[0024] The nanoparticles can have a Z-average particle size of from 10 nm to 1000 nm, from 25 nm to 1200 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. The nanoparticles can have a polydispersity index (PDI) of from 0.06 to 0.5, from 0.07 to 0.34, from 0.08 to 0.27, from 0.1 to 0.2, or from 0.12 to 0.18.

[0025] The API and a supplemental hydrophobic compound can be co-encapsulated in the nanoparticles. For example, the supplemental hydrophobic compound can be a therapeutic, an imaging agent, or an agrochemical compound.

[0026] 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, or 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.

[0027] 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. The counterion can include a fatty acid, an alkyl hydrogen sulfate, an alkylsulfonic acid, or an alkyl quaternary ammonium cation.

[0028] The polymer can include hydroxypropyl methylcellulose acetate succinate (HPMCAS), polystyrene-block-polyethylene glycol (PS-b-PEG), or polycaprolactone-block-polyethylene glycol (PCL-b-PEG). The polymer can include a block copolymer, for example an amphiphilic block copolymer. The block copolymer can have a molecular weight of about 10 kDa or less.

BRIEF DESCRIPTION OF THE DRAWINGS

[0029] FIG. **1** illustrates the Mechanism of ion pairing-based Flash NanoPrecipitation. FNP of pre-ion paired API. Hydrophilic active pharmaceutical ingredients are created as a hydrophobic salt by pre-pairing the API with a hydrophobic counterion. Pre-ion paired APIs are dissolved in organic solvent alongside an amphiphilic block-copolymer, and rapidly micromixed against water. Hydrophobic API ion pairs precipitate into NCs and self-assemble into NCs. FNP with in situ ion pairing. Hydrophilic APIs are dissolved in water and rapidly micromixed against organic solvent containing a hydrophobic API counterion and an amphiphilic block-copolymer. Ion pairing of the API occurs during mixing, producing a hydrophobic API ion pair that precipitates in the presence of an amphiphilic block-copolymer, resulting in the formation of NCs.

[0030] FIG. **2** shows the chemical structure of gentamicin (at top) and polymyxin B (at bottom), hydrophilic active pharmaceutical ingredients tested within the study presented herein. Gentamicin (Log P=−4.21) is an aminoglycoside having a molecular weight of 478 Da that functions by inhibiting protein synthesis. Polymyxin B (Log P=−5.62) is a macrocyclic cationic peptide having a molecular weight of 1302 Da that functions by forming pores on cell membranes. Both gentamicin and polymyxin B are active against gram-negative bacteria.

[0031] FIG. **3** shows ion pairs screened and tested within the study presented herein. A wide variety of anionic salts were used and paired against gentamicin and polymyxin B. Salts that could precipitate APIs into NCs in the FNC process are named in bold. Salts that precipitated APIs out of water, but not into NCs in the FNC process are italicized.

[0032] FIG. **4** provides a graph presenting the results of screening of ion pair (IP) properties for FNP-based NC assembly with polymyxin. The physical properties (pKa and c Log P) of ion pairs that failed to precipitate APIs (diamonds), that precipitated APIs but failed to produce NCs (circles), and that precipitated APIs and produced NCs (squares) are shown. The following IPs that precipitated APIs and produced NCs are labeled: sodium oleate (OA), pamoic acid disodium salt (PA), sodium dodecylbenzene sulfonate (DBS), and sodium dodecyl sulfate (SDS).

[0033] FIG. **5**A provides a graph illustrating the modeling of API precipitation conditions by utilizing equation (10). The fraction of API that is precipitated with varying saturation solubilities of the API:IP complex and with varying tendencies of complex formation (complexation strength) is shown. Saturation solubility is noted with [API:IP]sat and has units of mol L^{-1}. Complexation strength is noted with K_s and has dimensions of mol^{-1} L^{-1}. The amounts of API and IP included in the reaction are at a one-to-one ratio at 1 M.

[0034] FIG. **5**B provides a graph illustrating the modeling of API precipitation conditions by utilizing equation (10). The fraction of API that is precipitated with varying saturation solubilities of the API:IP complex, and by varying the amount of API in the reaction. The amounts of API and IP included in the reaction are at a one to one ratio. $[API]_0$ has dimensions of M. Precipitation yields can be increased by decreasing complex saturation solubility, by increasing complexation strength, or by increasing the concentration of the reaction.

[0035] FIG. **6**A provides a graph of size distributions of NPs formed using gentamycin as a pre-formed API:IP complex using the IPs sodium dodecyl sulfate (SDS), decyl sulfate (DS), sodium dodecylbenzene sulfonate (DBS), and pamoic acid disodium salt (PA). Compositions of NC formulations are given in Table 1.

[0036] FIG. **6**B provides a graph of size distributions of NPs formed using polymyxin B as a pre-formed API:IP complex using the IPs sodium dodecyl sulfate (SDS), decyl sulfate (DS), sodium dodecylbenzene sulfonate (DBS), and pamoic acid disodium salt (PA). Compositions of NC formulations are given in Table 1.

[0037] FIG. **6**C provides a graph of size distributions of NPs formed with in situ ion pairing of polymyxin B using the IPs sodium dodecyl sulfate (SDS), sodium dodecylbenzene sulfonate (DBS), pamoic acid disodium salt (PA), and sodium oleate (OA). Compositions of NC formulations are given in Table 1.

[0038] FIG. **7**A provides a graph showing release rates (fraction released as a function of time) of polymyxin B NCs when using 1:1 API to IP charge ratio for the IPs sodium dodecyl sulfate (SDS), sodium dodecylbenzene sulfonate (DBS), and sodium oleate (OA).