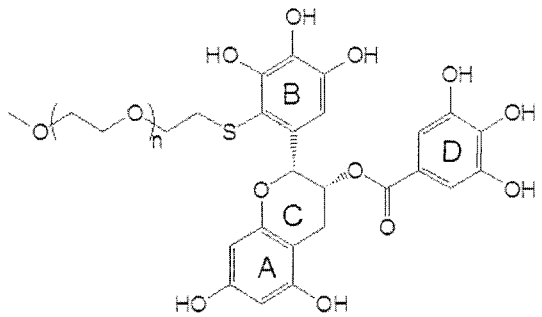
13. The polymer-flavonoid conjugate of claim 12, wherein said polymer is selected from the group consisting of a polysaccharide, polyacrylamide, poly(N-isopropylacrylamide), poly(oxazoline), polyethylenimine, poly(acrylic acid), polymethacrylate, poly(ethylene glycol), poly(ethylene oxide), poly(vinyl alcohol), poly(vinylpyrrolidinone), polyethers, poly(allylamine), polyanhydrides, poly(*β*-amino ester), poly(butylene succinate), polycaprolactone, polycarbonate, polydioxanone, poly(glycerol), polyglycolic acid, poly(3-hydroxypropionic acid), poly(2-hydroxyethyl methacrylate), poly(*N*-(2-hydroxypropyl)methacrylamide), polylactic acid, poly(lactic-*co*-glycolic acid), poly(ortho esters), poly(2-oxazoline), poly(sebacic acid), poly(terephthalate-*co*-phosphate) and copolymers thereof, or optionally

wherein said flavonoid is selected from the group consisting of (-)-epicatechin, (+)-epicatechin, (-)-catechin, (+)-catechin, epicatechin gallate, epigallocatechin, epigallocatechin gallate, Fisetinidol, Gallocatechin, Gallocatechin gallate, Mesquitol and Robinetinidol, ellagitannin, gallotannin, oolongtheanin, phlorotannin, tannin, theacitrin, theadibenzotropolone, theaflavin, theanaphthoquinone, thearubigins, theasinensin and mixtures thereof, or more optionally

wherein said polymer is conjugated to a flavonoid via a linker selected from the group consisting of a thioether, imine, amine, azo and 1,2,3-triazole group, or further optionally

where said polymer is poly(ethylene glycol), said flavonoid is epigallocatechin-3-gallate and said linker is thioether.

14. The polymer-flavonoid conjugate of claim 12, wherein said conjugate has the following formula
[Chem. 2]



wherein n is in the range of 20 to 910.

15. A method for forming the polymer-flavonoid conjugate of any one of claims 12 to 14 comprising the step of conjugating said flavonoid with said polymer via nucleophilic addition under basic conditions, wherein said polymer has a free nucleophilic group and said nucleophilic group is selected from the group consisting of a thiol, an amine, a diazoalkane and an azide.

16. The method of claim 15, wherein said conjugating step is undertaken at a reaction time of between 1 to 24 hours, or

further comprising the step of conducting the conjugating step in a solvent that substantially prevents aggregation of said flavonoid, or

further comprising the step of adding a scavenging agent to prevent H_2O_2-mediated oxidation of said nucleophilic group to thereby increase the efficiency of said conjugating step.

17. The method of any one of claims 15 to 16, wherein said basic conditions is in the pH range of more than 7 to 10.

18. Use of a micellar nanocomplex comprising a micelle and an agent encapsulated within said micelle as a drug delivery vehicle, wherein said micelle comprises a polymer-flavonoid conjugate, and wherein said polymer is bonded to the B ring of said flavonoid, or optionally

wherein the micellar nanocomplex delivers the encapsulated agent to a targeted tumor site *in vivo*.

19. The micellar nanocomplex of any one of claims 1 to 11 for use in treating a tumor.

20. Use of the micellar nanocomplex of any one of claims 1 to 11 in the manufacture of a medicament for the treatment of a tumor.