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(54) **Title:** POLYMER SYSTEMS AND THEIR APPLICATIONS IN DIAGNOSTICS AND DRUG DELIVERY

(57) **Abstract:** The present invention provides a biodegradable "precision polymer system" (poly system) and methods for preparing pharmaceutically effective "precision polymer nanosystems" (polymer nanosystem) for delivery and/or targeting of drugs or drug like compounds.



POLYMER SYSTEMS AND THEIR APPLICATIONS IN DIAGNOSTICS AND DRUG
DELIVERY

CROSS-REFERENCES TO RELATED APPLICATIONS

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[0001] This application claims the benefit under 35 U.S.C. § 119(e) of U.S. Provisional Patent Application No. 62/149,563, filed April 18, 2015, which is incorporated herein by reference in its entirety as if fully set forth herein.

FIELD OF THE INVENTION

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[0002] The present invention provides a biodegradable polymer system and methods for preparing pharmaceutically effective polymer nanosystems for delivery and/or targeting of drugs or drug like compounds.

BACKGROUND OF THE INVENTION

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[0003] Biodegradable polymers have been used as surgical sutures, wound dressings, and as drug delivery systems. Among them, polylactide (PLA), polyglycolide (PGA) and their copolymers (PLGA) have attracted the most attention.

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[0004] Currently there are few synthetic or natural polymeric materials that can be used for the controlled and targeted delivery of drugs, including peptide and protein drugs, because of strict regulatory compliance requirements such as biocompatibility, low toxicity, having a clearly defined degradation pathway, and safety of the polymers and degradation products. The most widely investigated and advanced biodegradable polymers in regard to available toxicological and clinical data are the aliphatic poly(α -hydroxy acids), such as poly(D-, L-, or D, L-lactic acid) (PLA) with varying stereochemistry (L, D or DL), poly(glycolic acid) (PGA) and their copolymers (PLGA). These polymers are commercially available and are presently used as bioresorbable sutures and in biodegradable microsphere drug delivery systems.

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[0005] Even though there has been some success, the success at large is limited by the inability of the commercially available polymers as platforms for wide variety of drugs with distinct physicochemical attributes eg solubility, molecular weight, permeability.

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Additionally, currently known copolymer-based drug carriers do not exhibit efficient targeted delivery of drug compositions.

[0006] Thus, it would be beneficial to have a polymer system that have the ability to optimize ligand-receptor stoichiometry facilitating a receptor-specific targeted delivery combined with tunable release property and further lends itself to facilitate the delivery of compounds with distinct physicochemical attributes.

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SUMMARY OF THE INVENTION

[0007] The present invention provides biodegradable polymer system compositions and methods for preparing a pharmaceutically effective polymer nanosystems for delivery and/or targeting of drugs or drug like compounds.

[0008] The present invention also provides a method for preparing the biodegradable drug delivery composition and a method for effectively administering such a composition to whole body systems eg animals, humans. The drug delivery composition of the present invention can be administered without an aqueous vehicle, or can be administered after being reconstituted in an aqueous vehicle to afford a stable suspension. The administration can be done by peroral means. Additionally, the drug compositions may be administered via the nose or skin and can be injectable.

[0009] The present invention describes a novel biodegradable polymer system compositions and methods for preparing pharmaceutically effective polymer nanosystems for delivery of drugs or drug like compounds precisely where it is needed in the body with minimal non-target effects. Embodiments of the invention are directed to creating biodegradable repeating units with a specific biological function that can form polymer nanosystem with defined size and function e.g., improve intestinal uptake of the polymer nanosystem containing bioactive(s) and/or direct them to a specific site of action to deliver the pay load e.g., tumor epithelium or inflamed endothelium or a specific organ of interest. These polymer systems/polymer nanosystems go beyond the current available systems in that they allow optimization of ligand-receptor stoichiometry which is the key to achieve ideal receptor mediated delivery of the bioactives. Most nanomedicines that are currently under development are single bioactive based. However, the polymer nanosystems allow a combination of bioactives, where such systems are advantageous in the treatment of several diseases e.g., diabetes, cancer, cardiovascular. These systems offers flexibility of converting the molecules that are administered by injections to orally/peroral viable medicines, and can avoid refrigerated storage. These polymer systems/polymer nanosystems can serve as a

platform technology for a variety of bioactives and diseases in that, the bioactive(s) encapsulated and the surface ligands specific to receptor can be varied in a manner that suits a disease of interest. These polymer nanosystems can be designed such a way by varying the molecular weight of the building blocks so that the encapsulated bioactive(s) are released over several days. These polymer nanosystems can be appropriately tailored making them route independent, in that they can be administered via mouth, nose, skin or can be injectable. These polymer nanosystems can be ideal for existing bioactives to improve their performance as well as for new indications.

[00010] The composition of the present invention comprises: 1) one or more biodegradable block copolymer drug carriers comprising A-B, A-B-A or B-A-B block, with chain linkers imparting periodic pendent carboxyl or amine functional groups throughout the polymer backbone, wherein the A block is a biodegradable polyester and the B block is polyethylene glycol (PEG) with the weight percentage of the A block is between 1% to 99%; and chain linker is an aromatic or aliphatic tetracarboxylic dianhydride and 2) a polyethylene glycol (PEG), a PEG derivative, or a mixtures of PEG and a PEG derivative.

[00011] Examples of suitable biodegradable polymers includes ABA- or BAB-type triblock copolymers, or AB-type diblock copolymers based on biodegradable polyester A-blocks and hydrophilic B polymer block(s) consisting of polyethylene glycol (PEG). The biodegradable polyesters are synthesized from monomers selected from the group consisting of D,L-lactide, D-lactide, L-lactide, D,L-lactic acid, D-lactic acid, L-lactic acid, glycolide, glycolic acid, ϵ -caprolactone, 1,4-dioxan-2-one, ϵ -hydroxy hexanoic acid, γ -butyrolactone, γ -hydroxy butyric acid, δ -valerolactone, δ -hydroxy valeric acid, hydroxybutyric acids, malic acid, and copolymers thereof. Polyethylene glycol (PEG) is also sometimes referred to as poly(ethylene oxide) (PEO) or poly(oxyethylene) and the terms can be used interchangeably for the purposes of this invention.

[00012] The biodegradable block copolymer drug carriers suitable for the present invention can form homogeneous suspensions in an aqueous or any other suitable vehicle as desired. Homogeneous suspensions of the drug delivery compositions include all flowing forms of the compositions of the present invention, with or without water, drug(s), and any additives or excipients as necessary to prepare formulations that are pharmaceutically and therapeutically useful. The drug may be present as either a true solution or in a colloidal state such as emulsion or a suspension. All forms can act to facilitate administration of the

drug and enhance the therapeutic effect. Such therapeutic effects may be optimized by controlling the copolymer molecular weights, compositions, and the relative ratios of the hydrophilic and hydrophobic blocks, ratios of drug to copolymer, ratios of copolymer to PEG and/or PEG derivatives, concentration of the conjugated ligands to pendent carboxyl or amine functional groups, the particle size and both drug and copolymer concentrations in the final administered dosage form. Additional advantages of this invention will become apparent from the following detailed description of the various embodiments.

BRIEF DESCRIPTION OF THE DRAWINGS

[00013] FIG. 1A shows the decrease in molecular weight of hP2-400 over a period of 96 hours in PBS at 37 °C;

[00014] FIG. 1B shows the degradation profile of hP2-400 over a period of 96 hours in PBS at 37 °C;

[00015] FIG. 1C shows the decrease in molecular weight of hP2-1000H over a period of 96 hours in PBS at 37 °C;

[00016] FIG. 1D shows the degradation profile of hP2-1000H over a period of 96 hours in PBS at 37 °C;

[00017] FIG. 1E shows the decrease in molecular weight of hP2-2000H over a period of 96 hours in PBS at 37 °C;

[00018] FIG. 1F shows the degradation profile of hP2-2000H over a period of 96 hours in PBS at 37 °C;

[00019] FIG. 2A shows the mean fluorescent intensity of fluorescent P2Ns of hP2-400 in RBCs; and

[00020] FIG. 2B shows the mean fluorescent intensity of fluorescent P2Ns of hP2-400 in plasma.

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

[00021] “Biodegradable” means that the block copolymer or oligomer can chemically break down or degrade within the body to form nontoxic components. The rate of degradation can be the same or different from the rate of drug release.

5 [00022] “Drug” shall mean any organic or inorganic compound or substance having biological or pharmacological activity that can be adapted or used for a therapeutic purpose.

[00023] “Peptide,” “polypeptide,” “oligopeptide” and “protein” shall be used interchangeably when referring to peptide or protein drugs and shall not be limited as to any
10 particular molecular weight, peptide sequence or length, field of bioactivity or therapeutic use unless specifically stated.

[00024] “PLA” shall mean a polymer derived from the poly-condensation of lactic acid or by the ring opening polymerization of lactide.

[00025] “Biodegradable polyester refers to any polymer preferably synthesized
15 from monomers selected from the group consisting of D,L-lactide, D-lactide, L-lactide, D,L-lactic acid, D-lactic acid, L-lactic acid, glycolide, glycolic acid, ϵ -caprolactone, 1,4-dioxan-2-one, ϵ -hydroxy hexanoic acid, γ -butyrolactone, γ -hydroxy butyric acid, δ -valerolactone, δ -hydroxy valeric acid, hydroxybutyric acid, malic acid, ethyleneglycol and mixtures thereof.

[00026] In one embodiment, the biodegradable polymer system comprises
20 ABA-type or BAB-type triblock copolymers, AB-type diblock copolymers or mixtures thereof, where the A-blocks are relatively hydrophobic and comprises a biodegradable polyester, and the B-blocks are relatively hydrophilic and comprises polyethylene glycol (PEG).

[00027] In another embodiment, the biodegradable polymer system comprises
25 multiblock ABA- or BAB-type copolymers of lactic acid and ethylene glycol with periodically spaced side chain carboxyl groups. Multiple pendent carboxyl groups are imparted into the PLA-PEG backbone via the incorporation of an aromatic or aliphatic tetracarboxylic anhydride moiety in the chain extension step. In certain embodiments of the

invention, the tetracarboxylic dianhydrides that are used are pyromellitic dianhydride and cyclohexane tetracarboxylic dianhydride.

[00028] In addition, an embodiment of the present invention is directed to a variation of polymer system that is synthesized with a diamine linker conjugated to the carboxyl groups, such that one of the amine moieties of the linker is covalently bonded to the carboxyl of the polymer while the other remains free for conjugating ligands. The two variations of the polymer, with free carboxyl and amine unit, provides the flexibility to attach the ligands with either a free hydroxyl amine or carboxyl functionality respectively, without the need of any further alteration of either the polymer or ligand.

[00029] As proof of concept some embodiments of the present invention, have been synthesized with PLA and PEG blocks and aromatic or aliphatic linkers imparting multiple pendent carboxyl groups in the polymer backbone. The polymers are characterized using nuclear magnetic resonance (NMR) and gel permeation chromatography (GPC) to verify their chemistry and evaluate their molecular weight. As described above, carboxyl groups for certain embodiments of invention are capped with diamine moieties. Both the variations of polymer nanosystem, with pendent carboxyl and amine groups are further conjugated to ligands with free reactive hydroxyl, amine or carboxyl functionalities. Polymers thus obtained can be used to form polymer nanosystem by appropriate methods. The X-ray photoelectron spectroscopy (XPS) analysis performed on the polymer nanosystem shows that the ligands attached to the polymer system are displayed on the surface of the polymer nanosystem, which is imperative for their availability for binding to the respective receptors on the cells.

[00030] The PEG, PEG derivatives or mixtures thereof used in the present invention dissolves or uniformly mixes with the biodegradable block copolymer and so reduces the viscosity and increases the fluidity of the composition. The compositions of the present invention are flowable liquids or can be easily formulated with an aqueous vehicle to afford a homogeneous uniform colloidal system. The composition can be easily administered as is or reconstituted with an aqueous or appropriate vehicle. After the administration, the block copolymer drug carrier may or may not form a drug depot. Therefore, the liquid PEG, PEG derivative or mixtures thereof of the present invention should be a material that does not cause loss of activity of the physiologically active substance.

[00031] Drugs that may be incorporated with the drug delivery compositions of the present invention can be any bioactive agent, but particular advantage is achieved with bioactive agents having limited solubility or dispersibility in an aqueous or hydrophilic environment, or any bioactive agent that requires enhanced solubility or permeability. In addition, the choice of ligand conjugated to the polymer system will play an important role in the absorption and targetability of the polymer nanosystem and encapsulated drugs, thus enhancing their site/target specificity.

[00032] The present invention thus provides compositions comprising biodegradable block copolymer drug carriers and PEG, PEG derivatives or mixtures thereof that are powders or can be rapidly reconstituted in an aqueous vehicle to afford useful forms that are uniform colloidal systems. The drug solution formed with the drug delivery compositions of the present invention has desirable physical stability, therapeutic efficacy, and toxicology. The PEG, PEG derivatives or mixtures thereof of the present invention can be used for water soluble or water insoluble block copolymeric drug carriers, particularly for biodegradable di- or triblock copolymers that have reverse gelation properties and/or polymers that can enhance the solubility of drugs, especially hydrophobic drugs.

WORKING EXAMPLES

ABBREVIATIONS

CH₂Cl₂ Methylene Chloride

20 DIEA N,N-diisopropylpropylamine

DMAB Didodecyldimethylammonium bromide

DMAP 4-Dimethylaminopyridine

DMF N,N-dimethylformamide

EDA Ethylenediamine

25 EDC 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide

GA Gambogic acid

GaL Galactose

RGD	Arginylglycylaspartic acid
PVA	Poly(vinyl alcohol)
TFA	Trifluoroacetic acid
TfR	Transferrin receptor
5 TPGS	D- α -Tocopheryl polyethylene glycol 1000 succinate
NS	Nanosystems
P2s	Precision polymers
PLGA	Poly(lactide-co-glycolide)
P2Ns	Ligand functional precision polymer nanosystems

10 **Example 1**

[00033] This example describes the synthesis of PLA-PEG400 block pre-polymer from l-lactide and 7% (w/w) PEG-400.

[00034] A 250 ml three necked round-bottomed flask fitted with a reflux condenser, magnetic stirrer, heat-on-block and under a gentle purge of nitrogen, was charged
 15 with l-Lactide (18.0 g; 0.125 mol), PEG400 (3.52 g; 2.65 ml; 0.0088 mol), Stannous Octoate (21.52 mg; 17.20 μ l; 0.1% w/w), Toluene (50 ml). The reaction mixture was heated to a temperature of 115°C while stirring to allow the solvent to reflux. The reaction was carried out under these conditions for 24 h, after which reaction mixture was cooled and solvent was evaporated under reduced pressure. The residue left upon evaporation of solvent was
 20 dissolved in 12 ml methylene chloride and precipitated in 400 ml cold diethyl ether under vigorous stirring. The white polymer was obtained by filtration under suction and dried under vacuum to a constant dry weight (16 mg).

Example 2

[00035] This example describes the chain extension of the pre-polymer from
 25 example 1 with the incorporation of an aromatic linker to impart multifunctionality.

[00036] A 250 ml three necked round-bottomed flask fitted with a reflux condenser, magnetic stirrer, heat-on-block and under a gentle purge of nitrogen was charged with PLA-PEG400 (7 g; 0.6364 mmol), Pyromellitic dianhydride (166.56mg; 0.7636 mmol), Triethylamine (128.81 mg; 177.42 μ l; 1.2728 mol), Stannous Octoate (7 mg; 5.6 μ l; 0.1 w/w) and Toluene (40 ml). The reaction mixture was heated to a temperature of 115°C while stirring to allow the solvent to reflux. The reaction was carried out under these conditions for 24 h, after which reaction mixture was cooled and solvent was evaporated under reduced pressure. The residue dissolved in 10 ml methylene chloride and precipitated in 500 ml cold diethyl ether under vigorous stirring. The white polymer was collected by filtration under suction and dried under vacuum to a constant dry weight (6.2 g).

Example 3

[00037] This example describes the chain extension of the pre-polymer from example 1 with the incorporation of an aliphatic linker to impart multifunctionality.

[00038] A 250 ml three necked round-bottomed flask fitted with a reflux condenser, magnetic stirrer, heat-on-block and under a gentle purge of nitrogen, was charged with PLA-PEG400 (8 g; 0.7273 mmol), Cyclohexane tetracarboxylic dianhydride (195.66 mg; 0.8728 mmol), Triethylamine (147.25 mg; 202.82 μ l; 1.455 mmol), Stannous Octoate (8 mg; 6.4 μ l; 0.1% w/w) and Toluene (50 ml). The reaction mixture was heated to a temperature of 115°C while stirring to allow the solvent to reflux. The reaction was carried out under these conditions for 24 h, after which reaction mixture was cooled and solvent was evaporated under reduced pressure. The residue dissolved in 10 ml methylene chloride and precipitated in 400 ml cold diethyl ether under vigorous stirring. The white polymer was collected by filtration under suction and dried under vacuum to a constant dry weight (6.1 g).

Example 4

[00039] This examples describes the synthetic process of the aminated version of hP2-400 (hP2-400-EDA) described in example 3 using EDA.

[00040] A 50 ml three necked round bottomed flask equipped with magnetic stirrer and under a gentle purge of nitrogen was charged with hP2-400 (250 mg; 0.0142mmol; 11 COOH/mol), EDC (40.83 mg; 0.2131 mmol) and DMF (3 ml) and stirred at room temperature for 30 min. n-boc-EDA (34.12 mg; 33.72 μ l; 0.213 mmol) and DIEA (27.53 mg;

37.1 μ l) were subsequently added to the sitting solution and the reaction was continued for 18 h. The polymer was obtained by precipitation after pouring the reaction mixture in cold water. The precipitate was washed twice with water and dried under vacuum. The dried polymer was dissolved in 2.2 ml of 10:1 mixture of CH_2Cl_2 :TFA and stirred at room temperature for 1 h under nitrogen atmosphere. The solvent was then stripped off on a rotary evaporator and product washed with water to get a white polymer. The hP2-400-EDA polymer was dried under vacuum to a constant dry weight (195 mg).

Example 5

[00041] This examples describes synthesis process of the thioester version of pP2-400 described in example 2 using 2-mercaptoethanol.

[00042] A 50 ml three necked round bottomed flask equipped with magnetic stirrer, condensor and a heat-on block, and under a gentle purge of nitrogen was charged with pP2-400 (100 mg; 0.011mmol; 13 COOH/mol), 2-mercaptoethanol (12.89 mg; 11.61 μ l; 0.165 mmol), methanesulfonic acid (15.86mg; 10.71 μ l; 0.165 mmol) and DMF (2ml). The reaction mixture was stirred at 100°C for 24 h, after which the product was obtained by precipitation in cold water. The product was further washed four times with water until the sulfur smell was eliminated and dried under vacuum to a constant dry weight (57.7 mg).

Example 6

[00043] This examples describes the conjugation of Gambogic acid to the aminated hP2-400 described in example 4.

[00044] A 50 ml three necked round bottomed flask equipped with magnetic stirrer and under a gentle purge of nitrogen was charged with gambogic acid (65.2 mg; 0.1037 mmol), EDC (29.83 mg; 0.1556 mmol) and CH_2Cl_2 (1 ml) and stirred at ambient temperature for 30 min. hP2-400-EDA (125 mg; 0.0069 mmol) pre-dissolved in CH_2Cl_2 (2 ml) and DIEA (20.11 mg; 27.1 μ l; 0.1556 mmol) were subsequently added to the stirring solution and the reaction was carried out at these conditions for another 18 h. The product was obtained by precipitation in cold ether. The polymer was further washed one with ether and another time with water and dried under vacuum to a constant dry weight (104 mg).

Example 7

[00045] This example describes the conjugation of Galactose to hP2-400 described in example 3.

[00046] A 50 ml three necked round bottomed flask equipped with magnetic
5 stirrer and a heat-on block, and under a gentle purge of nitrogen was charged with hP2-400 (250 mg; 0.0142mmol; 11 COOH/mol), D-galactose (38.39 mg; 0.2131 mmol), methanesulfonic acid (20.48 mg; 13.83 μ l; 0.2131 mmol) and DMF (3ml). The reaction mixture was stirred at 60°C for 24 h, after which the product was obtained by precipitation in cold water. The product was further washed twice with water and dried under vacuum to a
10 constant dry weight (242.1 mg).

Example 8

[00047] This example describes the conjugation of arginylglycylaspartic acid (RGD peptide) to hP2-400 described in example 3.

[00048] A 50 ml three necked round bottomed flask equipped with magnetic
15 stirrer and under a gentle purge of nitrogen was charged with hP2-400 (150 mg; 0.0085mmol; 11 COOH/mol), EDC (24.44 mg; 0.1275 mmol) and DMF (2 ml) and stirred at room temperature for 30 min. RGD (44.16 mg; 0.1275 mmol) pre-dissolved in 1 ml DMF and DIEA (16.48 mg; 22.21 μ l; 0.1275 mmol) were subsequently added to the stirring solution and the reaction was continued at these conditions for 18 h. The product was obtained by
20 precipitation in cold water. The polymer was further washed twice in water and dried under vacuum to a constant dry weight (122 mg).

Example 9

[00049] This example describes the conjugation of fluorescent probe, Fluorescein to aminated hP2-400 described in example 4.

25 [00050] A 50 ml three necked round bottomed flask equipped with magnetic stirrer and under a gentle purge of nitrogen was charged with hP2-400-EDA (25 mg; 0.00128 mmol; 9 NH₂/mol), NHS-Fluorescein (7.24 mg; 0.0153 mmol), DIEA (1.98 mg; 2.7 μ l; 0.0153 mmol) and DMF (1 ml). The reaction mixture was stirred in dark under inert atmosphere for 18 h. The product was obtained by precipitation in cold water. The polymer

was further washed twice in water and dried under vacuum to a constant dry weight (12.5 mg).

Example 10

5 [00051] This example describes the conjugation of Hesperetin to pP2-400 described in example 2.

[00052] A 50 ml three necked round bottomed flask equipped with magnetic stirrer and under a gentle purge of nitrogen was charged with pP2-400 (100 mg; 0.0105 mmol; 11 COOH/mol), EDC (30.19 mg; 0.1575 mmol) and DMF (1 ml) and stirred at room temperature for 30 min. Hesperetin (47.61 mg; 0.1575 mmol) and DMAP (1.92 mg; 0.01575 mmol) pre-dissolved in 1 ml DMF were subsequently added to the stirring solution and the reaction was continued at these conditions for 18 h. The product was obtained by precipitation in cold water. The polymer was further washed twice and dried under vacuum to a constant dry weight.

Example 11

15 [00053] This example describes the conjugation of L-Lysine to pP2-400 described in example 2.

[00054] A 50 ml three necked round bottom flask equipped with a magnetic stirrer and under a gentle purge of nitrogen was charged with pP2-400 (100 mg; 0.1 mmol; 11 COOH/mol), EDC (28.75 mg; 0.15 mmol) and DMF (0.5 ml) and stirred at ambient temperature for 30 min. L-Lysine (21.93 mg; 0.15 mmol) predissolved in DMF (0.5 ml) and DIEA (19.39mg; 26.13 µl; 0.15 mmol) were subsequently added to the reaction flask and the reaction was carried out under nitrogen atmosphere and room temperature for 18 h. A pale yellow product was obtained by precipitation in water. The polymer was further washed twice with water and dried under vacuum to a constant dry weight (82.9 mg).

Example 12

[00055] This example describes the conjugation of Cysteine to pP2-400 described in example 2.

[00056] A 50 ml three necked round bottom flask equipped with a magnetic stirrer and under a gentle purge of nitrogen was charged with pP2-400 (100 mg; 0.1 mmol; 11 COOH/mol), EDC (28.75 mg; 0.15 mmol) and DMF (0.5 ml) and stirred at ambient temperature for 30 min. Cysteine (18.17 mg; 0.15 mmol) predissolved in DMF (0.5 ml) and DIEA (19.39 mg; 26.13 µl; 0.15 mmol) were subsequently added to the reaction flask and the reaction was carried out under nitrogen atmosphere and room temperature for 18 h. A pale yellow polymer was obtained by precipitation in water. The polymer was further washed twice with water and dried under vacuum to a constant dry weight (65.1 mg).

Example 13

10 [00057] This example describes the conjugation of Arginine to pP2-400 described in example 2.

[00058] A 50 ml three necked round bottom flask equipped with a magnetic stirrer and under a gentle purge of nitrogen was charged with pP2-400 (100 mg; 0.1 mmol; 11 COOH/mol), EDC (28.75 mg; 0.15 mmol) and DMF (0.5 ml) and stirred at ambient temperature for 30 min. l-Arginine (26.13 mg; 0.15 mmol) predissolved in DMF (0.5 ml) and DIEA (19.39 mg; 26.13 µl; 0.15 mmol) were subsequently added to the reaction flask and the reaction was carried out under nitrogen atmosphere and room temperature for 18 h. A pale yellow polymer was obtained by precipitation in water. The polymer was further washed twice with water and dried under vacuum to a constant dry weight (87.6 mg).

20 **Example 14**

[00059] This example describes the conjugation of Paclitaxel to pP2-400 described in example 2.

[00060] A 50 ml three necked round bottomed flask equipped with magnetic stirrer and under a gentle purge of nitrogen was charged with pP2-400 (100 mg; 0.0072mmol; 10 COOH/mol), EDC (20.70 mg; 0.108 mmol) and DMF (0.5 ml) and stirred at room temperature for 30 min. Paclitaxel (92.2 mg; 0.108 mmol) and DMAP (1.32 mg; 0.0108 mmol) pre-dissolved in 0.5 ml DMF were subsequently added to the stirring solution and the reaction was continued at these conditions for 18 h. The product was obtained by precipitation in cold 1:1 mixture of ethanol and ethyl ether. The polymer was further washed twice and dried under vacuum to a constant dry weight (75 mg).

Example 15

[00061] This example describes the conjugation of Paclitaxel to hP2-400 described in example 3.

[00062] A 50 ml three necked round bottomed flask equipped with magnetic stirrer and under a gentle purge of nitrogen was charged with hP2-400 (100 mg; 0.00521 mmol; 9 COOH/mol), EDC (11.98 mg; 0.0625 mmol) and DMF (0.5 ml) and stirred at room temperature for 30 min. Paclitaxel (53.37 mg; 0.0625 mmol) and DMAP (0.76 mg; 0.00625 mmol) pre-dissolved in 0.5 ml DMF were subsequently added to the stirring solution and the reaction was continued at these conditions for 18 h. The product was obtained by precipitation in cold 1:1 mixture of ethanol and ethyl ether. The polymer was further washed twice and dried under vacuum to a constant dry weight (75 mg).

Example 16

[00063] This example describes the conjugation of Cisplatin to hP2-400 described in example 2.

[00064] A 50 ml three necked round bottom flask equipped with a magnetic stirrer and under a gentle purge of nitrogen was charged with pP2-400 (100 mg; 0.1 mmol; 8 COOH/mol), EDC (19.71 mg; 0.1 mmol) and DMF (1 ml) and stirred at ambient temperature for 30 min. Cisplatin (30 mg; 0.1 mmol) predissolved in DMF (1 ml) and DIEA (12.92 mg; 17.42 µl; 0.1 mmol) were subsequently added to the reaction flask and the reaction was carried out in the dark under nitrogen atmosphere and room temperature for 24 h. A yellow conjugated polymer was obtained by precipitation in water. The polymer was further washed twice with water and dried under vacuum to a constant dry weight (84.3 mg).

Example 17

[00065] This example describes the conjugation of Gemcitabine to pP2-400 described in example 2.

[00066] A 50 ml three necked round bottom flask equipped with a magnetic stirrer and under a gentle purge of nitrogen was charged with pP2-400 (100 mg; 0.1 mmol; 8 COOH/mol), EDC (19.71 mg; 0.1 mmol) and DMF (1 ml) and stirred at ambient temperature for 30 min. Gemcitabine (26.32 mg; 0.1 mmol) predissolved in DMF (1 ml) and DIEA (12.92

mg; 17.42 μ l; 0.1 mmol) were subsequently added to the reaction flask and the reaction was carried out in the dark under nitrogen atmosphere and room temperature for 24 h. A yellow conjugated polymer was obtained by precipitation in water. The polymer further washed twice with water and dried under vacuum to a constant dry weight (80.6 mg).

5 **Example 18**

[00067] This example describes the conjugation of Withaferin A to pP2-2000H (A variation of pP2-400 described in example 2 with 2000 g/mol PEG chains and higher lactide concentration per chain of final polymer).

[00068] A 50 ml three necked round bottomed flask equipped with magnetic
10 stirrer and under a gentle purge of nitrogen was charged with pP2-2000H (50 mg; 0.0017 mmol; 7 COOH/mol), EDC (3.26 mg; 0.017 mmol) and DMF (1 ml) and stirred at room temperature for 30 min. Withaferin A (8.0 mg; 0.017 mmol) and DMAP (0.21 mg; 0.0017 mmol) pre-dissolved in 1 ml DMF were subsequently added to the stirring solution and the
15 reaction was continued at these conditions for 18 h. The product was obtained by precipitation in cold water. The polymer was further washed twice and dried under vacuum to a constant dry weight.

Example 19

[00069] This example describes the conjugation of diagnostic agents to P2s.

[00070] P2s can be functionalized with diagnostic agents e.g. MRI and
20 ultrasound contrast agents, Near-IR fluorescent agents etc. by coupling them to the carboxyl or amine functionality of the P2s via ester or amide bonds based on the available functional unit of the agent. Both the processes involve activation of carboxyl on either the polymer or the diagnostic moiety by EDC followed by either amination in the presence of DIEA or esterification in the presence of DMAP. Alternatively, Fischer esterification can be employed
25 to conjugate a moiety with hydroxyl functionality to the carboxylated P2, if the said moiety can withstand higher temperatures and strong acid catalyst.

Example 20

[00071] This example describes the use of P2s for coupling moieties of different functionalities.

[00072] The methods described in examples 4-19 can be employed on any and all P2s listed in table 3. All P2s can be aminated or thiolated and coupled to ligands, labeling and diagnostic agents, drug molecules etc. as described for the model P2s in the above mentioned examples. The choice of polymer is subject to the requirements for the end product in terms of level of multifunctionality, molecular weight and degradation profile. Fig. 1A shows the decrease in molecular weight of hP2-400 and Fig. 1B shows the degradation profile of hP2-400 over a period of 96 hours. Fig. 1C shows the decrease in molecular weight of hP2-1000H and Fig. 1D shows the degradation profile of hP2-1000H over a period of 96 hours. Fig. 1E shows the decrease in molecular weight of hP2-2000H and Fig. 1F shows the degradation profile of hP2-2000H over a period of 96 hours.

Example 21

[00073] This example describes the general preparation of NS of P2s.

[00074] Due to the multifunctional nature of P2s, large amount of ligand molecules can be attached to the polymer chains resulting in an increase in weight without the increase in chain length. To compensate for the lower level of backbone polymer available in conjugated polymers, additional plain P2s are added equal to the amount of ligand available on the polymer. To prepare NS, 25 mg of P2s or conjugated P2s (with additional plain P2s equal to cumulative ligand weight) were solubilized in 1.25 ml (2% w/v) mixture of CH₂Cl₂ and Ethyl acetate (based on their solubility; table1) and emulsified in a 2.5 ml (0.1-2 %w/v) solution of a stabilizer like DMAB, PVA, TPGS or a combination of the stabilizers. The emulsion was stirred at 1500 rpm for 5 min followed by homogenization at 15000 rpm for 7 min. The final emulsion was diluted with 10 ml water and stirred at 1000 rpm for 3 h. The NS were collected by centrifugation at 15000-20000xg at 4°C for 30 minutes. The pellets of NS were suspended in 0.5 ml 5% (w/v) solution of trehalose dehydrate in water and freeze dried. The emulsification process can be modified based on the physico-chemistry of different drugs to be encapsulated to maximize entrapment efficiency.

Example 22

[00075] This example described the preparation of fluorescent P2Ns from hP2-400, hP2-400-GA, hP2-400-Gal and hP2-400-RGD described in examples 3, 6, 7 and 8 with incorporation of hP2-400-fluorescein described in example 9.

[00076] Due to the multifunctional nature of hP2-400, large amount of ligand molecules can be attached to the polymer chains resulting in an increase in weight without the increase in chain length. To compensate for the lower level of backbone polymer available in conjugated hP2-400, additional plain hP2-400 was added equal to the amount of
5 ligand available on the polymer. To prepare NS, 25 mg of hP2-400 or conjugated hP2-400 (with additional plain polymer equal to cumulative ligand weight) were mixed with 1 mg hP2-400-fluorescein and the mixture was solubilized in 1.25 ml (2% w/v) in a 1:4 mixture of CH₂Cl₂ and ethyl acetate. The organic phase was emulsified in a 2.5 ml (1% or 0.5 %w/v) solution of DMAB. The emulsion was stirred at 1500 rpm for 5 min followed by
10 homogenization at 15000 rpm for 7 min. The final emulsion was diluted with 10 ml water and stirred at 100 rpm for 3 h. The NS were collected by centrifugation at 15000-20000xg at 4°C for 30 minutes. The pellets of NS were suspended in 0.5 ml 5% (w/v) solution of trehalose dehydrate in water and freeze dried.

Example 23

15 [00077] This example describes the encapsulation of Paclitaxel in NS of P2s.

[00078] To prepare paclitaxel loaded NS, 50 mg P2s and paclitaxel (5, 10, 15 or 20% w/w based on loading amount) were solubilized in 5 ml mixture of CH₂Cl₂ and ethyl acetate (based on their solubility; table1) and emulsified in a 5 ml (1% w/v) solution of DMAB. The emulsion was stirred at 1500 rpm for 5 min followed by homogenization at
20 15000 rpm for 5 min. The final emulsion was diluted with 20 ml water and stirred at 1000 rpm for 3 h. The NS were collected by centrifugation at 15000xg at 4°C for 30 minutes. The pellets of NS were suspended in 0.5 ml 5% (w/v) solution of trehalose dehydrate in water and freeze dried.

Example 24

25 [00079] This example describes the encapsulation of Insulin in NS of P2s.

[00080] Insulin loaded P2s-NS were prepared using a double emulsion technique. 50 mg P2s were dissolved in 3 ml mixture of CH₂Cl₂ and ethyl acetate (based on their solubility; table1). Insulin was separately dissolved in 0.5 ml 1.5% (w/v) solution of PVA in 0.01M HCl in an amount equal to 5, 10 or 15% (w/w) of the polymer content based
30 on intended loading. The aqueous phase containing insulin was emulsified in the organic

phase containing polymer and stirred at 1500 rpm for 3 min. this primary emulsion was then added to 10.5 ml 1.5% (w.v) PVA solution in water to form a secondary emulsion which was further stirred for 3 min at 1500 rpm. The emulsion was homogenized at 15000 rpm for 7 min followed by dilution in 20 ml water. The final suspension was stirred for 3 h at 1000 rpm to
5 allow the organic solvent to diffuse out and evaporate. The NS were collected by centrifugation at 15000xg at 4°C for 30 minutes. The pellets of NS were suspended in 0.5 ml 5% (w/v) solution of trehalose dehydrate in water and freeze dried.

Example 25

[00081] This example describes the encapsulation of Cyclosporine A in
10 P2s_NS.

[00082] To prepare cyclosporine A loaded NS, 50 mg P2s and cyclosporine A (5, 10 or 15% w/w based on loading amount) were solubilized in 2.5 ml mixture of CH₂Cl₂ and Ethyl acetate (based on their solubility; table1) and emulsified in a 5 ml (0.1% w/v) solution of DMAB. The emulsion was stirred at 1500 rpm for 1 min followed by probe
15 sonication at 20% amplitude for 30 s. The final emulsion was diluted with 20 ml water and stirred at 1000 rpm for 3 h. The NS were collected by centrifugation at 15000xg at 4°C for 30 minutes. The pellets of NS were suspended in 0.5 ml 5% (w/v) solution of trehalose dehydrate in water and freeze dried.

Example 26

20 [00083] This example describes the uptake of fluorescent P2Ns of hP2-400 described in example 22 in Caco-2 cells monolayers.

[00084] Freeze-dried fluorescent P2NS and PLGA NS (plain or conjugated to GA, Gal or RGD) were suspended in dH₂O at a concentration of 50 and 250 µg/ml respectively. Caco-2 cells were incubated with the 200 µl of F-NS suspension for 5 min at 37
25 °C/5% CO₂, followed by addition serum free medium and further incubation for 1h at 37 °C/5% CO₂. The cells were washed three times with phosphate buffered saline (PBS, pH 7.4) and further processed for fluorescent microscopy and FACS for uptake.

Example 27

[00085] This example describes the evaluation of non –competitive binding of fluorescent P2Ns-GA of hP2-400 described in example 22 to transferrin receptor (TfR) in Caco-2 cells monolayers.

5 [00086] The TfR on Caco-2 mololayers were blocked using human specific TfR primary antibody by incubating for 30 min at 37°C in CO₂ incubator. After three consecutive washings with PBS, P2Ns-GA were added and incubated for further 1 h. These were then washed with PBS 3 times and trypsinized and subjected to FACS analysis.

Example 28

10 [00087] This example describes the uptake of fluorescent P2Ns of hP2-400 described in example 22 in *ex vivo* intestinal tissue.

[00088] To study the uptake of P2Ns in intestinal tissue, 4 µm cryosections of previously excised small intestine were treated with fluorescent plain or ligand conjugated P2Ns suspension in PBS. After 1h incubation at 37°C, the sections were washed multiple
15 times to remove unbound un-internalized NS followed by staining of actin and mounting with mountant containing DAPI.

Example 29

[00089] This example describes the evaluation of non –competitive binding of fluorescent P2Ns-GA of hP2-400 described in example 22 to transferrin receptor (TfR) in *ex*
20 *vivo* small intestine tissue sections.

[00090] The TfR on 4 µm cryosections of previously excised small intestine were blocked using human/mouse specific TfR primary antibody by incubating for 30 min at 37°C in CO₂ incubator. After three consecutive washings with PBS, P2Ns-GA were added and incubated for further 1 h. These were then washed with PBS 3 times and processed for
25 microscopic evaluation.

Example 30

[00091] This example describes the kinetics of fluorescent P2Ns of hP2-400 described in example 22 *in vivo* in Sprague Dawley rats.

[00092] Male Sprague Dawley rats (300-320 g) were dosed perorally with fluorescent plain and conjugated P2Ns (16 mg/rat). Blood was collected via heart puncture at terminal sacrifice at 2, 12 and 24 h. Plasma and RBCs were processed for fluorescence quantification. The plasma kinetics shows ligand specific variable absorption, where those with no ligands were absorbed over extended periods of times suggesting they are lodged in the intestine. Fig. 2A shows the mean fluorescent intensity of fluorescent P2Ns of hP2-400 in RBCs. Fig. 2B shows the mean fluorescent intensity of fluorescent P2Ns of hP2-400 in plasma.

Table 1

[00093] Solubility of hP2s in mixture of methylene chloride and ethyl acetate

Polymer	Ratio (methylene chloride: ethyl acetate)
hP2-400	1:4
hP2-400LP	1:4
hP2-1000	2:3
hP2-2000	3:2
hP2-1000H	1:4
hP2-2000H	1:4

Table 2

[00094] Molecular weights and composition of different PLA-PEG prepolymers with varying chain lengths of PEG and ratios of lactide or lactic acid to ethylene glycol and the constituent PEG molecules

Prepolymer	PEG Chain MW	Lactide:EG	LA:EG	Lactide:PEG	LA:PEG	MW_n	MW_w	PDI
PLA-PEG400	400	1.59	3.17	14.29	28.57	11000	13000	1.2
PLA-PEG400LP	400	3.17	6.35	28.57	57.14	16000	18200	1.1
PLA-PEG1000	1000	0.65	1.30	14.29	28.57	5300	6100	1.2
PLA-PEG2000	2000	0.32	0.63	14.29	28.57	8600	9500	1.1
PLA-PEG1000H	1000	1.59	3.18	34.98	69.96	16100	18300	1.1
PLA-PEG2000H	2000	1.59	3.18	71.55	143.10	18600	22000	1.2

Table 3

[00095] Range of P2s prepared by chain extending prepolymers from table 1 with their respective molecular weight profiles and mol/mol carboxyl side groups perdiolically placed along the polymer chains.

*PMDA: Pyromellitic dianhydride; HCDA: Cyclohexanetetracarboxylic dianhydride

Prepolymer	Polymer	Linker	MWn	MWw	PDI	mol/mol carboxyls
PLA-PEG400	pP2-400	PMDA	15700	22300	1.4	7
	hP2-400	HCDA	19200	30900	1.6	9
PLA-PEG400LP	pP2-400LP	PMDA	27700	44300	1.6	10
	hP2-400LP	HCDA	24500	37500	1.5	10
PLA-PEG1000	pP2-1000	PMDA	6000	7300	1.2	5
	hP2-1000	HCDA	9700	13800	1.4	6
PLA-PEG2000	pP2-2000	PMDA	11000	12700	1.2	8
	hP2-2000	HCDA	11700	14400	1.2	6
PLA-PEG1000H	pP2-1000H	PMDA	18100	22300	1.2	12
	hP2-1000H	HCDA	19700	26100	1.3	12
PLA-PEG2000H	pP2-2000H	PMDA	28800	38100	1.3	7
	hP2-2000H	HCDA	33000	44600	1.4	11

Table 4

10 [00096] Particle size and entrapment efficiency of Paclitaxel in P2s-NS and conventional PLGA (for comparison)

Polymer	5%		10%		15%		20%	
	Size	%EE	Size	%EE	Size	%EE	Size	%EE
PLGA	172±15	51±5	The method failed to produce particles beyond 5% paclitaxel load					
hP2-400	146±7	39±3	117±8	33±4	145±16	44±3	124±7	44±4
hP2-1000H	114±8	25±5	The method failed to produce particles beyond 5% paclitaxel load					
hP2-2000H	170±2	33±6	The method failed to produce particles beyond 5% paclitaxel load					

Table 5

[00097] Particle size and entrapment efficiency of Insulin in P2s-NS and conventional PLGA (for comparison)

Polymer	5%		10%		15%	
	Size	%EE	Size	%EE	Size	%EE
PLGA	249±15	47±5	264±9	46±2	262±12	46±6
hP2-400	351±25	37±4	340±23	48±5	276±12	62±4
hP2-2000H	305±56	10±0.2	343±10	12±2	363±10	7±1

5

Table 6

[00098] Particle size and entrapment efficiency of Cyclosporine A in hP2-2000H

Polymer	5%		10%		15%	
	Size	%EE	Size	%EE	Size	%EE
hP2-2000H	208±7	49±2	211±9	49±3	206±3	50±1

10

[00099] While the invention has been particularly shown and described with references to example embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

15

CLAIMS

What is claimed is:

1. A composition comprising:

one or more biodegradable block copolymer drug carriers comprising A-B, A-B-A or B-A-B
5 block copolymers, wherein the A block is a biodegradable polyester and the B block is
polyethylene glycol (PEG); and a plurality of pendent carboxyl groups derived from aromatic
or aliphatic dianhydrides incorporated within the block copolymer backbone.
2. The composition according to claim 1, wherein the free pendent carboxyl groups are
covalently bonded to a ligand with amine, carboxyl or hydroxyl functionality.
- 10 3. The composition according to claim 1, further comprising a diamine linker that is
conjugated to the carboxyl groups of the block copolymer backbone.
4. The composition according to claim 1, wherein the free amine moiety of the diamine
linker is covalently connected to a ligand.
5. The composition according to claim 1 further comprising a drug physically
15 encapsulated or coupled to contrast or near IR agents.
6. The composition according to claim 1 further comprising a single or multiple drugs
chemically conjugated to the polymer system forming polymer-drug conjugates.
7. The composition according to claim 5-6, wherein the drug has limited aqueous
solubility or permeability or both.
- 20 8. The composition according to claims 1-7, wherein the composition forms polymer
nanosystems or drug conjugates for therapy or diagnosis.
9. An aqueous composition comprising the composition of claim 1 reconstituted in an
aqueous vehicle, wherein said composition is a uniform colloidal system.
10. The composition according to claim 8, wherein the composition comprises covalently
25 bound ligands on the surface that interact non-competitively with receptors on the cell
membranes for receptor-mediated uptake.

11. The composition according to claim 10, wherein the composition comprises two or more ligands to tailor the distribution profile of the composition in the subject.
12. A method of administration comprising reconstituting the composition of claim 1 by addition of water or an aqueous solution to form a uniform colloidal system; and
5 administering the uniform colloidal system to a subject.
13. The method of administration of claim 10, wherein the administering step is through the oral or peroral route.
14. The method of administration of claim 10, wherein the administering step is by nose, skin or injection.

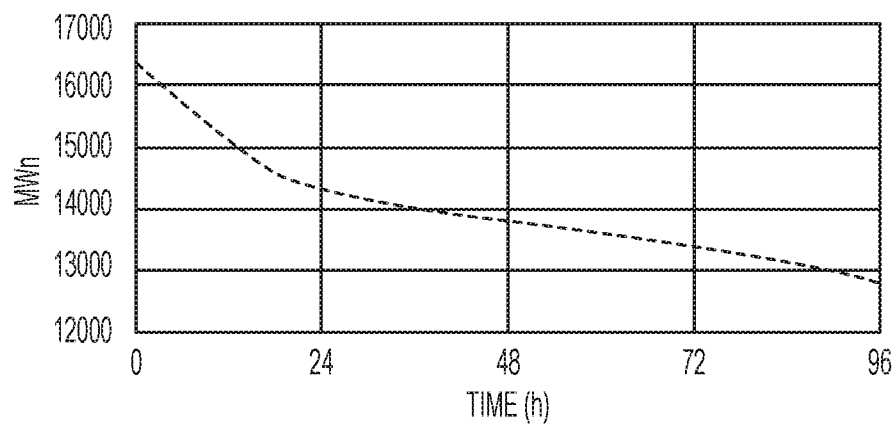


FIG. 1A

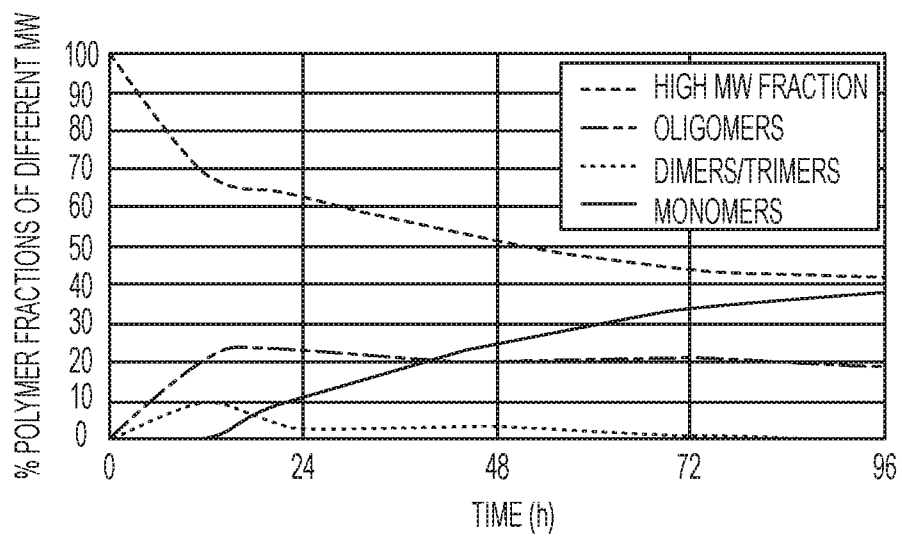


FIG. 1B

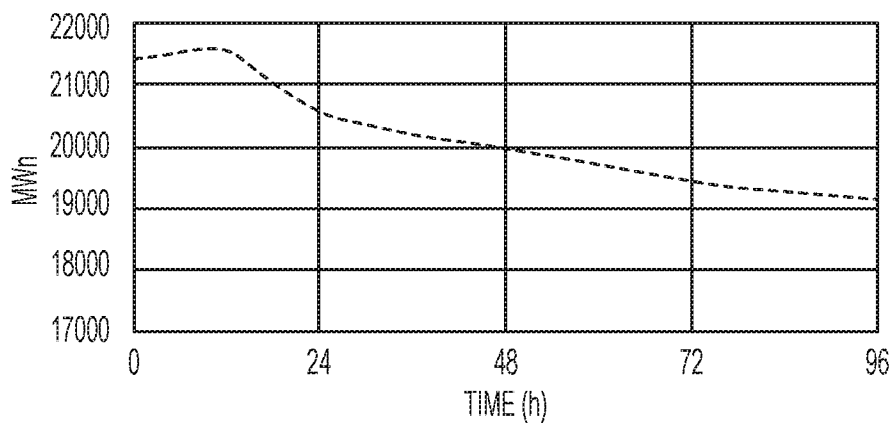


FIG. 1C

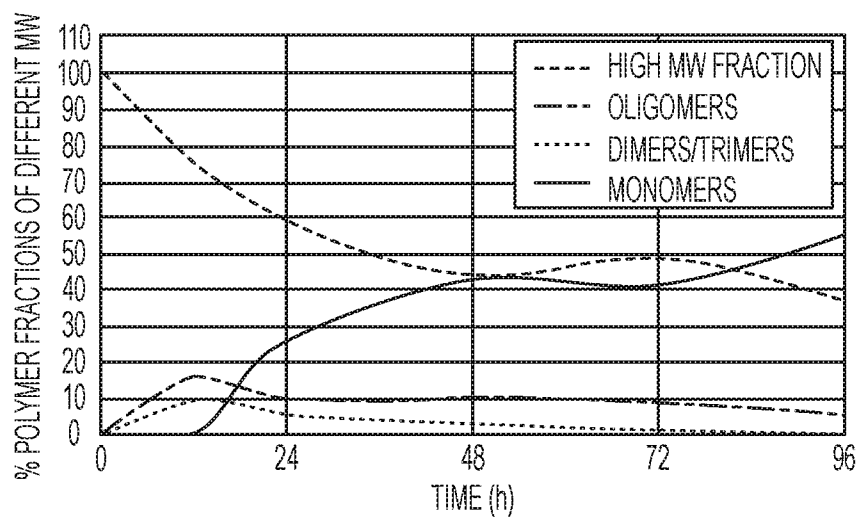


FIG. 1D

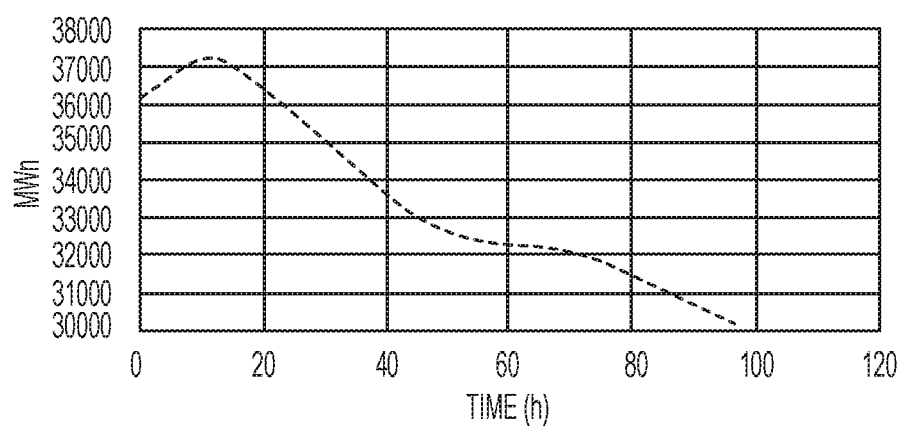


FIG. 1E

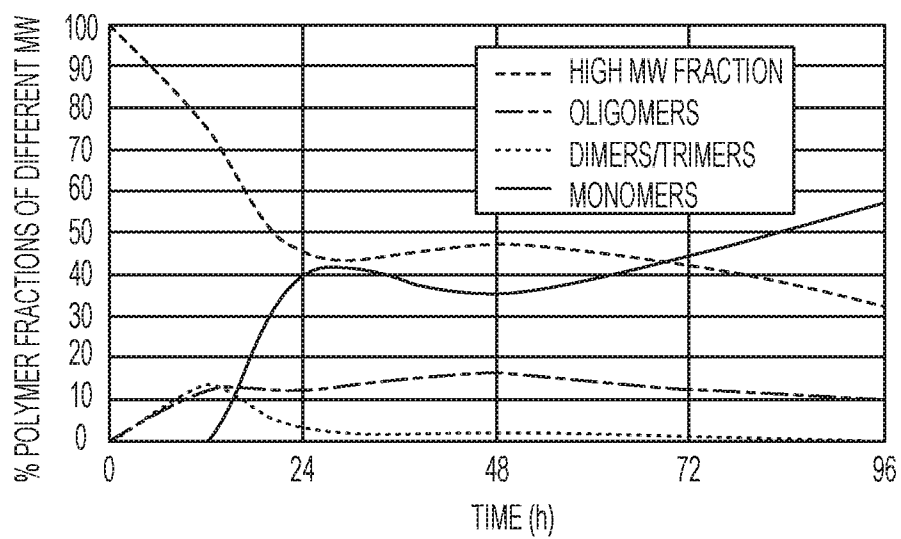


FIG. 1F

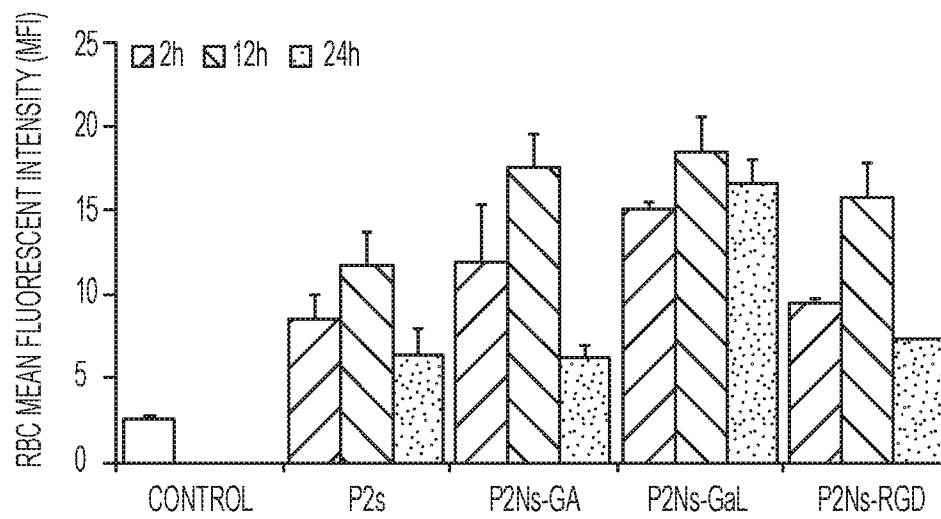


FIG. 2A

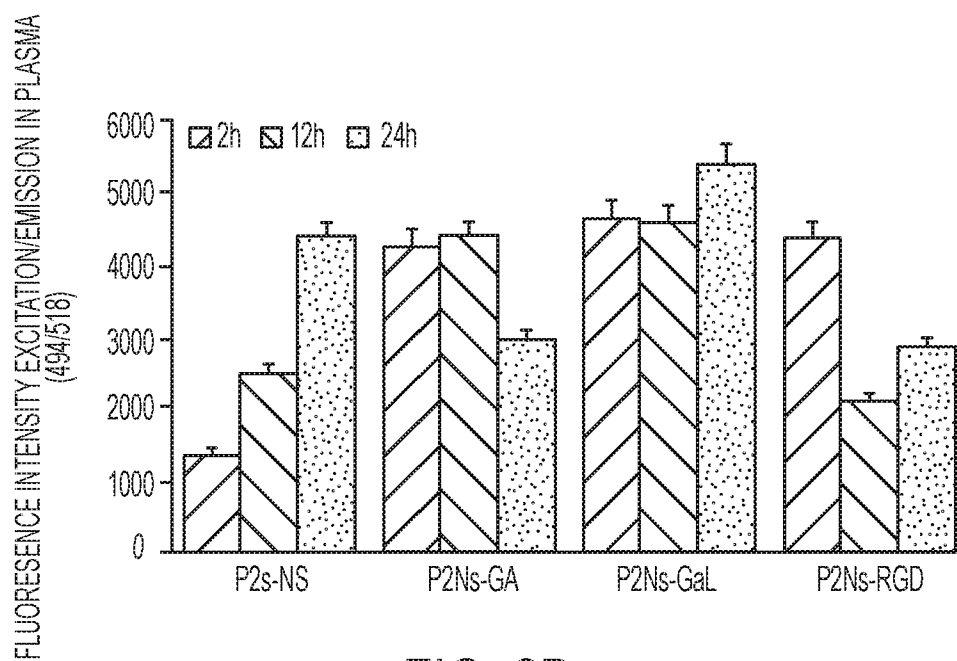


FIG. 2B

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 16/28104

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C08G 63/91; C08L 67/00 (2016.01)

CPC - C08G 63/08; C08L 67/04; C08G 63/664

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

CPC: C08G 63/08; C08L 67/04; C08G 63/664

IPC: C08G 63/91; C08L 67/00 (2016.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 525/415, 525/408 (See Search Words Below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PATBASE: Full-text = AU BE BR CA CH CN DE DK EP ES FI FR GB IN JP KR SE TH TW US WO

Google: Scholar/Patents: copolymer diblock triblock A-B A-B-A drug carrier PLA-PEG covalent diamine pendant amine carboxylic dianhydride

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US2003/0068377 A1 (FOWERS et.al.) 10 April 2003 (10.04.2003) para [0004];[0008];[0012]-[0014];[0033];[0044]-[0046]	1-6; 9;12
Y	US 2010/0260743 A1 (DIWAN et.al.) 14 October 2010 (14.10.2014) para [0008]-[0017];[0021]-[0022];[0034];[0035];[0039];[0040];[0042];[0054];[0055]	1-6; 9;12

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

08 June 2016 (08.06.2018)

Date of mailing of the international search report

18 JUL 2016

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-8300

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 16/28104

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 7, 8, 10, 11, 13-14
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.