Description

Title of Invention: POLYCARBONATES BEARING AROMATIC N-HETEROCYCLES FOR DRUG DELIVERY

Background

[0001] The present invention relates to polycarbonates bearing aromatic N-heterocycles for drug delivery, and more specifically to water dispersible nanoparticles formed with aromatic N-heterocycle-functionalized polycarbonates and catechol-functionalized polycarbonates for delivering drugs used in medical treatments.

[0002] Drug delivery systems that rely on polymers as vehicles for carrying a drug have several deficiencies, particularly those involving hydrophobic drugs (e.g., Doxorubicin, an anthracycline antibiotic used in chemotherapy, known for its hydrophobicity, toxicity, and difficulty in packaging in a water based delivery system). Generally, the polymers are non-biodegradable. Another deficiency is the susceptibility of nanoparticles to serum protein induced aggregation, which causes undesirable particle size growth in the blood stream. Another deficiency is the propensity of drug carriers to leak drug in the blood stream, which can lower the efficacy of the drug with respect to its intended target and expose patients to toxic side effects of the released drug that the drug-loaded particle was intended to mitigate. Another deficiency is the cytotoxicity of the polymer vehicle itself.

[0003] As a result, a need exists for a biodegradable, non-cytotoxic drug delivery system that is not susceptible to protein induced aggregation (i.e., is "anti-fouling" in the blood stream), and does not prematurely release drug before reaching an intended cell target.

Summary

[0004] ~~Accordingly~~In a first aspect, there is provided a nanoparticle~~ is disclosed~~, comprising:

a drug;

a first block polymer comprising i) a first poly(ethylene oxide) block (first PEO block) and ii) a first polycarbonate block linked to the first PEO block, wherein a) the first polycarbonate block comprises a first repeat unit comprising an aliphatic carbonate backbone portion and a side chain linked to the backbone portion, b) the side chain of the first repeat unit comprises an aromatic nitrogen-containing heterocycle (N-heterocycle), and c) the N-heterocycle of the side chain of the first repeat unit is present as a base, a hydrosalt of the base, a sulfobetaine adduct of the base, or a combination thereof; and

a second block polymer comprising i) a second PEO block and ii) a second poly-carbonate block linked to the second PEO block, wherein a) the second polycarbonate block comprises a second repeat unit comprising an aliphatic carbonate backbone

portion and a side chain linked to the backbone portion and b) the side chain of the second repeat unit comprises a catechol group;
wherein
the drug, the first block polymer, and the second block polymer of the nanoparticle are bound at least by non-covalent interactions,
the nanoparticle is water-dispersible, and
the nanoparticle is capable of controlled release of the drug in a medical treatment.

[0005] ~~Also disclosed~~In another aspect, there is provided a method, comprising:
forming a first mixture comprising a drug and a water miscible organic solvent;
forming a second mixture by dissolving together in water a first block polymer and a second block polymer;
combining the first mixture and the second mixture, thereby forming a third mixture; and
removing the organic solvent from the third mixture, thereby forming a water dispersible nanoparticle comprising the drug, the first block polymer, and the second block polymer bound at least by non-covalent interactions;
wherein
the first block polymer comprises i) a first poly(ethylene oxide) block (first PEO block) and ii) a first polycarbonate block linked to the first PEO block, wherein the first polycarbonate block comprises a first repeat unit, the first repeat unit comprises an aliphatic carbonate backbone portion and a side chain linked to the backbone portion, the side chain of the first repeat unit comprises an aromatic nitrogen-containing heterocycle (N-heterocycle), and the N-heterocycle has the form of a base, a hydrosalt of the base, a sulfobetaine adduct of the base, or a combination thereof,
the second block polymer comprises i) a second PEO block and ii) a second polycarbonate block linked to the second PEO block, wherein the second polycarbonate block comprises a second repeat unit comprising an aliphatic carbonate backbone portion and a side chain linked to the backbone portion, and the side chain of the second repeat unit comprises a catechol group, and
the nanoparticle is capable of controlled release of the drug in a medical treatment.

[0006] ~~Also disclosed~~In another aspect, there is provided a nanoparticle, comprising:
a) a drug;
b) a first block polymer having the formula (1):

L" is a divalent linking group comprising 2 or more carbons,
R" is a monovalent radical selected from the group consisting of hydrogen and alkyl groups comprising 1 to 6 carbons, and
W" is a monovalent end group comprising 1 to 10 carbons;
wherein
components a), b), and c) of the nanoparticle are bound at least by non-covalent interactions,
the nanoparticle is dispersible in water, and
the nanoparticle is capable of controlled release of the drug in a medical treatment.

[0007] ~~Also disclosed~~In another aspect, there is provided a polycarbonate, comprising: a first repeat unit comprising an aliphatic carbonate backbone portion and a side chain linked to the backbone portion, the side chain comprising an aromatic nitrogen-containing heterocycle (N-heterocycle), wherein the N-heterocycle is present in the first repeat unit as a free base (non-charged form), a hydrosalt of the free base, a sulfobetaine adduct of the free base, or a combination thereof.

[0008] The above-described and other features and advantages of the present invention will be appreciated and understood by those skilled in the art from the following detailed description, drawings, and appended claims.

Brief Description of Drawings

[0009] [fig. 1] Fig. 1 is bar chart showing the toxicity profile of sulfobetaine polymer S-1 to HEK293 cells. S-1 is not cytotoxic.
[fig. 2] Fig. 2 is bar chart showing the toxicity profile of sulfobetaine polymer S-2 to HEK293 cells. S-2 is not cytotoxic.
[fig. 3] Fig. 3 is bar chart showing the toxicity profile of sulfobetaine polymer S-3 to HEK293 cells. S-3 is not cytotoxic.
[fig. 4] Fig. 4 is bar chart showing the toxicity profile of poly(ethylene glycol), Mn 5000, (5K PEG) to HEK293 cells. The 5K PEG is not cytotoxic.
[fig. 5] Fig. 5 is bar chart showing the toxicity profile of poly(ethylene glycol), Mn 10000, (10K PEG) to HEK293 cells. The 10K PEG is not cytotoxic.
[fig. 6] Fig. 6 is a graph showing the particle size growth of S-1, S-2 and S-3 versus incubation time up to 48 hours using phosphate buffered saline (PBS) containing 10% serum. Polymer-protein aggregation was observed with S-3. No polymer-protein aggregation was observed with S-1 and S-2.
[fig. 7] Fig. 7 is a bar chart showing the drug loading content (wt%) of Examples 42 to 48.
[fig. 8] Fig. 8 is a graph comparing the drug release profile for the nanoparticles of Example 47 containing 19 wt% Doxorubicin (DOX) with DOX-loaded urea-acid