HYDROPHOBIC ION PAIRING AND FLASH NANOPRECIPITATION FOR FORMATION OF CONTROLLED-RELEASE NANOCARRIER FORMULATIONS

[0001] This International Application claims the benefit of the filing date of U.S. Provisional Application 62/581,394, filed Nov. 3, 2017, which is incorporated by reference in its entirety herein.

[0002] This invention was made with government support under Grant No. GM-066134 awarded by the National Institutes of Health and Grant No. CNS-0612345 awarded by the National Science Foundation. The government has certain rights in the invention.

BACKGROUND OF THE INVENTION

[0003] Sequestration of active pharmaceutical ingredients (APIs) into drug carriers has been considered for producing formulations with biological efficacy.

SUMMARY OF THE INVENTION

[0004] In an embodiment of the invention, a nanoparticle includes a modified salt including a water-soluble active pharmaceutical ingredient (API) ion paired with a hydrophobic counterion of an ion pairing (IP) reagent and a nanoparticle encapsulant material substantially surrounding the modified salt. The API can be an antibacterial and/or a biologic. The API can be an antimicrobial small molecule, a peptide, a protein, or an aminoglycoside. The API can have an aqueous solubility of greater than 10 mg/ml, a log P value less than −2 in an aqueous solution at pH of 7, and/or 1, 2, 3, 4, 5, 6, or more ionic groups. The API can be other than an oligonucleotide. The API can be gentamycin, polymyxin B, mastoparan 7, sub5, LL37, colistin, ecumicin, OZ439, ovalbumin, or lysozyme.

[0005] The counterion can have a log P value of 2 or greater at a pH of 7. The counterion can have a log P value of greater than 5, and the release profile of the API can exhibit a plateau in the release rate with time. The counterion can have 1, 2, or more ionic sites. The counterion can be an anionic counterion that has a pKa value of from −2 to 5. The counterion can have a pKb value of greater than 3. The counterion can be a quaternized cationic species. The counterion can have an ionic site selected from the group consisting of a carboxylic acid, sulfate, sulfonate, or amine. The IP reagent can be sodium hexanoate, sodium decanoate, benzenesulfonic acid monohydrate, sodium 2-naphthalenesulfonate, (1R)-(−)-10-camphorsulfonic acid, sodium 1,2-ethanesulfonate, sodium 1-heptanesulfonate, sodium 1-octanesulfonate monohydrate, sodium 1-decanesulfonate, or sodium deoxycholate. The IP reagent can be sodium dodecyl sulfate (SDS), sodium decyl sulfate (DS), sodium dodecylbenzene sulfonate (DBS), sodium myristate (MA), sodium oleate (OA), or pamoic acid disodium salt (PA). The counterion can be dodecyl hydrogen sulfate, decyl hydrogen sulfate, dodecylbenzene sulfonic acid, or myristic acid. The counterion can be oleic acid or pamoic acid.

[0006] The nanoparticle encapsulant material can be a self-assembling material. The nanoparticle encapsulant material can be hydroxypropyl methylcellulose acetate succinate (HPMCAS), polystyrene-block-polyethylene glycol (PS-b-PEG), or polycaprolactone-block-polyethylene glycol (PCL-b-PEG). For example, the nanoparticle encapsulant material can be 1.6 kDa polystyrene-block-5 kDa polyethylene glycol or 5 kDa polycaprolactone-block-5 kDa polyethylene glycol.

[0007] The nanoparticle can include a polyethylene glycol coating on the nanoparticle.

[0008] The nanoparticle can have a particle size of from 10 nm to 1000 nm, from 10 nm to 1200 nm, from 25 nm to 1000 nm, from 50 nm to 500 nm, from 75 nm to 400 nm, from 100 nm to 350 nm, from 100 nm to 250 nm, or from 100 nm to 150 nm.

[0009] The API and a supplemental hydrophobic compound can be co-encapsulated within the nanoparticle. For example, the supplemental hydrophobic compound can be a therapeutic, imaging agent, or agrochemical compound.

[0010] The API can include gentamycin, polymyxin B, mastoporan 7, sub5, LL37, colistin, ecumicin, OZ439, ovalbumin, or lysozyme. The API can include an antimicrobial small molecule, for example, an antimicrobial small molecule having a molecular weight of less than 1000 Da. The API can include an aminoglycoside, for example, a 4,6-disubstituted deoxystreptamine trisaccharide. The API can include an oligopeptide, such as a linear oligopeptide or a cyclic oligopeptide, which can have a molecular weight of from 1000 Da to 2000 Da. The API can include a protein, such as an anionic protein or a cationic protein, which can have a molecular weight of greater than 2000 Da.

[0011] The IP reagent can include sodium dodecyl sulfate (SDS), sodium decyl sulfate (DS), sodium dodecylbenzene sulfonate (DBS), sodium myristate (MA), sodium oleate (OA), pamoic acid disodium salt (PA), vitamin E succinate, or sodium dextran sulfate (DXS). The counterion can include dodecyl hydrogen sulfate, decyl hydrogen sulfate, dodecylbenzene sulfonic acid, myristic acid, oleic acid, pamoic acid, vitamin E succinic acid, or dextran hydrogen sulfate, or a salt, such as an alkali metal (e.g., lithium (Li), sodium (Na), potassium (K), rubidium (Rb), or caesium (Cs)) salt, of any of these. The counterion can include a fatty acid, an alkyl hydrogen sulfate, an alkylsulfonic acid, an alkyl quaternary ammonium cation, or a salt, such as an alkali metal salt, of any of these.

[0012] The nanoparticle encapsulant material can include hydroxypropyl methylcellulose acetate succinate (HPMCAS), polystyrene-block-polyethylene glycol (PS-b-PEG), or polycaprolactone-block-polyethylene glycol (PCL-b-PEG). The nanoparticle encapsulant material can include a block copolymer, such as an amphiphilic block copolymer, which can have a molecular weight of about 10 kDa or less.

[0013] In an embodiment the active pharmaceutical ingredient is gentamycin, the ion pairing reagent is sodium dodecyl sulfate (SDS), and the nanoparticle encapsulation material is polycaprolactone-block-polyethylene glycol block copolymer. In an embodiment the active pharmaceutical ingredient is polymyxin B, the ion pairing reagent is sodium dodecyl sulfate (SDS), and the nanoparticle encapsulation material is polycaprolactone-block-polyethylene glycol block copolymer. In an embodiment, the active pharmaceutical ingredient is polymyxin B, the ion pairing reagent is sodium dodecylbenzene sulfonate (DBS), and the nanoparticle encapsulation material is polycaprolactone-block-polyethylene glycol block copolymer. In an embodiment the active pharmaceutical ingredient is polymyxin B, the ion pairing reagent is sodium oleate, and the nanoparticle encapsulation material is polycaprolactone-block-polyethylene glycol block copolymer. In an embodiment, the active