Claims

1. A method of orally administering a hemoglobin based oxygen carrier to a subject in need thereof by providing at least one of the following delivery systems containing the hemoglobin based oxygen carrier:

(a) nanoparticle solution;

(b) enteric-coated capsule; and/or

(c) enteric-coated tablet,

wherein the delivery system is configured to release the hemoglobin based oxygen carrier in the intestinal tract such that the hemoglobin is delivered to the subject's bloodstream in a substantially undegraded form.

2. The method according to claim 1, wherein said hemoglobin-based oxygen carrier comprises one or more of purified hemoglobin, cross-linked hemoglobin, non-polymeric tetrameric hemoglobin, polymeric hemoglobin, or conjugated hemoglobin.

3. The method according to claim 1, wherein the delivery system comprises a nanoparticle solution and the nanoparticle solution comprises one or more of chitosan, an anionic polymer, and/or a positively charged nanoparticle.

4. The method according to claim 3, wherein said chitosan is selected from chitosan, chitin, chitosan oligosaccharide, or derivatives thereof.

5. The method according to claim 3, wherein said anionic polymer is selected from poly(methacrylic acid)-poly(methyl methacrylate) copolymer, hydroxyl propylmethylcellulose phthalate or gamma-glutamic acid.

6. The method according to claim 1, wherein the delivery system is enteric coated capsules and the enteric coated capsules comprise polyacrylic resin coated gelatin capsules filled with a lyophilized form of the hemoglobin based oxygen carrier and one or more stabilizer, cryoprotectant, or intestinal absorption enhancer.

~~7. The method according to claim 6, wherein said intestinal absorption enhancer is selected from polyoxyethylene-20-sorbitan-monooleate, poly(ethylene oxide)-poly(propylene oxide)- poly(ethylene oxide) tri-block copolymer, cyclodextrin, oleic acid, sodium decanoate, sodium octanoate, sodium deoxycholate or sodium cholate.~~

~~8. The method according to claim 1, wherein the delivery system is an entericcoated tablet and the enteric-coated tablet comprises a lyophilized form of the hemoglobin based oxygen carrier and one or more stabilizer, cryoprotectant, intestinal absorption enhancer, or tablet forming excipient.~~

~~9. The method according to claim 8, wherein the enteric-coated tablet further comprises a coating material selected from one or more of poly(methacrylic acid)-poly(methyl methacrylate) copolymer, hydroxypropyl methylcellulose phthalate or cellulose acetate phthalate.~~

~~10. An oral hemoglobin based oxygen carrier delivery system comprising a nanoparticle solution of claim 1.~~

~~11.~~1. An oral hemoglobin based oxygen carrier delivery system configured to release a hemoglobin based oxygen carrier in the intestinal tract of a patient such that the hemoglobin is delivered to the patient's bloodstream in a substantially undegraded form, the system comprising an entericcoated capsule ~~of claim 1~~ surrounding a pharmaceutical composition comprising a nanoparticle solution including hemoglobin-loaded nanoparticles, the hemoglobin-based oxygen carrier comprising one or more of purified hemoglobin, cross linked hemoglobin, non-polymeric tetrameric hemoglobin, polymeric hemoglobin, or conjugated hemoglobin, and the hemoglobin-loaded nanoparticles being embedded into a polyelectrolyte complex under an aqueous-based condition at room temperature via polyelectrolyte complexation to result in a plurality of positively charged hemoglobin-loaded nanoparticles having an average particle size equal to or more than 150nm, a zeta potential of 41±10mV, and an encapsulation efficiency of about 28.7% or more.

~~12.~~ 2. An oral hemoglobin based oxygen carrier delivery system configured to release a hemoglobin based oxygen carrier in the intestinal tract of a patient such that the hemoglobin is delivered to the patient's bloodstream in a substantially undegraded form, the system

comprising an enteric-coated tablet surrounding a pharmaceutical composition comprising a nanoparticle solution including hemoglobin-loaded nanoparticles, the hemoglobin-based oxygen carrier comprising one or more of purified hemoglobin, cross-linked hemoglobin, non-polymeric tetrameric hemoglobin, polymeric hemoglobin, or conjugated hemoglobin, and the hemoglobin-loaded nanoparticles being embedded into a polyelectrolyte complex under an aqueous-based condition at room temperature via polyelectrolyte complexation to result in a plurality of positively charged hemoglobin-loaded nanoparticles having an average particle size equal to or more than 150nm, a zeta potential of 41±10mV, and an encapsulation efficiency of about 28.7% or more ~~of claim 1~~.

~~13. An oral hemoglobin based oxygen carrier delivery system comprising two or more of a nanoparticle solution, enteric-coated capsule, or enteric-coated tablet of claim 1.~~

~~14. A method of preventing and/or treating high altitude syndrome (HAS) and/or hypoxic conditions by orally administering the hemoglobin based oxygen carrier delivery system to a subject according to claim 1, wherein said delivery system is configured to deliver the hemoglobin-based oxygen carrier in a controlled release manner to a target site along the intestinal tract of the subject, wherein said delivering to the target site along the intestinal tract is pH-dependent.~~

~~15. A method of preventing and/or treating anemia and/or hypoxic conditions by orally administering the hemoglobin based oxygen carrier delivery system to a subject according to claim 1, wherein said delivery system is configured to deliver the hemoglobin-based oxygen carrier in a controlled release manner to a target site along the intestinal tract of the subject, wherein said delivering to the target site along the intestinal tract is pH-dependent.~~

~~16. A method of preparing a hemoglobin-based oxygen carrier formulation comprising:~~

~~a) embedding at least one hemoglobin molecule in a polyelectrolyte complex via polyelectrolyte complexation under an aqueous-based condition at room temperature to form positively-charged hemoglobin-loaded nanoparticles; or~~

~~b) lyophilizing a hemoglobin-containing solution followed by encapsulating the lyophilized hemoglobin molecule into an enteric-coated capsule or an enteric-coated tablet.~~

~~17. The method of claim 16, wherein a solution containing an anionic polymer and the hemoglobin is premixed and adjusted to a pH that is above the isoelectric point of the hemoglobin in order to induce a positive charge on the protein surface of the haemoglobin such that a strong affinity with the anionic polymer is formed prior to said embedding or said encapsulating.~~

~~18. The method of claim 17, wherein vitamin C or N-acetyl cysteine (NAC) is added into the solution as a stabilizer after the pH is adjusted.~~

~~19. The method of claim 16, wherein cryoprotectants and intestinal absorption enhancers are added into the hemoglobin-containing solution prior to said lyophilizing.~~

~~20. The method claim 19, wherein said cryoprotectants are one or more of glucose, sucrose or trehalose.~~

~~21. The method claim 19, wherein said intestinal absorption enhancers are one or more of polyoxyethylene-20-sorbitan monooleate, poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) tri-block copolymer, cyclodextrin, oleic acid, sodium decanoate, sodium octanoate, sodium deoxycholate or sodium cholate.~~

~~22.~~ 3. ~~The method of claim 16, wherein said enteric-coated tablet further comprises tablet forming excipient~~ The system of claim 1 or 2, wherein the polyelectrolyte complex comprises chitosan and anionic polymer.

4. The system of claim 3, wherein the chitosan is selected from chitin, chitosan oligosaccharide, or derivatives thereof.

5. The system of claim 3, wherein the anionic polymer is selected from poly(methacrylic acid)-poly(methyl methacrylate) copolymer, hydroxyl propylmethylcellulose phthalate or gamma-glutamic acid.