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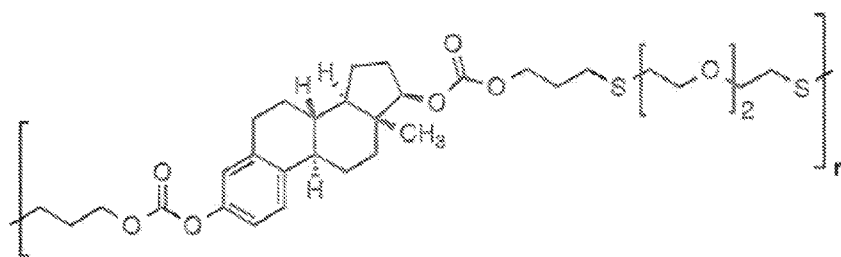


FIG. 1B

(57) Abstract: The poly(pro-drug) material includes one or more alternating therapeutic compounds and biodegradable hydrocarbyl groups. The therapeutic compounds and biodegradable hydrocarbyl groups are separated by cleavable linker compounds. The therapeutic compounds, such as estrogen, curcumin, and fmgolimod, include a plurality of substitutable functional groups that provide reaction sites for complexing with the cleavable linkers and in turn one or more polymers, such that the poly(pro-drug) material ends up composed of the therapeutic compound itself. In aqueous media and at physiological temperature and pH, the poly(pro-drug) materials degrade to release the therapeutic compounds from the material with a zero-order release profile. Advantageously, the poly(pro-drug) materials release the therapeutic compounds on time scales of years. The poly(pro-drug) materials also exhibit reduced to allow for prolonged implantation within a patient. These materials are enticing for a myriad of biomedical applications, including veterinary medicine, cancer treatments, birth control, and hormone replacement therapy.



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SYNTHESIS AND PROCESSING OF POLY(PRO-DRUG) MATERIALS FOR EXTENDED DRUG RELEASE AND USES THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

- 5 **[0001]** This application claims the benefit of U.S. Provisional Patent Application Nos. 62/912,744, filed on October 9, 2019, and 62/746,243, filed on October 16, 2018, which are incorporated herein by reference in their entireties.

BACKGROUND

- 10 **[0002]** Injuries to the Central Nervous System (CNS), including Spinal Cord Injury (SCI) and Traumatic Brain Injury (TBI), present some of the most notoriously intractable problems in modern medicine. For example, SCI affects approximately 17,000 patients per year in the USA, with dismally poor clinical outcomes; some extent of tetraplegia or paraplegia occurs in 99.2% of patients. Compelling epidemiological evidence suggests that females have significant SCI recovery advantages, relative to males. Interestingly, the major
15 female sex hormone, 17 β - Estradiol (E2), exhibits neurotrophic and neuroprotective effects, which might contribute to functional recovery. E2 reduces inflammation, glial cell reactivity, oxidative stress, and glutamate excitotoxic neuronal death, while also providing neurotrophism in the CNS. Since traumatic CNS injuries persist for years after the initial insult, there is an urgent unmet need for contact guidance scaffolds capable of releasing
20 neuroprotective and regenerative drugs for this long duration.

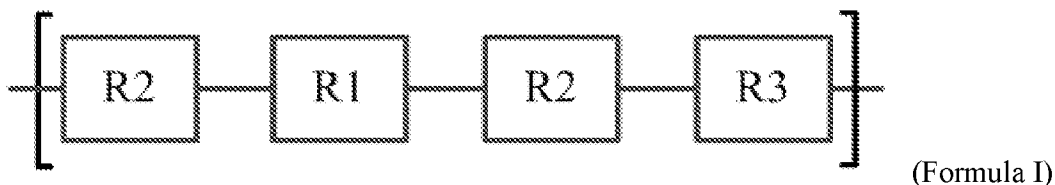
- 25 **[0003]** Estrogen therapies are commonly used by doctors and veterinarians for these and other medical applications. Currently, the majority of products that provide extended release of estrogen are hormonal birth control products that deliver estrogen over time via diffusion. Estring® (Pfizer Health AB, Sweden) and Nuvaring® (Merck Sharp & Dohme B.V. Besloten Vennootschap, Netherlands). Estring®, for example, releases estrogen for approximately 90 days before needing to be removed from a patient and replaced. Other biomaterial estrogen delivery approaches consist of incorporating estrogen into polymeric nanospheres for diffusive estrogen release. This approach, however, has only provided estrogen release for as long as 8 days, and requires co-loading with the protein albumin to achieve this release

duration. Estrogen is also commonly delivered orally using drugs like Premarin® (Wyeth LLC, Delaware) or Menest® (Monarch Pharmaceuticals, LLC, Tennessee).

[0004] Pharmaceutical estrogen delivery approaches also include pro-drug formulations of estrogen. Pro-drugs of estrogen are widespread and currently in clinical use for hormonal therapy, breast and prostate cancers, breast enhancement, treatment of menopause symptoms, and birth control. The vast majority are alkyl esters (e.g., estradiol cypionate, estradiol valerate, estradiol benzoate, estradiol undecylate) administered by intramuscular injection. Typically they are injected once per month with a half-life of ~5 days. Polyestradiol phosphate (PEP), brand name Estradurin® (Ayerst Laboratories, Delaware), is an oligomeric pro-drug of estrogen composed of phosphate bonds. This pro-drug is administered in oil by intramuscular injection, once per month. The polymers are relatively ill-defined short oligomers with extensive chain branching. The average number of estrogen molecules in one Estradurin® oligomer is approximately 13. Estradurin® is currently discontinued in the United States.

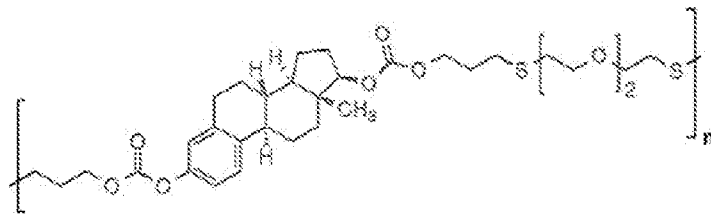
SUMMARY

[0005] Some embodiments of the present disclosure are directed to a poly(pro-drug) material comprising one or more polymers according to Formula I:



In some embodiments, R1 includes one or more therapeutic compounds. In some embodiments, R2 includes one or more cleavable linker compounds. In some embodiments, R3 includes one or more biodegradable hydrocarbyl groups. In some embodiments, the therapeutic compound includes an estrogen, curcumin, fingolimod, or combinations thereof. In some embodiments, the cleavable linker compound includes an ester, a urethane, a carbonate, or combinations thereof bound to the therapeutic compound. In some embodiments, the biodegradable hydrocarbyl group includes a hydrocarbyl chain having at least two carbons. In some embodiments, the biodegradable hydrocarbyl group includes poly(ethylene glycol), poly(ethylene glycol) dithiol, or combinations thereof. In some embodiments, the material has a therapeutic compound release rate of about 0.01% and about

0.25% per day at physiological temperature and pH. In some embodiments, the one or more polymers have a molecular weight between about 80 kDa and about 90 kDa. In some embodiments, the one or more polymers include the structure according to Formula II:



(Formula II)

5 In some embodiments, n is greater than about 25.

[0006] Some embodiments of the present disclosure are directed to a method of making a poly(pro-drug) material. In some embodiments, the method includes providing a reaction medium including a therapeutic compound and a linker compound, wherein the therapeutic compound includes at least two substitutable functional groups. In some embodiments, the at least two substitutable functional groups includes one or more hydroxyl groups, phenoxy groups, amine groups, carboxyl groups, thiol groups, or combinations thereof. In some embodiments, the method includes functionalizing the at least two substitutable functional groups with the linker compound to form a pro-drug. In some embodiments, the linker compound includes allyl chloroformate, toluenediisocyanate, or combinations thereof. In some embodiments, the linker compound includes an ester group, a urethane group, a carbonate group, or combinations thereof for binding to the therapeutic compound. In some embodiments, the method includes copolymerizing the pro-drug with one or more hydrocarbyl groups, the hydrocarbyl groups including hydrocarbyl monomers, hydrocarbyl oligomers, hydrocarbyl polymers, or combinations thereof.

20 **[0007]** Some embodiments of the present disclosure are directed to a method of providing local therapeutic effects. In some embodiments, the method includes providing a solution including a poly(pro-drug) of the following Formula I. In some embodiments, the method includes casting the solution as a polymeric layer. In some embodiments, casting the pro-drug solution as a polymeric layer includes electrospinning the pro-drug solution on a
25 substrate. In some embodiments, the method includes implanting the polymeric layer in a patient at a location in need of a desired effect of the therapeutic compound. In some embodiments, the method includes degrading the poly(pro-drug) at physiological temperature

and pH to release the one or more therapeutic compounds at a rate of about 0.01% and about 0.25% per day.

BRIEF DESCRIPTION OF THE DRAWINGS

[0008] FIGs. 1A-1B are a schematic representations of chemical structures of poly(pro-
5 drug) materials according to some embodiments of the present disclosure;

[0009] FIG. 2 is a graph portraying a release profile of therapeutic compounds from
poly(pro-drug) materials according to some embodiments of the present disclosure;

[0010] FIG. 3 is a chart of a method of making poly(pro-drug) materials according to
some embodiments of the present disclosure;

10 [0011] FIGs. 4A-4B are charts of methods of providing therapeutic effects from
poly(pro-drug) materials according to some embodiments of the present disclosure;

[0012] FIG. 5A is a gel permeation chromatography graph confirming formation of
poly(pro-drug) materials according to some embodiments of the present disclosure;

15 [0013] FIG. 5B is a nuclear magnetic resonance graph confirming formation of poly(pro-
drug) materials according to some embodiments of the present disclosure;

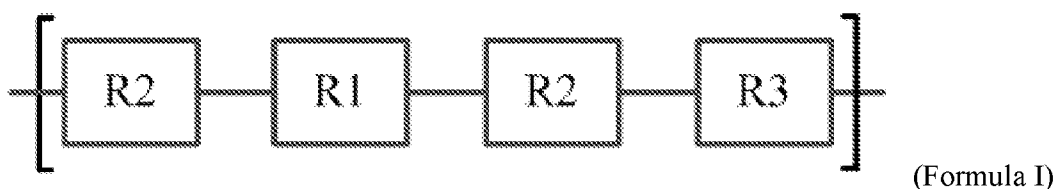
[0014] FIG. 6A is a differential scanning calorimetry graph identifying the glass
transition temperature of poly(pro-drug) materials according to some embodiments of the
present disclosure;

20 [0015] FIG. 6B is a graph showing thermogravimetric analysis of poly(pro-drug)
materials according to some embodiments of the present disclosure; and

[0016] FIG. 7 is a graph portraying induction of neurite growth according to some
embodiments of the present disclosure.

DETAILED DESCRIPTION

25 [0017] Referring now to FIGs. 1A-1B, aspects of the disclosed subject matter include a
poly(pro-drug) material including one or more polymers. In some embodiments, the
polymers include a structure according to following formula:



[0018] In some embodiments, the polymers have an average molecular weight between about 50 kDa and about 120 kDa. In some embodiments, the polymers have an average molecular weight between about 60 kDa and about 110 kDa. In some embodiments, the polymers have an average molecular weight between about 70 kDa and about 100 kDa. In some embodiments, the polymers have an average molecular weight between about 80 kDa and about 90 kDa.

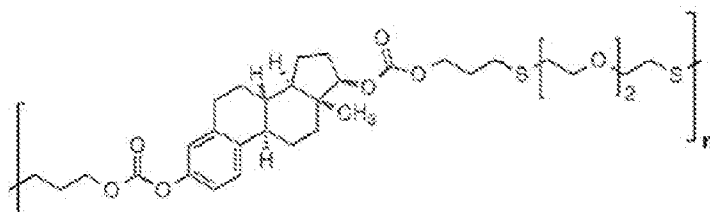
[0019] In some embodiments, R1 of Formula I includes one or more therapeutic compounds. In some embodiments, R1 includes a plurality of therapeutic compounds. In some embodiments, R1 includes two or more different therapeutic compounds. In some embodiments, the therapeutic compound includes an estrogen, curcumin, fingolimod, or combinations thereof. In some embodiments, the polymers include more than about 25 therapeutic compounds, on average. In some embodiments, the polymers include more than about 50 therapeutic compounds, on average. In some embodiments, the polymers include more than about 100 therapeutic compounds, on average. In some embodiments, the polymers include more than about 150 therapeutic compounds, on average.

[0020] In some embodiments, R2 of Formula I includes one or more linkers. In some embodiments, the one or more linkers include chemical compounds. In some embodiments, the one or more linkers are cleavable, e.g., via hydrolytic degradation. In some embodiments, the one or more linkers include an ester, a urethane, a carbonate, or combinations thereof bound to the therapeutic compound.

[0021] In some embodiments, R3 of Formula I includes one or more hydrocarbyl groups. As used herein, the term “hydrocarbyl” is used to refer to saturated and unsaturated hydrocarbon compounds, including chains, rings, or combinations thereof, and can also include amounts of oxygen, sulfur, nitrogen, etc. In some embodiments, the hydrocarbyl group includes at least 2, 4, 6, 8, 10, 12, 14, 16, or 18 carbons. In some embodiments, the hydrocarbyl group includes more than 18 carbons. In some embodiments, the hydrocarbyl

group includes poly(ethylene glycol), poly(ethylene glycol) dithiol, or combinations thereof. In some embodiments, the one or more hydrocarbyl groups is biodegradable.

[0022] In some embodiments, the polymers include a structure according to the following formula:



(Formula II)

In some embodiments, n is greater than about 25. In some embodiments, n is greater than about 50. In some embodiments, n is greater than about 100. In some embodiments, n is greater than about 150.

[0023] In some embodiments, the poly(pro-drug) material includes a plurality of polymers according to Formulas I and/or II to form a polymer network. In some embodiments, at least some of the polymers in the polymer network are crosslinked. In some embodiments, the polymers of the polymer network are generally aligned. In some embodiments, the therapeutic compound has generally uniform distribution across the polymer network. In some embodiments, the therapeutic compound has a nonuniform distribution across the polymer network. In some embodiments, all therapeutic compounds in the polymer network have the same intended therapeutic effect. In some embodiments, the polymer network includes a first therapeutic compound and a second therapeutic compound, the first therapeutic compound having a different therapeutic effect than the second therapeutic compound. In some embodiments, these effects are provided locally, systemically, or combinations thereof. In some embodiments, the therapeutic effect is anti-inflammatory, cell reactivity, antioxidative, cytotoxic, anticytotoxic, etc., or combinations thereof. In some embodiments, the polymers include one or more side chains. In some embodiments, the one or more side chains include hydrocarbyl groups, ionic groups, or combinations thereof.

[0024] In some embodiments, the therapeutic compound is released from the poly(pro-drug) material by degrading the linkers, the hydrocarbyl groups, bonds between the therapeutic compounds and the linkers, the bonds between the linkers and the hydrocarbyl

groups, or combinations thereof. In some embodiments, the poly(pro-drug) material is degraded by aqueous media. In some embodiments, the degradation includes hydrolysis of the linkers, the hydrocarbyl groups, the bonds between the therapeutic compound and the linkers, the bonds between the linker and the hydrocarbyl groups, or combinations thereof.

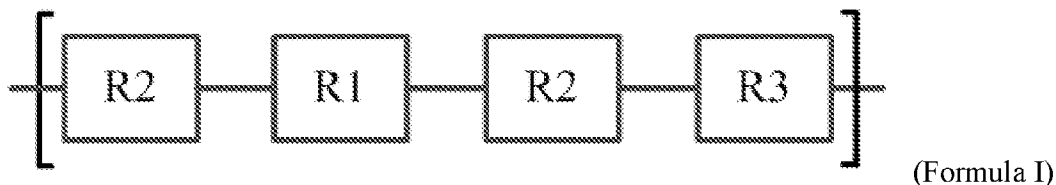
5 Referring now to FIG. 2, some embodiments of the poly(pro-drug) material of the present disclosure advantageously degrade over time scales significantly longer than those previously disclosed in the art. This slow degradation enables the poly(pro-drug) material to degrade *in vivo* over the course of several months to several years. The slow degradation of the polymeric network thus prolongs release of the therapeutic compound into the surrounding
10 environment because the therapeutic compound is incorporated into the degrading polymeric network itself. As shown in FIG. 2, the release profile of therapeutic compounds from the poly(pro-drug) materials according to some embodiments of the present disclosure are generally linear. In some embodiments, the poly(pro-drug) material has a therapeutic compound release rate of about 0.01% and about 0.25% per day at physiological temperature
15 and pH.

[0025] Referring now to FIG. 3, some embodiments of the present disclosure are directed to a method 300 of making a poly(pro-drug) material such as that described above. At 302, a reaction medium is provided. In some embodiments, the reaction medium includes a therapeutic compound and a linker compound. In some embodiments, the reaction medium
20 includes two or more different therapeutic compounds. In some embodiments, the therapeutic compound includes at least two substitutable functional groups. In some embodiments, the at least two substitutable functional groups include one or more hydroxyl groups, phenoxy groups, amine groups, carboxyl groups, thiol groups, or combinations thereof. In some embodiments, the therapeutic compound includes an estrogen, curcumin,
25 fingolimod, or combinations thereof. In some embodiments, the linker compound includes one or more ester groups, urethane groups, carbonate groups, or combinations thereof for binding to the therapeutic compound. In some embodiments, the linker compound includes allyl chloroformate, toluenediisocyanate, or combinations thereof.

[0026] At 304, the at least two substitutable functional groups are functionalized with the
30 linker to form a pro-drug. At 306, the pro-drug is copolymerized with one or more hydrocarbyl groups. In some embodiments, the hydrocarbyl groups include hydrocarbyl monomers, hydrocarbyl oligomers, hydrocarbyl polymers, or combinations thereof. In some

embodiments, the hydrocarbyl group includes poly(ethylene glycol), poly(ethylene glycol) dithiol, or combinations thereof. The relatively simple reaction pathways can be used to tune both the stiffness of the poly(pro-drug) material and release of therapeutic compounds from that material. In some embodiments, the stiffness of the poly(pro-drug) material is reduced by use of longer hydrocarbyl groups between the therapeutic compounds.

[0027] Referring now to FIGs. 4A-4B, some embodiments of the present disclosure are directed to a method 400 of providing therapeutic effects. In some embodiments, these effects are provided locally, systemically, or combinations thereof. As discussed above, in some embodiments, the therapeutic effect is anti-inflammatory, cell reactivity, antioxidative, cytotoxic, anticytotoxic, etc., or combinations thereof. At 402, a solution is provided that includes a poly(pro-drug) of the following Formula I:



As discussed above, in some embodiments, R1 includes one or more therapeutic compounds, R2 includes one or more cleavable linker compounds, and R3 includes one or more biodegradable hydrocarbyl groups. At 404A, the solution is cast as a polymeric layer. In some embodiments, the polymeric layer is shaped into a film, a tube, a stent, a fiber, other structure, etc., or combinations thereof. Referring now specifically to FIG. 4B, in some embodiments, casting the pro-drug solution as a polymeric layer includes depositing the pro-drug solution on a substrate. In some embodiments, the polymeric layer is dip coated, electrospun, or combinations thereof. In some embodiments, the substrate is implantable, e.g., is sized, shaped, and composed for implantation in a human, animal, etc. In some embodiments, the substrate includes an electrode, a tube, a stent, a fiber, structure composed of plastic, metallic, or natural materials, etc.

[0028] Referring again to both FIGs. 4A-4B, at 406, the polymeric layer is implanted in a patient at a location in need of a desired therapeutic effect of the therapeutic compound. As discussed above, in some embodiments, the therapeutic compound includes an estrogen, curcumin, fingolimod, or combinations thereof.

[0029] In some embodiments, the poly(pro-drug) degrades after implanting in the patient, releasing the therapeutic compound into the surrounding tissue. As discussed above, in some embodiments, the poly(pro-drug) releases the one or more therapeutic compounds at a rate of about 0.01% and about 0.25% per day at physiological temperature and pH.

5 Because the implanted poly(pro-drug) is, in part, composed of the therapeutic compound, traditional elements such as carrier polymers or compound loading procedures are no longer needed. The longer release time prolongs the duration of the therapeutic effect, which reduces the frequency of which an implanted structure would need to be replaced and further improves the biocompatibility of the structure.

10 EXAMPLE

[0030] Samples of a poly(pro-drug) material (P1) consistent with the embodiments described above were prepared. Characterization by gel permeation chromatography (GPC, FIG. 5A) confirmed the formation of high MW polymer ($M_w = 84$ kDa, $\bar{D} = 3.73$) and the 1H and ^{13}C NMR (FIG. 5B) were fully consistent with the proposed chemical structure of the
15 polymer.

[0031] Thermal characterization of the poly(pro-drug) material by DSC revealed a low glass transition temperature ($T_g \sim 11$ °C, FIG. 6A), which is consistent with the soft, rubbery properties of this material at room temperature mainly due to the presence of the flexible oligo(ethylene glycol) linker units in the backbone. This property is atypical of
20 polycarbonates, which are more commonly polymers of stiff/rigid units giving rise to a brittle, glassy solid at room temperature. Thermogravimetric Analysis (TGA) showed decomposition beginning at 270 °C (FIG. 6B), which is typical of a synthetic polycarbonate.

[0032] The hydrophobicity and mechanical properties of the poly(pro-drug) material were compared to poly(L-lactic acid) (PLLA), a polyester commonly used in biomaterials.
25 The poly(pro-drug) material films are modestly hydrophobic ($94.2 \pm 0.6^\circ$) compared to PLLA films ($74.5 \pm 0.7^\circ$), according to static water contact angle goniometry images (FIG. 6C). The observed hydrophobicity of the poly(pro-drug) material films is thus comparable to many common polymeric biomaterials. Nanoindentation (FIG. 6D) demonstrates that the Young's modulus (E_r) of the poly(pro-drug) material films (0.11 ± 0.06 GPa) is approximately 49-fold
30 lower than that of PLLA films (5.38 ± 1.06 GPa), and the hardness (H) of P1 (7 ± 3 MPa) is approximately 37-fold lower than that of PLLA (257 ± 158 MPa).

[0033] Poly(pro-drug) material fiber degradation was studied under accelerated degradation conditions at 60 and 79 °C (see again FIG. 3), because the very slow hydrolysis rates at 37 °C rendered the detection of full release impractical on the laboratory time scale. As discussed above, at all temperatures studied, a zero-order release profile was observed.

5 By estimating the activation energy from accelerated degradation experiments, the release at 37 °C from micron-scale electrospun fibers was predicted assuming Arrhenius behavior. The poly(pro-drug) material electrospun fibers release 0.21 % of the incorporated E2 in a scaffold per day. This predicted release rate translates to poly(pro-drug) material fibers that deliver ~50 ng of E2 daily, corresponding to a ~180 nM concentration in 1 mL of release
10 buffer.

[0034] In contrast, thick films of the poly(pro-drug) material release E2 even more slowly in terms of percentages, at a rate of 0.016% of the incorporated E2 mass in the scaffold per day (equivalent to 266 ± 19 ng/day in terms of mass) at 37 °C. It would thus require as long as 17 years to fully degrade the entire thin film at physiological temperature
15 and pH. Because the thick films include a much larger absolute quantity of E2 relative to the micron-scale fibers, release of E2 from the films was directly observed.

[0035] To examine the bioactivity of E2 released during poly(pro-drug) material degradation and the effects of sustained E2 release on neurons, whole dorsal root ganglion (DRG) were cultured on poly(pro-drug) material films to examine the ability of the
20 poly(pro-drug) material to promote neurite extension. To analyze material-derived neurite extension, DRG were cultured onto three types of scaffolds: 1) PLLA fibers electrospun onto a PLLA film (PLLA/PLLA), 2) PLLA fibers electrospun on to a PLLA film with a 100 nM bolus of exogenous E2 at the beginning of culture (PLLA/PLLA + Exo E2), and 3) PLLA fibers electrospun onto a poly(pro-drug) material film (PLLA/P1). A bolus of E2 was used as
25 a comparison to demonstrate the benefit of sustained E2 release relative to a one-time injection. PLLA fibers were used in this experiment to isolate the effects of E2 released the poly(pro-drug) material as the only factor influencing DRG neurite extension.

[0036] The average neurite outgrowth from DRG cultured onto PLLA/P1 scaffolds ($1153 \pm 347.0\mu\text{m}$) was significantly greater than neurite outgrowth from DRG cultured
30 onto PLLA/PLLA scaffolds ($0 \pm 0\mu\text{m}$, $p < 0.001$, one-way ANOVA) or DRG cultured onto PLLA/PLLA scaffolds with bolus E2 ($526.7 \pm 273.4\mu\text{m}$, $p = 0.028$, one-way ANOVA). These results show that the poly(pro-drug) material induces DRG neurite outgrowth that was

significantly greater than the neurite outgrowth observed when a one-time bolus of E2 was administered (FIG. 7).

[0037] Methods and systems of the present disclosure are advantageous in that they provide safe, longer-term therapeutic compound release for a variety of applications.

5 Incorporating prolonged-release therapeutic compounds into coatings for implantable structures, or into implantable structures themselves, provides an added therapeutic benefit to these structures. In the case of estrogen as described here, otherwise inert structures can be endowed with neuroprotective and tissue regenerative properties, e.g., at locations having suffered a nerve injury.

10 **[0038]** In comparison to Estradurin®, the poly(pro-drug) materials of the present disclosure is a substantially longer polymer where the drug is presented as a component of the material itself. The material is also able to cast as a coating on a substrate via multiple processes, such as dip coating or electrospinning. Additionally, the overall reaction scheme allows incorporation of the therapeutic compounds into polycarbonate networks for more
15 sustained release relative to PE, PAE, and PEP.

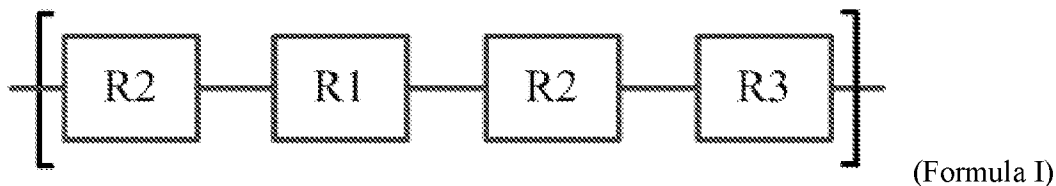
[0039] The longest term estrogen releasing products on the market include Estradurin®, which provides estrogen delivery for approximately one month, and Estring®, which releases estrogen via diffusion for up to 90 days. The control of drug release over years-long time scales is unprecedented in the field, and all components released from the material are
20 generally recognized as safe. The poly(pro-drug) materials also exhibit advantageously reduced stiffness relative to previous materials, increasing their viability as candidates for long-term implantation. Thus, the present disclosure improves upon similar products because the estrogen-release duration is significantly increased, and the material will not need to be removed from a patient since the implantable device will fully degrade over time without any
25 toxic byproducts. In view of the above, the methods and systems of the presents disclosure are enticing for a myriad of biomedical applications, including veterinary medicine, cancer treatments, birth control, and hormone replacement therapy.

[0040] Although the invention has been described and illustrated with respect to exemplary embodiments thereof, it should be understood by those skilled in the art that the
30 foregoing and various other changes, omissions and additions may be made therein and thereto, without parting from the spirit and scope of the present invention.

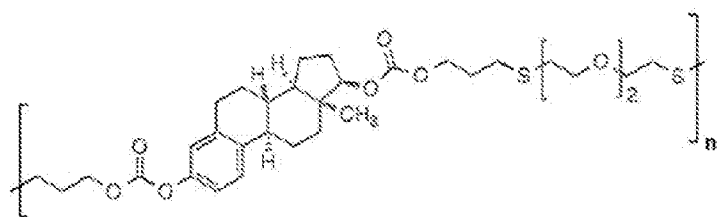
CLAIMS

What is claimed is:

1. A poly(pro-drug) material comprising one or more polymers according to Formula I:



- 5 wherein R1 includes one or more therapeutic compounds, R2 includes one or more cleavable linker compounds, and R3 includes one or more biodegradable hydrocarbyl groups.
2. The poly(pro-drug) material according to claim 1, wherein the therapeutic compound includes an estrogen, curcumin, fingolimod, or combinations thereof.
- 10 3. The poly(pro-drug) material according to claim 1, wherein the cleavable linker compound includes an ester, a urethane, a carbonate, or combinations thereof bound to the therapeutic compound.
4. The poly(pro-drug) material according to claim 1, wherein the biodegradable hydrocarbyl group includes a hydrocarbyl chain having at least two carbons.
- 15 5. The poly(pro-drug) material according to claim 4, wherein the biodegradable hydrocarbyl group includes poly(ethylene glycol), poly(ethylene glycol) dithiol, or combinations thereof.
6. The poly(pro-drug) material according to claim 1, wherein the material has a therapeutic compound release rate of about 0.01% and about 0.25% per day at physiological temperature and pH.
- 20 7. The poly(pro-drug) material according to claim 1, wherein the one or more polymers have a molecular weight between about 80 kDa and about 90 kDa.
8. The poly(pro-drug) material according to claim 1, wherein the one or more polymers include the structure according to Formula II:



(Formula II)

9. The poly(pro-drug) material according to claim 8, wherein n is greater than about 25.

10. A method of making a poly(pro-drug) material, comprising:

providing a reaction medium including a therapeutic compound and a linker compound, wherein the therapeutic compound includes at least two substitutable functional groups;

functionalizing the at least two substitutable functional groups with the linker compound to form a pro-drug; and

copolymerizing the pro-drug with one or more hydrocarbyl groups, the hydrocarbyl groups including hydrocarbyl monomers, hydrocarbyl oligomers, hydrocarbyl polymers, or combinations thereof.

11. The method according to claim 10, wherein the at least two substitutable functional groups includes one or more hydroxyl groups, phenoxyl groups, amine groups, carboxyl groups, thiol groups, or combinations thereof.

12. The method according to claim 10, wherein the therapeutic compound includes an estrogen, curcumin, fingolimod, or combinations thereof.

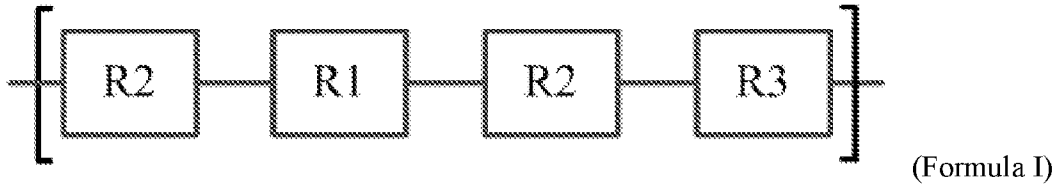
13. The method according to claim 10, wherein the linker compound includes an ester group, a urethane group, a carbonate group, or combinations thereof for binding to the therapeutic compound.

14. The method according to claim 13, wherein the linker compound includes allyl chloroformate, toluenediisocyanate, or combinations thereof.

15. The method according to claim 10, wherein the hydrocarbyl group includes poly(ethylene glycol), poly(ethylene glycol) dithiol, or combinations thereof.

16. A method of providing local therapeutic effects comprising:

providing a solution including a poly(pro-drug) of the following Formula I:



wherein R1 includes one or more therapeutic compounds, R2 includes one or more cleavable linker compounds, and R3 includes one or more biodegradable hydrocarbyl groups;

casting the solution as a polymeric layer; and

implanting the polymeric layer in a patient at a location in need of a desired effect of the therapeutic compound.

17. The method according to claim 16, wherein casting the poly(pro-drug) solution as a polymeric layer includes electrospinning the poly(pro-drug) solution on a substrate.

18. The method according to claim 16, wherein the therapeutic compound includes an estrogen, curcumin, fingolimod, or combinations thereof.

19. The method according to claim 16, wherein the one or more biodegradable hydrocarbyl groups include poly(ethylene glycol), poly(ethylene glycol) dithiol, or combinations thereof.

20. The method according to claim 16, further comprising degrading the poly(pro-drug) at physiological temperature and pH to release the one or more therapeutic compounds at a rate of about 0.01% and about 0.25% per day.

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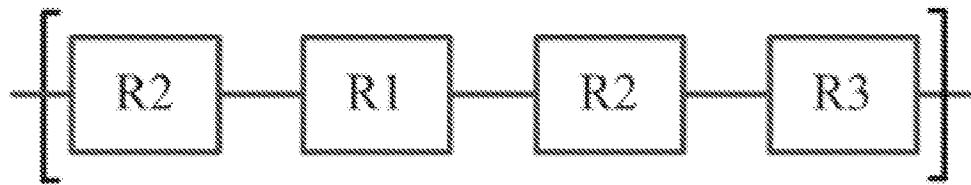


FIG. 1A

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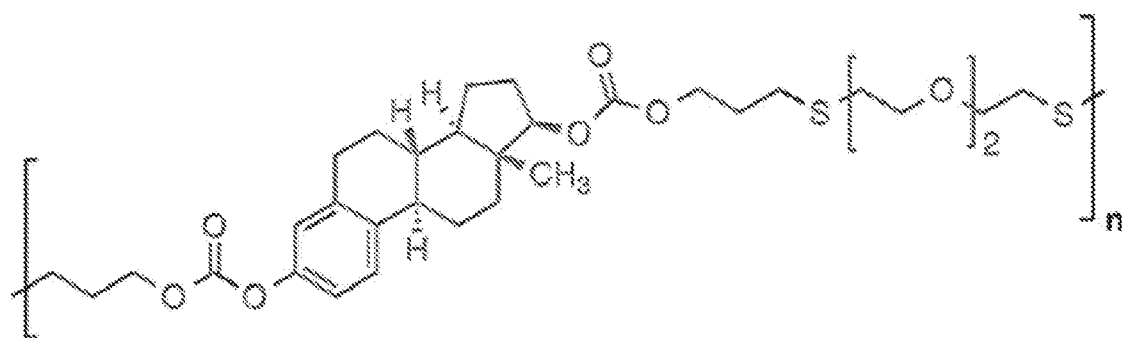


FIG. 1B

3 / 11

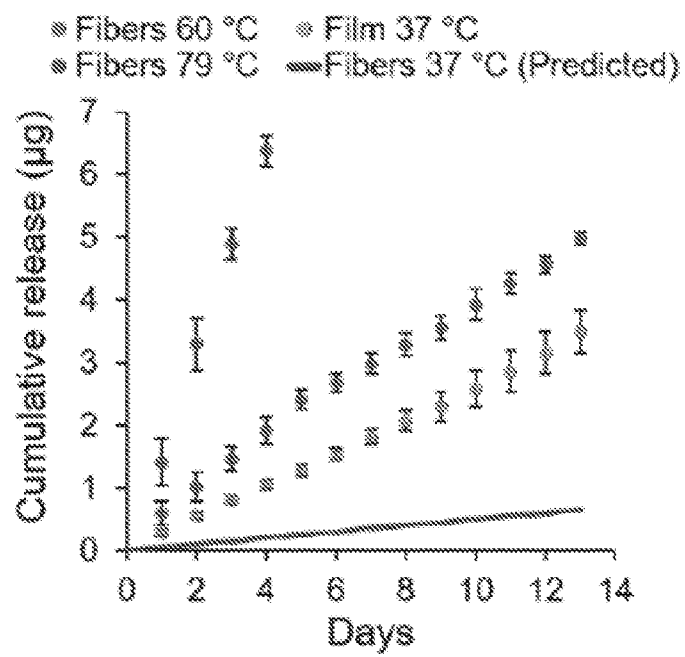


FIG. 2

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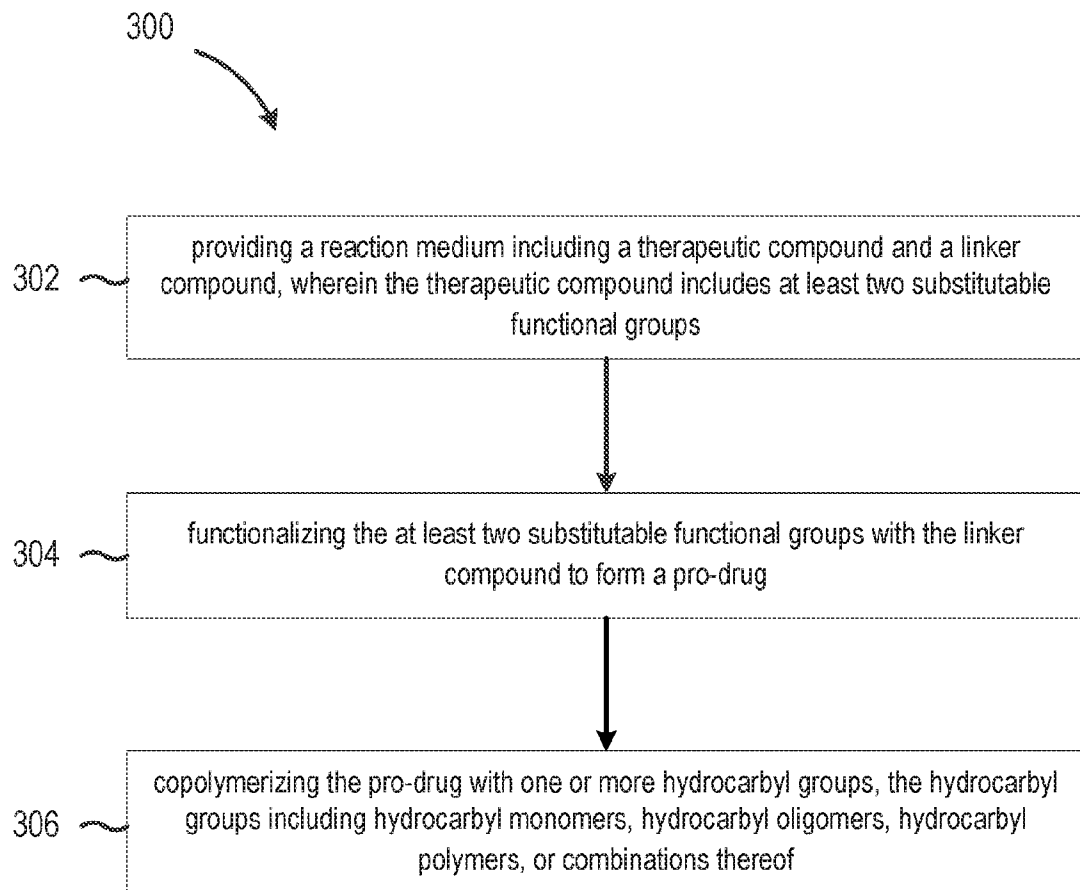


FIG. 3

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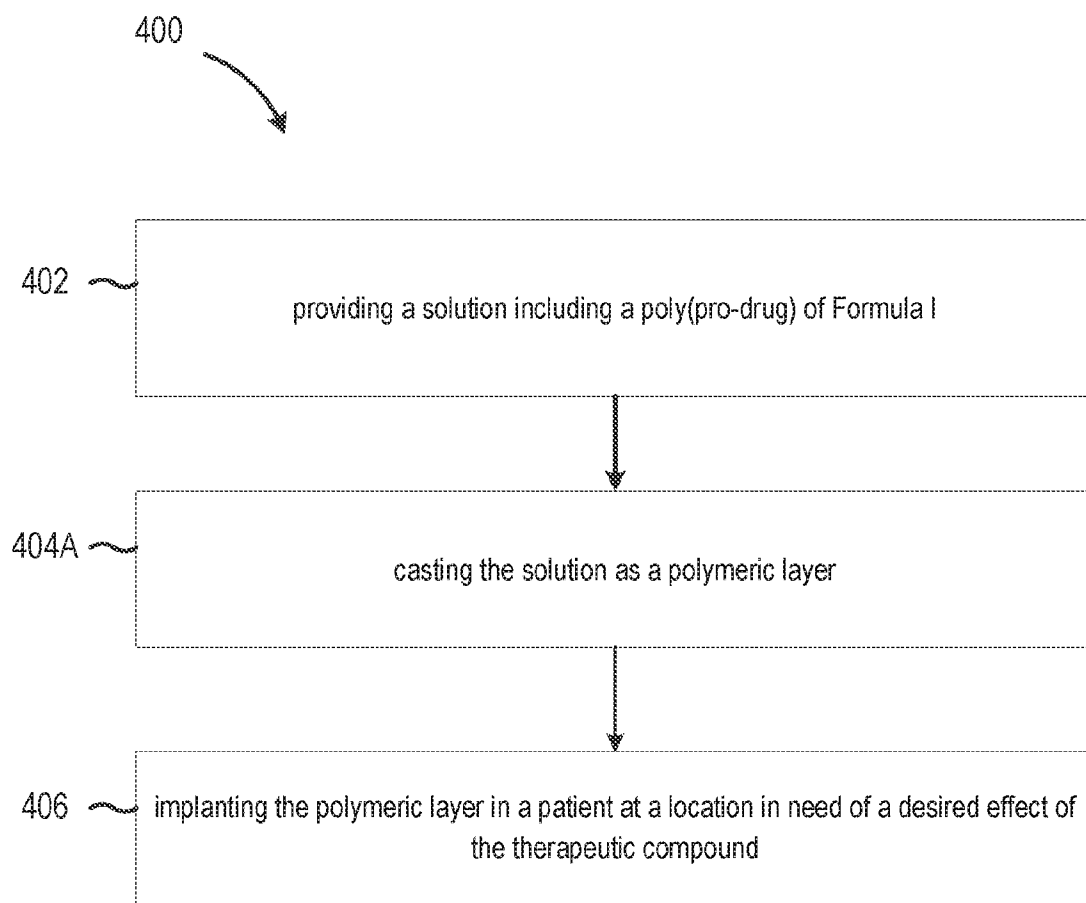


FIG. 4A

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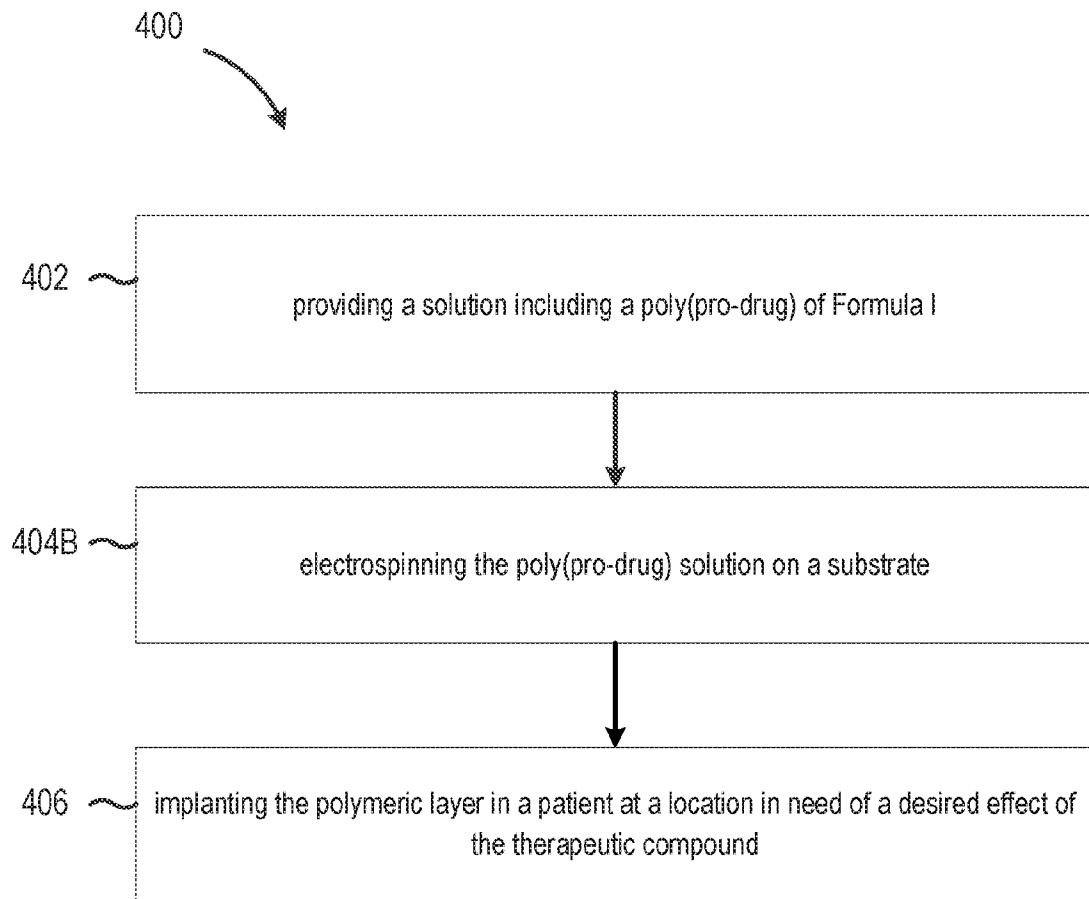


FIG. 4B

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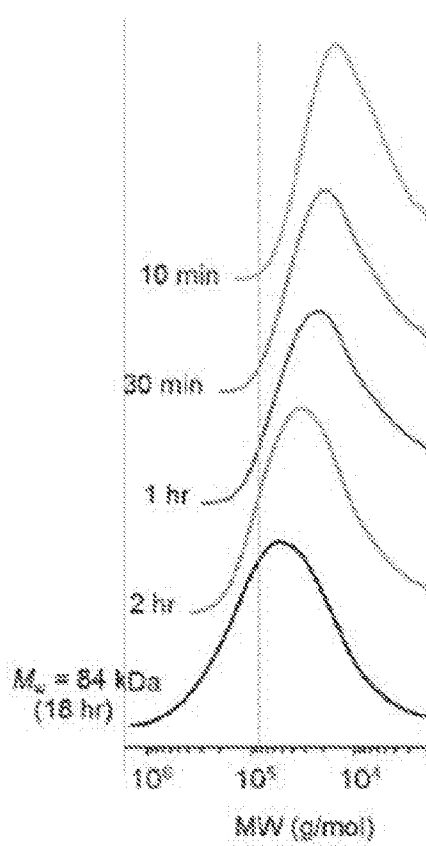


FIG. 5A

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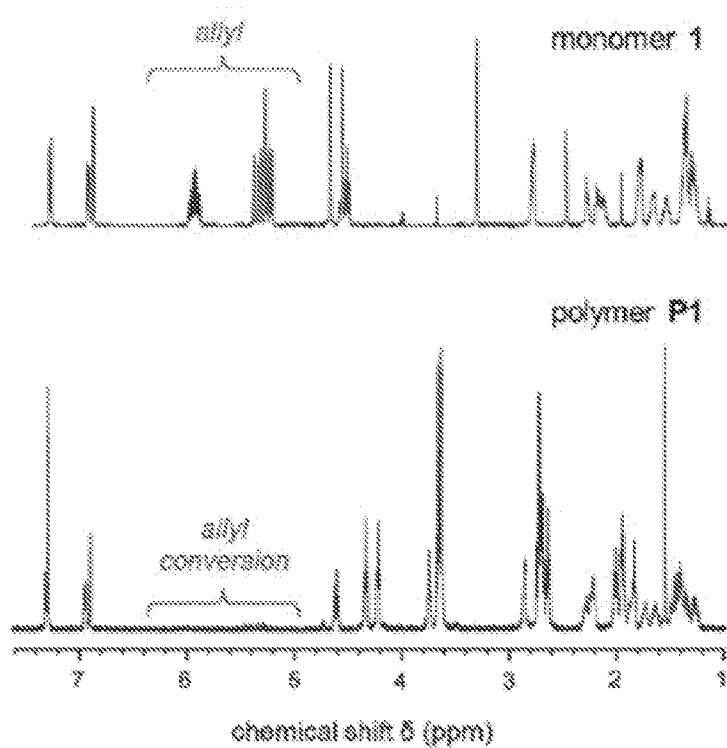


FIG. 5B

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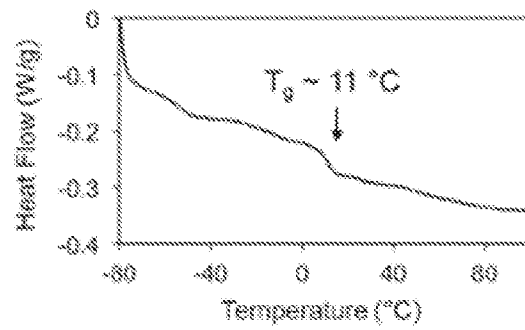


FIG. 6A

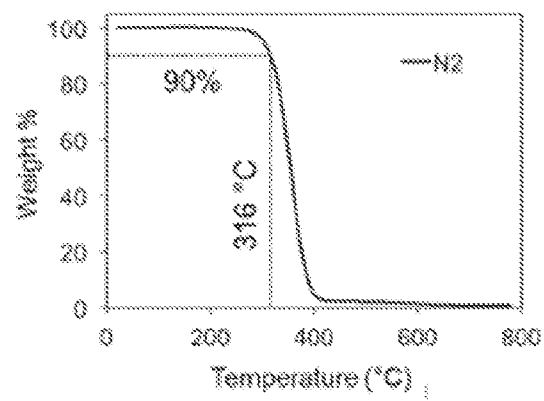


FIG. 6B

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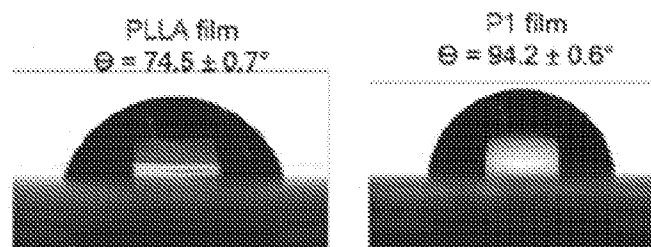


FIG. 6C

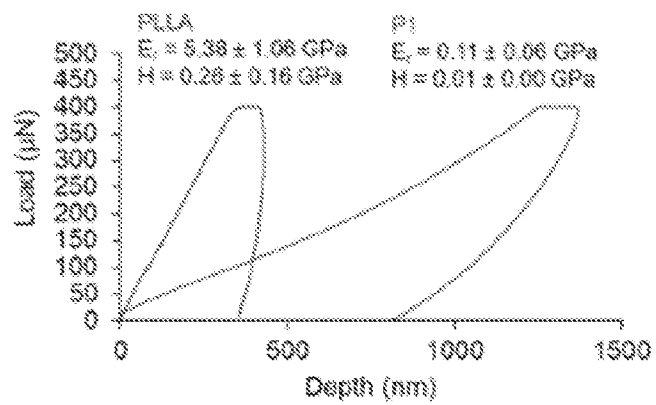


FIG. 6D

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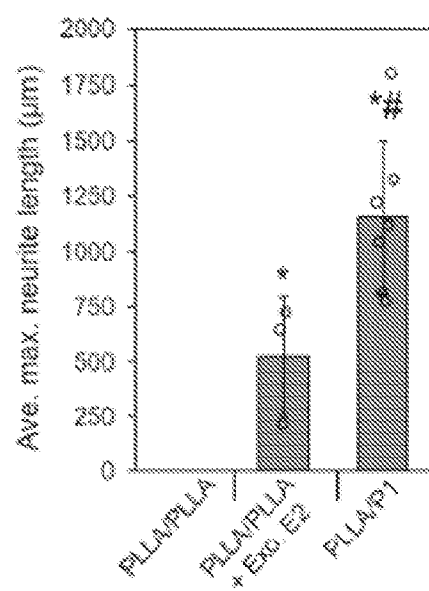


FIG. 7

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 19/56539

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 31/522; A61K 9/00; A61K 9/50 (2019.01)

CPC - A61K 31/522; A61K 9/0019; A61K 9/5089; A61K 9/5153

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)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History document

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

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- A	~ Zhang et al. 'Facile Fabrication of 10-Hydroxycamptothecin-Backboned Amphiphilic Polyprodrug with Precisely Tailored Drug Loading Content for Controlled Release', Bioconjugate Chemistry, 30 May 2018 (30.05.2018), Vol.29, pages2239-2247; Title, Abstract, p2242	1-7 ----- 8-9
A	~ Patel et al. 'Curcumin Targets FOLFOX-surviving Colon Cancer Cells via Inhibition of EGFRs and IGF-1R', Anticancer Research, February 2010, Vol.30, pages319-325; p319	2
A	~ Xu et al. 'Smart and hyper-fast responsive polyprodrug nanoplatfrom for targeted cancer therapy', Biomaterials, 23 October 2015 (23.10.2015), Vol.76, pages238-249; p242	8-9
A	US 2010/0190933 A1 (Zhao et al.) 29 July 2010 (29.07.2010); Abstract, para[0229]	8-9
A	US 2017/0168041 A1 (National University of Singapore) 15 June 2017 (15.06.2017); entire document	1-9
A, P	~ D'Amato et al. 'Vastly extended drug release from poly(pro-17B-estradiol) materials facilitates in vitro neurotrophism and neuroprotection', Nature Communications, 23 October 2019 (23.10.2019), Vol.10, pages1-12; entire document	1-9

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

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

"D" document cited by the applicant in the international application

"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

09 December 2019

Date of mailing of the international search report

12 FEB 2020

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 Young

Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 19/56539

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.:
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:

---please see supplemental box---

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.:
1-9

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.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/US 19/56539

---Box III: lack of unity

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I: Claims 1-9 directed to a poly(pro-drug) material comprising one or more polymers according to Formula I.

Group II: Claims 10-15 directed to a method of making a poly(pro-drug) material, comprising: providing a reaction medium including a therapeutic compound and a linker compound, wherein the therapeutic compound includes at least two substitutable functional groups; functionalizing the at least two substitutable functional groups with the linker compound to form a pro-drug; and copolymerizing the pro-drug with one or more hydrocarbyl groups, the hydrocarbyl groups including hydrocarbyl monomers, hydrocarbyl oligomers, hydrocarbyl polymers, or combinations thereof.

Group III: Claims 16-20 directed to a method of providing local therapeutic effects comprising: providing a solution including a poly(pro-drug) of the following Formula I, casting the solution as a polymeric layer; and implanting the polymeric layer in a patient at a location in need of a desired effect of the therapeutic compound.

The inventions listed as Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features:

Group I requires a poly(pro-drug) material comprising one or more polymers according to Formula I, not required by group II

Groups II requires a method of making a poly(pro-drug) material, not required by groups I and III

Groups III requires a method of providing local therapeutic effects comprising: providing a solution including a poly(pro-drug) of the following Formula I, casting the solution as a polymeric layer; and implanting the polymeric layer in a patient at a location in need of a desired effect of the therapeutic compound, not required by groups I-II

Common Technical Features:

Groups I-III share the technical feature of a poly(pro-drug) material.

Groups I and III share the technical feature of a poly(pro-drug) of the following Formula I.

However, these shared technical features do not represent a contribution over prior art, because the shared technical feature is being anticipated by the journal article entitled 'Facile Fabrication of 10-Hydroxycamptothecin-Backboned Amphiphilic Polyprodrug with Precisely Tailored Drug Loading Content for Controlled Release' by Zhang et al. (hereinafter 'Zhang'). Zhang discloses a poly(pro-drug) of the following Formula I (Abstract Figure "Amphiphilic polyprodrug"), wherein R1 includes one therapeutic compound (Abstract "an anticancer drug, 10-hydroxycamptothecin (HCPT)"), R2 includes one or more cleavable linker compounds (Abstract Figure "OC(O)O(CH₂)₂SS(CH₂)₂N₃"), and R3 includes one or more biodegradable hydrocarbyl groups (Abstract Figure "PEG").

As the shared technical features were known in the art at the time of the invention, they cannot be considered common technical features that would otherwise unify the groups. Therefore, Groups I-III lack unity under PCT Rule 13.