Oral administration has been recognized as one of the most attractive systemic drug delivery routes due to its flexibility in dosage formulations and high patient compliance which comes with ease of administration. However, orally administered drugs are subjected to various environmental issues within the body, including extreme pH variation, enzyme degradation, mucus barrier, and cell penetration through the gastrointestinal tract, which influence drug integrity and absorption as well as limited bioavailability. Moreover, ocular delivery *via* systemic administration is often hindered due to the blood-ocular barrier that prevents drug penetration into the eye, leading to a drug bioavailability of less than 2%. This low bioavailability forces doses and administration frequency to be high in order to obtain therapeutic concentrations, which may consequently lead to severe systemic toxicity.

In view of the above, there is a need for the development of a composition or method for treating AMD that overcomes or at least ameliorates, one or more of the disadvantages described above.

Summary

There is provided a composition comprising a self-assembled nanocomplex, wherein the self-assembled nanocomplex comprises one or more active agent physically bound to one or more conjugate, wherein each conjugate comprises one or more flavonoid molecule and a first water-soluble polymer, and the nanocomplex is at least partially encapsulated by a second water-soluble polymer.

In one aspect, there is provided a composition comprising a self-assembled nanocomplex, wherein the self-assembled nanocomplex comprises one or more active agent physically bound to one or more conjugate, wherein each conjugate comprises one or more flavonoid molecule and a first water-soluble polymer, and the nanocomplex is at least partially encapsulated by a layer of a second water-soluble polymer.

Advantageously, a flavonoid-based nanocomplex (NC) is provided in the composition, formed by utilizing the favourable interaction between an active agent and the flavonoid moiety of a flavonoid-polymer conjugate, capable of loading various active agents. Advantageously, the nanocomplex may have a high loading content of the active agent.

Advantageously, the second water-soluble polymer may enable the nanocomplex to have a hydrophilic surface. The presence of the second water-soluble polymer on the nanocomplex surface may promote self-assembly of the one or more active agents with the one or more conjugates to result in greater stability of the nanocomplex as compared to the complex without the layer of the second water-soluble polymer. More advantageously, the presence of the second water-soluble polymer on the nanocomplex surface may allow for a protein to be used as the active agent while the complex without the second water-soluble polymer may not. More advantageously, the additional second water-soluble polymer on the nanocomplex may allow for control of the surface charge of the nanocomplex.

In another aspect, there is also provided a pharmaceutical composition or a pharmaceutical formulation comprising the composition as defined above.

There is provided a method of forming the composition as defined above comprising the steps of:

a) mixing a solution of an active agent and a solution of a flavonoid-first water-soluble polymer conjugate to form a mixture;

b) adding a second water-soluble polymer to the mixture of step (a) to form a nanocomplex;

wherein steps a) and b) may be performed simultaneously or sequentially, and

c) allowing the nanocomplex of step (b) to self-assemble, wherein the nanocomplex comprises the active agent physically bound to the flavonoid-first water-soluble polymer conjugate that is at least partially encapsulated by the second water-soluble polymer, wherein the flavonoid-first water-soluble polymer conjugate comprises one or more flavonoid molecules and a first water-soluble polymer.

In another aspect, there is provided a method of forming the composition as defined above comprising the steps of:

a) mixing a solution of an active agent and a solution of a flavonoid-first water-soluble polymer conjugate to form a mixture;

b) adding a second water-soluble polymer to the mixture of step (a) to form a nanocomplex;

wherein steps a) and b) may be performed simultaneously or sequentially, and

c) allowing the nanocomplex of step (b) to self-assemble, wherein the nanocomplex comprises the active agent physically bound to the flavonoid-first water-soluble polymer conjugate that is at least partially encapsulated by a layer of the second water-soluble polymer, wherein the flavonoid-first water-soluble polymer conjugate comprises one or more flavonoid molecules and a first water-soluble polymer.

Advantageously, the favourable interaction between the active agent and the flavonoid (such as epigallocatechin-3-*O*-gallate) may result in efficient self-assembly of the nanocomplex and encapsulation of the active agent by the first water-soluble polymer-flavonoid conjugate followed by the second water-soluble polymer.

In another aspect, there is provided the use of the composition as defined above, or the pharmaceutical composition or the pharmaceutical formulation as defined above, in inhibiting endothelial cell proliferation when activated by a proangiogenic growth factor *in vitro*.

In another aspect, there is provided a composition as defined above, or the pharmaceutical composition or the pharmaceutical formulation as defined above, for use as a medicament.

There is provided a method of treating an eye disease caused by angiogenesis comprising administering to a subject in need thereof a composition as defined above, or the pharmaceutical composition or the pharmaceutical formulation as defined above.

In another aspect, there is provided a composition or the pharmaceutical composition as defined above, or the pharmaceutical formulation as defined above, for use in treating an eye disease caused by angiogenesis.

There is provided the use of a composition as defined above, or the pharmaceutical composition or the pharmaceutical formulation as defined above, in the manufacture of a medicament for treating an eye disease caused by angiogenesis.

In another aspect, there is provided the use of a composition as defined above, or the pharmaceutical composition or the pharmaceutical formulation as defined above, in the manufacture of a medicament for treating an eye disease caused by angiogenesis in a subject in need thereof.

There is provided a method of treating an eye disease caused by angiogenesis, comprising administering a composition to a subject in need thereof, wherein the composition comprises a self-assembled nanocomplex, wherein the self-assembled nanocomplex comprises an ophthalmic anti-angiogenesis drug physically bound to one or more conjugate, each conjugate comprising one or more flavonoid molecule and a first water-soluble polymer.

There is provided a composition for use in treating an eye disease caused by angiogenesis, wherein the composition comprises a self-assembled nanocomplex, wherein the self-assembled nanocomplex comprises one or more ophthalmic anti-angiogenesis drug physically bound to one or more conjugate, each conjugate comprising one or more flavonoid molecule and a first water-soluble polymer.

Claims

1. A composition comprising a self-assembled nanocomplex, wherein the self-assembled nanocomplex comprises one or more active agent physically bound to one or more conjugate, wherein each conjugate comprises one or more flavonoid molecule and a first water-soluble polymer, and the nanocomplex is at least partially encapsulated by a layer of a second water-soluble polymer.

2. The composition according to claim 1, wherein the flavonoid is selected from the group consisting of (-)-epicatechin, (+)-epicatechin, (-)-catechin, (+)-catechin, (-)-epicatechin gallate, (+)-epicatechin gallate, epigallocatechin, epigallocatechin gallate, fisetinidol, gallocatechin, gallocatechin gallate, mesquitol, robinetinidol, ellagitannin, gallotannin, oolongtheanin, phlorotannin, tannin, theacitrin, theadibenzotropolone, theaflavin, theanaphthoquinone, thearubigins, theasinensin, quercetin, revastrol, rutin, curcumin isorhamnetin, kaempferol, myricetin, fisetin, hesperitin, naringenin, eriodictyol, genistein, daidzein, cyanidin, delphinidin, malvidin, pelargonidin, peonidin, daidzein, genistein, glycitein, biochanin A, formononetin, apigenin, luteolin, baiocalein, chrysin, and any mixture thereof.

3. The composition according to claim 1 or 2, wherein the flavonoid is a catechin-based flavonoid.

4. The composition according to any one of the preceding claims, wherein the active agent is a small molecule, a protein or an oligonucleotide.

5. The composition according to any one of the preceding claims, wherein the active agent is a therapeutic agent selected from the group consisting of a chemotherapeutic agent, an anti-inflammatory agent, an anti-oxidant agent, an ophthalmic anti-angiogenesis drug and any combination thereof, or wherein the active agent is present in the range of 0.1 wt% to 90 wt% of the total weight of the composition.

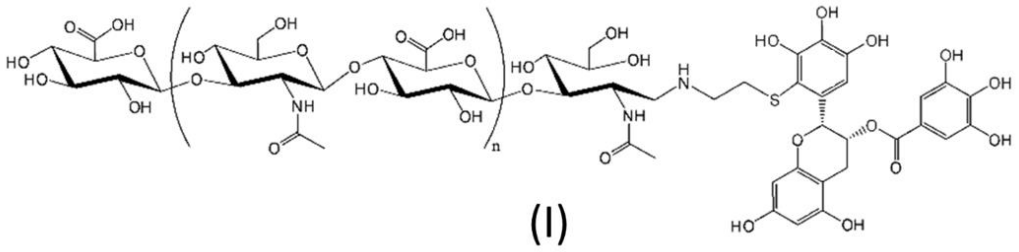
6. The composition according to any one of the preceding claims, wherein the first water-soluble polymer is the same as or is different from the second water-soluble polymer.

7. The composition according to claim 6, wherein the first water-soluble polymer and the second water-soluble polymer are independently selected from the group consisting of glycosaminoglycan, polysaccharide, polyacrylamide, poly(N-isopropylacrylamide), poly(oxazoline), polyethylenimine, poly(acrylic acid), polymethacrylate, poly(ethylene glycol), poly(ethylene oxide), poly(vinyl alcohol), poly(vinylpyrrolidinone), polyether, poly(allylamine), 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), hyaluronic acid, alginate, amylose,

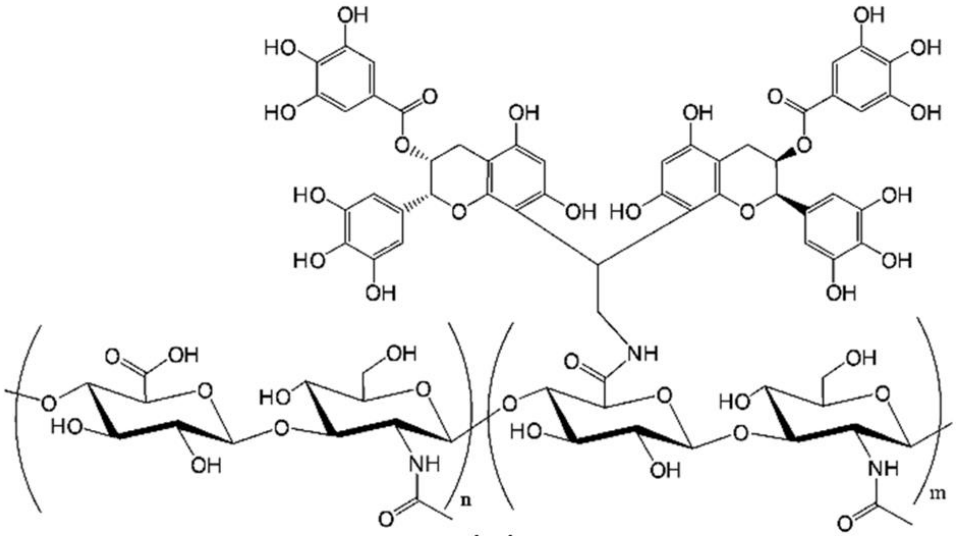
carrageenan, cyclodextrin, dextrin, dextran, ficoll, gelatin, gellan gum, guar gum, heparosan, pectin, polysucrose, pullulan, scleroglucan, xanthan gum, xyloglucan, chitosan, or any derivative thereof, cellulose derivative, keratin derivative, starch derivative, and any mixture thereof.

8. The composition according to any one of the preceding claims, wherein the one or more flavonoid molecule is covalently bound to the first water-soluble polymer.

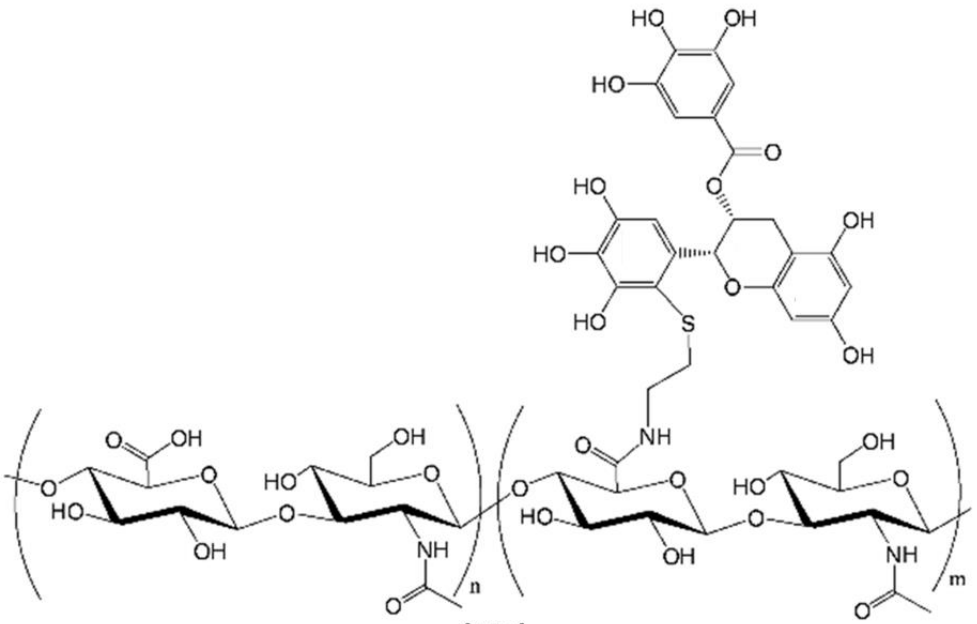
9. The composition according to any one of the preceding claims, wherein the conjugate has the structure depicted by any one of formula (I), (II) or (III):



(I)



(II)



(III)

wherein n and m are independently an integer in the range of 1 to 30,000.

10. The composition according to any one of the preceding claims, wherein the conjugate has a molecular weight in the range of 1 kDa to 10,000 kDa.

11. The composition according to any one of the preceding claims, wherein the nanocomplex has a hydrodynamic diameter in the range of 10 nm to 5000 nm, a polydispersity index in the range of 0.01 to 0.50, a surface charge in the range of -60 mV to 50 mV, or a drug loading content in the range of 0.1% to 90% by weight of the nanocomplex.

12. A pharmaceutical composition or a pharmaceutical formulation comprising the composition as defined in any one of claims 1 to 11.

13. A method of forming the composition according to any one of claims 1 to 11 comprising the steps of:

a) mixing a solution of an active agent and a solution of a flavonoid-first water-soluble polymer conjugate to form a mixture;

b) adding a second water-soluble polymer to the mixture of step (a) to form a nanocomplex;

wherein steps a) and b) may be performed simultaneously or sequentially, and

c) allowing the nanocomplex of step (b) to self-assemble, wherein the nanocomplex comprises the active agent physically bound to the flavonoid-first water-soluble polymer conjugate that is at least partially encapsulated by a layer of the second water-soluble

polymer, wherein the flavonoid-first water-soluble polymer conjugate comprises one or more flavonoid molecules and a first water-soluble polymer.

14. Use of the composition according to any one of claims 1 to 11, or the pharmaceutical composition or the pharmaceutical formulation of claim 12, in inhibiting endothelial cell proliferation when activated by a proangiogenic growth factor *in vitro*.

15. A composition according to any one of claims 1 to 11, or the pharmaceutical composition or the pharmaceutical formulation of claim 12, for use as a medicament.

16. A composition as claimed in any one of claims 1 to 11, or the pharmaceutical composition or the pharmaceutical formulation of claim 12, for use in treating an eye disease caused by angiogenesis.

17. The use of a composition according to any one of claims 1 to 11, or the pharmaceutical composition or the pharmaceutical formulation of claim 12, in the manufacture of a medicament for treating an eye disease caused by angiogenesis in a subject in need thereof.

18. The use of claim 17, wherein the composition is to be administered topically to an eye of the subject.

19. The use of claim 17, wherein the composition is to be administered intravitreally to an eye of the subject.

20. The use of claim 18, wherein an angiogenesis drug is to be further administered intravitreally to the eye of the subject.

21. The use of any one of claims 17 to 20, wherein the eye disease is selected from the group consisting of posterior eye disease, age-related macular degeneration, neovascular age-related macular degeneration, diabetic retinopathy, neovascular glaucoma, diabetic macular oedema, retinal vascular occlusion, and corneal neovascularization.

22. The use of any one of claims 17 to 21, wherein the composition is in liquid form or solution form.

23. The use of any one of claims 17 to 22, wherein the composition is to be administered once daily, twice daily, thrice daily, once weekly, once fortnightly, once monthly, once every 2 months, once every 3 months, once every 4 months, once every 5 months, once every 6 months, once every 9 months or once every 12 months.

24. Use of a composition in the manufacture of a medicament for treating an eye disease caused by angiogenesis, wherein the composition comprises a self-assembled nanocomplex, wherein the self-assembled nanocomplex comprises one or more ophthalmic anti-angiogenesis drug physically bound to one or more conjugate, each conjugate comprising one or more flavonoid molecule and a first water-soluble polymer.