(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 April 2017 (13.04.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/062871 A1

(51) International Patent Classification:
C08J 9/16 (2006.01) *C08J 9/22* (2006.01)

(21) International Application Number:
PCT/US2016/056135

(22) International Filing Date:
7 October 2016 (07.10.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

62/239,758	9 October 2015 (09.10.2015)	US
62/281,631	21 January 2016 (21.01.2016)	US
62/313,013	24 March 2016 (24.03.2016)	US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

WO 2017/062871 A1

(54) Title: CROSSLINKED PARTICLES

(57) Abstract: Disclosed are crosslinked particles (e.g., microparticles) that are capable of storing and releasing drugs. The particles can be macroparticles, microparticles, or nanoparticles and can be composed of polyester backbones. The particles can be loaded with a drug. The particles can degrade in vivo to release the drug. The particles can be prepared by crosslinking functionalized polyester backbones and loaded with a given drug. The particles of the present disclosure can be injected with a syringe. In some embodiments, the particles of the present disclosure are administered in connection with a surgery and release the drug after the site of the surgery for a period of 1-6 months.

CROSSLINKED PARTICLES

Related Applications

[0001] This application claims the benefit under 35 U.S.C §119(e) of U.S. Provisional Patent Application Ser. No. 62/239,758, filed October 9, 2015; U.S. Provisional Patent Application Ser. No. 62/281,631, filed January 21, 2016; and U.S. Provisional Patent Application Ser. No. 62/313,013, filed March 24, 2016, the disclosures of which are incorporated herein by reference in their entirety.

Field of the Invention

[0002] The present disclosure teaches crosslinked particles (e.g., microparticles or nanoparticles) that are capable of storing and releasing drugs. The particles can release drug by degradation, erosion, diffusion, or a combination of mechanisms.

Background of the Invention

[0003] Drug-eluting biodegradable nanoparticles can be used for a variety of biological applications, such as wound healing and arthritis treatment (see e.g., US 7,935,782 and WO 2009/061854, the entire contents of which are hereby incorporated by reference in their entirety). However, it can be difficult to control particle size and morphology to achieve nanoparticles with reproducible results. Additionally, previous attempts to produce crosslinked particles were limited in size and therefore could only be loaded with a limited amount of a given drug. Smaller particles also tended to biodegrade more quickly than larger particles, and were therefore unable to provide sustained release of for a desired duration.

[0004] Moreover, current drug delivery particles can suffer from a burst effect, wherein a substantial portion of a drug dispersed therein is released quickly released in a short period followed by a lower release rate. This has the effect of initially over dosing a patient and then later under dosing the patient.

Summary of the Invention

[0005] The present disclosure teaches particles (e.g., microparticles) that are crosslinked and can be used *in vivo*. The crosslinked particles can include a drug, and can release the drug when

used *in vivo*. In some embodiments, the drug is released as the particle degrades. The microparticles can thus be used to release drugs at the site of wounds, or after surgical procedures to release therapeutic agents and help speed recovery. Additionally, the particles of the current disclosure can be used for the treatment of arthritis. For example, particles comprising arthritis therapeutics can be administered to the site of arthritis pain (e.g., by injection). In some embodiments, the present disclosure provides crosslinked particles such as microparticles that have reproducible size and morphology. In some embodiments, the present disclosure also provides particles that can release a drug for a sustained period of time (e.g., greater than one month) and which do not suffer from a burst effect (e.g., a release of substantial amount of drug soon after immersion in a solvent).

[0006] In one aspect, the present disclosure provides a crosslinked degradable particle, comprising:

a plurality of polyester backbones, wherein the plurality of polyester backbones are crosslinked via thioethers, triazoles, or amides; and

a drug dispersed within the crosslinked degradable particle.

[0007] In another aspect, the present disclosure provides a crosslinked degradable particle, comprising:

a plurality of polymer backbones obtained from lactone monomer residues, wherein the plurality of polymer backbones are crosslinked via thioethers , triazoles, or amides; and

a drug dispersed within the crosslinked degradable particle, wherein the crosslinked degradable particle has a nominal diameter between 1 μm and 100 μm.

[0008] In another aspect, the present disclosure provides a crosslinked degradable particle, comprising:

a plurality of polymer backbones obtained from lactone monomer residues, wherein the plurality of polymer backbones are crosslinked via thioethers, triazoles, or amides; and

a drug dispersed within the crosslinked degradable particle, wherein the crosslinked degradable particle has a nominal diameter between 1 micron and 100 microns.

[0009] In another aspect, the present disclosure provides a method of preparing a crosslinked degradable particle, comprising:

combining a polyester containing a plurality of functional groups and a crosslinker to form a mixture; and
reacting the functional groups with crosslinkers to form a crosslinked degradable particle.

[0010] In another aspect, the present disclosure provides a method of preparing a crosslinked degradable particle, comprising:

dissolving a polyester containing a plurality of allyl groups, a dithiol, and a photoinitiator in at least one solvent to form a solution;
emulsifying the solution in an aqueous phase to form an emulsion;
irradiating the emulsion with UV light to react the dithiol with two of the allyl groups to form a crosslink; and

evaporating at least a portion of the solvent from the emulsion .

[0011] In another aspect, the present disclosure provides a method of preparing a crosslinked degradable particle, comprising:

dissolving a polyester containing a plurality of propargyl groups and a diazide in at least one solvent to form a solution;
emulsifying the solution in an aqueous phase to form an emulsion;
treating the emulsion to react the diazide with two of the propargyl groups to form a crosslink; and
evaporating at least a portion of the solvent from the emulsion .

[0012] In another aspect, the present disclosure provides method of preparing a crosslinked degradable particle, comprising:

dissolving a polyester containing a plurality of epoxide groups and a diamine in at least one solvent to form a solution;
emulsifying the solution in an aqueous phase to form an emulsion;
allowing the diamine to react with the epoxide groups to form a crosslink ; and

evaporating at least a portion of the solvent from the emulsion.

[0013] In another aspect, the present disclosure provides a method of preparing a crosslinked degradable particle, comprising:

dissolving a polyester containing a plurality of carboxylic acid groups and a diamine in at least one solvent to form a solution;
emulsifying the solution in an aqueous phase to form an emulsion;
treating the emulsion to react diamine to react with the carboxylic acid groups to form a crosslink; and

evaporating at least a portion of the solvent from the emulsion.

[0014] In another aspect, the present disclosure provides a method of reducing aggregation of a plurality of crosslinked degradable particles, comprising attaching a plurality of polyethylene glycol chains to an exterior of the plurality of crosslinked degradable particles.

[0015] In another aspect, the present disclosure provides a method of dispersing a drug within a crosslinked degradable particle, comprising:

swelling the crosslinked degradable particle with a solvent to form a swollen crosslinked degradable particle, wherein the solvent further comprises a drug dispersed therein; and

removing the crosslinked degradable particles from the solvent.

[0016] In another aspect, the present disclosure provides a method of preparing a crosslinked degradable implant, comprising:

dissolving a polyester containing a plurality of functional groups and a crosslinker in at least one solvent to form a solution;
treating the solution to react the crosslinker with two of the functional groups to form a crosslink;

wherein the crosslinked degradable implant has a diameter of at least about 1 millimeter.

[0017] In another aspect, the present disclosure provides a method of controlling an average size of a distribution of crosslinked degradable particles, comprising:

preparing a plurality of molds of uniform size and shape;

combining a polyester containing a plurality of functional groups and a crosslinker to form a mixture;
dispersing the mixture within the molds; and

treating the mixture to react the crosslinker with two of the functional groups to form a crosslink.

[0018] In another aspect, the present disclosure provides a method of controlling an average size of a distribution of crosslinked degradable particles, comprising:

combining a polyester containing a plurality of functional groups and a crosslinker in at least one nonaqueous solvent to form an emulsion wherein the nonaqueous solvent comprises droplets of uniform size,
wherein the polyester and crosslinker, are dissolved in the nonaqueous solvent droplets; and

treating the emulsion to react the crosslinker with two of the functional groups to form a crosslink, wherein the particles are crosslinked while dissolved in the nonaqueous solvent.

[0019] In another aspect, the present disclosure provides a crosslinked degradable particle, formed by:

forming a polyester containing a plurality of functional groups and a crosslinker to form a mixture; and

reacting the functional groups with crosslinkers to form a crosslinked degradable particle.

[0020] In another aspect, the present disclosure provides a method of treating a disease, comprising:

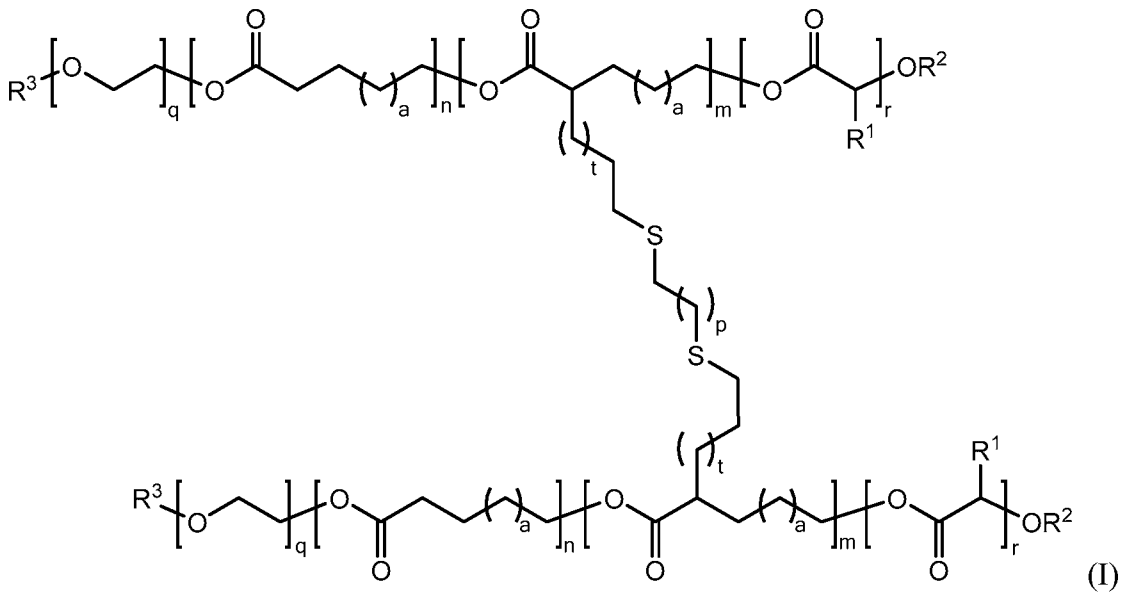
administering to a subject in need thereof a therapeutically effective amount of the crosslinked degradable particle of the present disclosure containing the drug.

[0021] In another aspect, the present disclosure provides use of a crosslinked degradable particle of the present disclosure for the treatment of a disease. In some embodiments, the crosslinked particle contains a drug.

[0022] In another aspect, the present disclosure provides the use of a crosslinked degradable particle of the present disclosure in the manufacture of a medicament for the treatment of a disease. In some embodiments, the crosslinked particle contains a drug.

[0023] In another aspect, the present disclosure provides a crosslinked degradable particle, comprising:

a polyester backbone of the Formula I:



(I)

wherein:

R^1 is independently, at each occurrence, –H, or –C_1-C_6 alkyl;

R^2 is independently, at each occurrence, –H, or –C_1-C_6 alkyl;

R^3 is independently, at each occurrence, –H, or –C_1-C_6 alkyl;

a is 0, 1, or 2;

m is independently, at each occurrence, an integer between 1 and 1000, inclusive;

n is independently, at each occurrence, an integer between 1 and 1000, inclusive;

p is independently, at each occurrence, an integer between 0 and 5, inclusive;

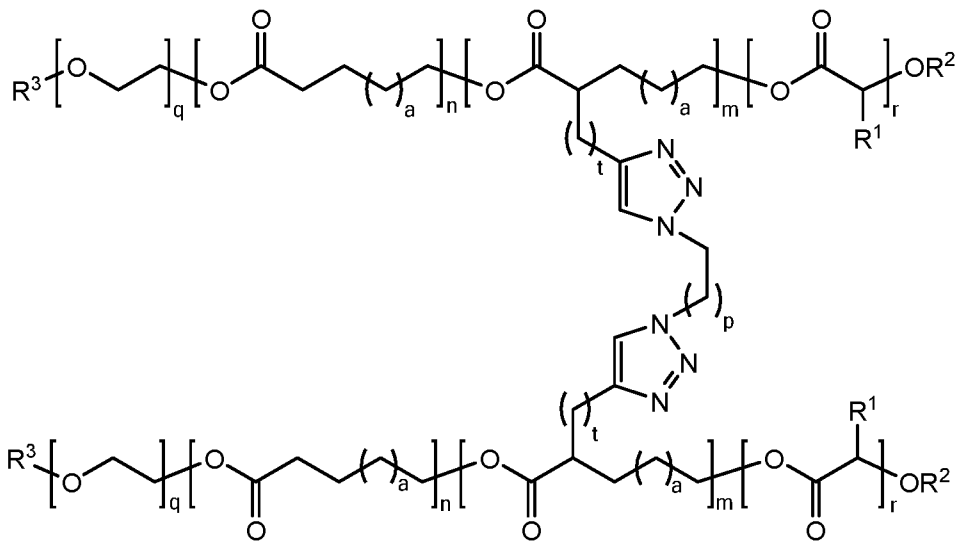
q is independently, at each occurrence, an integer between 0 and 1000, inclusive;

r is independently, at each occurrence, an integer between 0 and 1000, inclusive; and

t is independently, at each occurrence, an integer between 0 and 5, inclusive.

[0024] In another aspect, the present disclosure provides a crosslinked degradable particle, comprising:

a polyester backbone of the Formula II:



(II)

wherein:

R^1 is independently, at each occurrence, –H, or $–C_1$-C_6 alkyl;

R^2 is independently, at each occurrence, –H, or $–C_1$-C_6 alkyl;

R^3 is independently, at each occurrence, –H, or $–C_1$-C_6 alkyl;

a is 0, 1, or 2;

m is independently, at each occurrence, an integer between 1 and 1000, inclusive;

n is independently, at each occurrence, an integer between 1 and 1000, inclusive;

p is independently, at each occurrence, an integer between 0 and 5, inclusive;

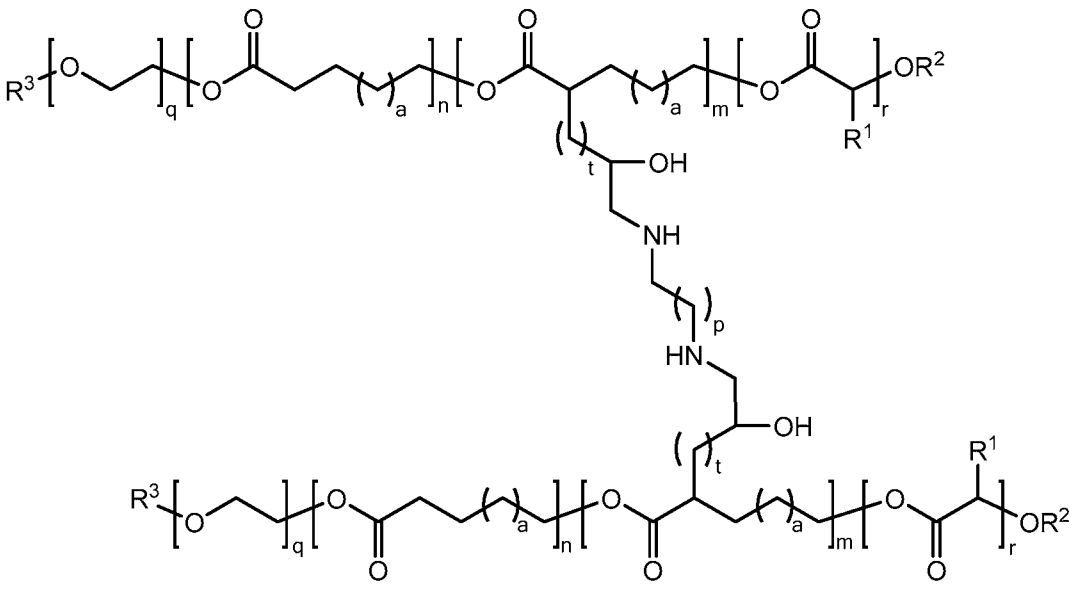
q is independently, at each occurrence, an integer between 0 and 1000, inclusive;

r is independently, at each occurrence, an integer between 0 and 1000, inclusive; and

t is independently, at each occurrence, an integer between 0 and 5, inclusive.

[0025] In another aspect, the present disclosure provides a crosslinked degradable particle, comprising:

a polyester backbone of the Formula III:



(III)

wherein:

R^1 is independently, at each occurrence, –H, or –C_1-C_6 alkyl;

R^2 is independently, at each occurrence, –H, or –C_1-C_6 alkyl;

R^3 is independently, at each occurrence, –H, or –C_1-C_6 alkyl;

a is 0, 1, or 2;

m is independently, at each occurrence, an integer between 1 and 1000, inclusive;

n is independently, at each occurrence, an integer between 1 and 1000, inclusive;

p is independently, at each occurrence, an integer between 0 and 5, inclusive;

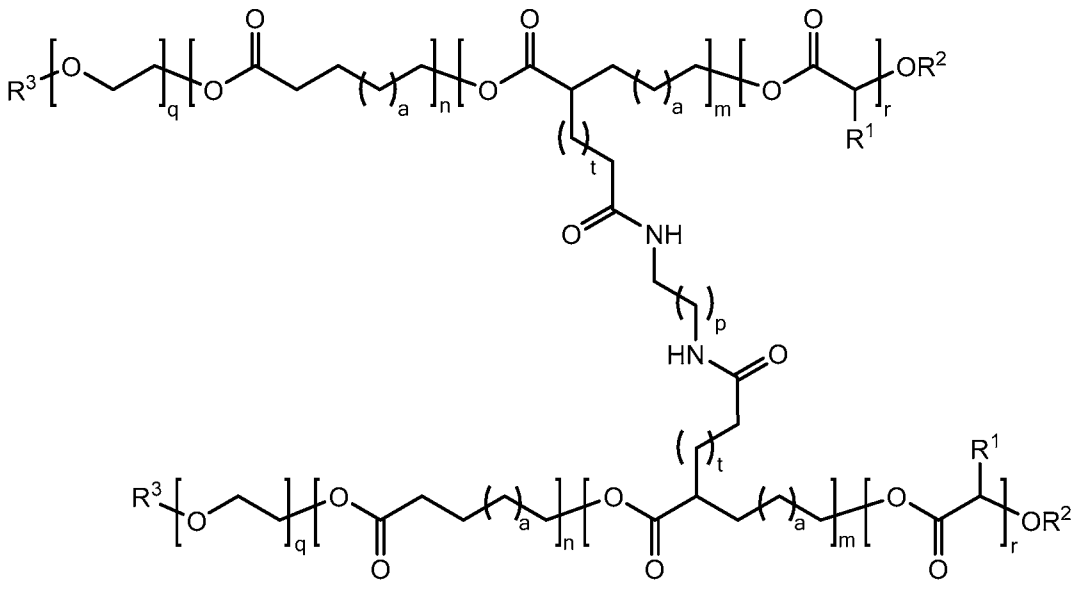
q is independently, at each occurrence, an integer between 0 and 1000, inclusive;

r is independently, at each occurrence, an integer between 0 and 1000, inclusive; and

t is independently, at each occurrence, an integer between 0 and 5, inclusive.

[0026] In another aspect, the present disclosure provides a crosslinked degradable particle, comprising:

a polyester backbone of the Formula IV:



(IV)

wherein:

R^1 is independently, at each occurrence, –H, or $–C_1$-C_6 alkyl;

R^2 is independently, at each occurrence, –H, or $–C_1$-C_6 alkyl;

R^3 is independently, at each occurrence, –H, or $–C_1$-C_6 alkyl;

a is 0, 1, or 2;

m is independently, at each occurrence, an integer between 1 and 1000, inclusive;

n is independently, at each occurrence, an integer between 1 and 1000, inclusive;

p is independently, at each occurrence, an integer between 0 and 5, inclusive;

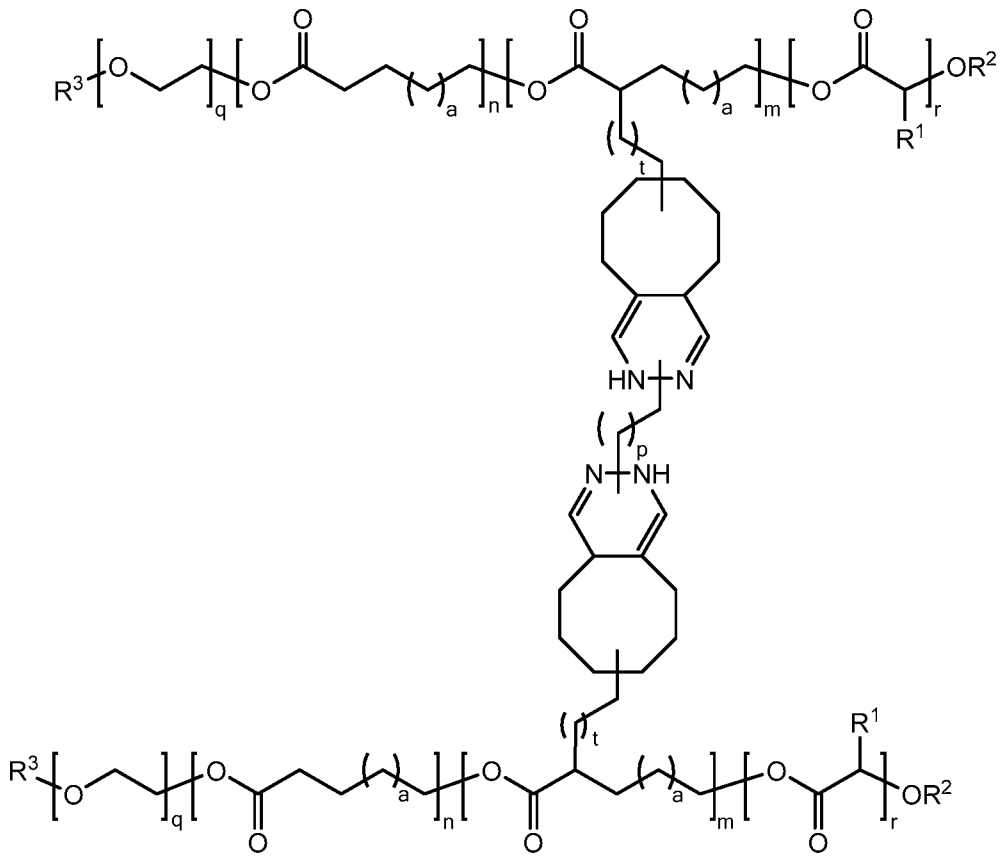
q is independently, at each occurrence, an integer between 0 and 1000, inclusive;

r is independently, at each occurrence, an integer between 0 and 1000, inclusive; and

t is independently, at each occurrence, an integer between 0 and 5, inclusive.

[0027] In another aspect, the present disclosure provides a crosslinked degradable particle, comprising:

a polyester backbone of the Formula V:



(V)

wherein:

R^1 is independently, at each occurrence, –H, or $–C_1$-C_6 alkyl;

R^2 is independently, at each occurrence, –H, or $–C_1$-C_6 alkyl;

R^3 is independently, at each occurrence, –H, or $–C_1$-C_6 alkyl;

a is 0, 1, or 2;

m is independently, at each occurrence, an integer between 1 and 1000, inclusive;

n is independently, at each occurrence, an integer between 1 and 1000, inclusive;

p is independently, at each occurrence, an integer between 0 and 5, inclusive;

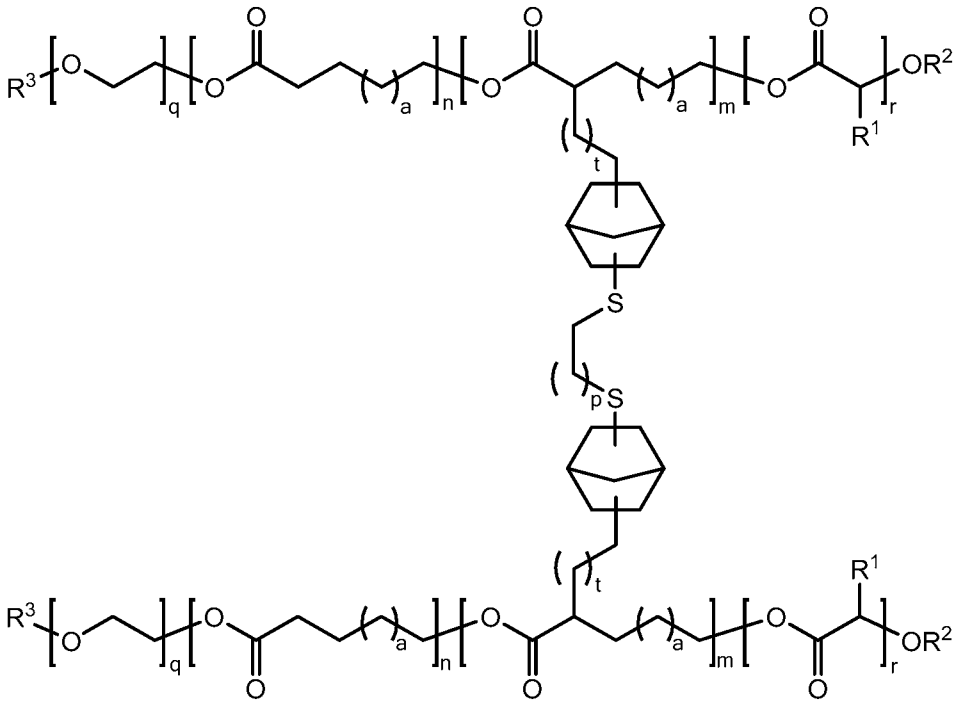
q is independently, at each occurrence, an integer between 0 and 1000, inclusive;

r is independently, at each occurrence, an integer between 0 and 1000, inclusive; and

t is independently, at each occurrence, an integer between 0 and 5, inclusive.

[0028] In another aspect, the present disclosure provides a crosslinked degradable particle, comprising:

a polyester backbone of the Formula VI:



(VI)

wherein:

R^1 is independently, at each occurrence, –H, or $–C_1$-C_6 alkyl;

R^2 is independently, at each occurrence, –H, or $–C_1$-C_6 alkyl;

R^3 is independently, at each occurrence, –H, or $–C_1$-C_6 alkyl;

a is 0, 1, or 2;

m is independently, at each occurrence, an integer between 1 and 1000, inclusive;

n is independently, at each occurrence, an integer between 1 and 1000, inclusive;

p is independently, at each occurrence, an integer between 0 and 5, inclusive;

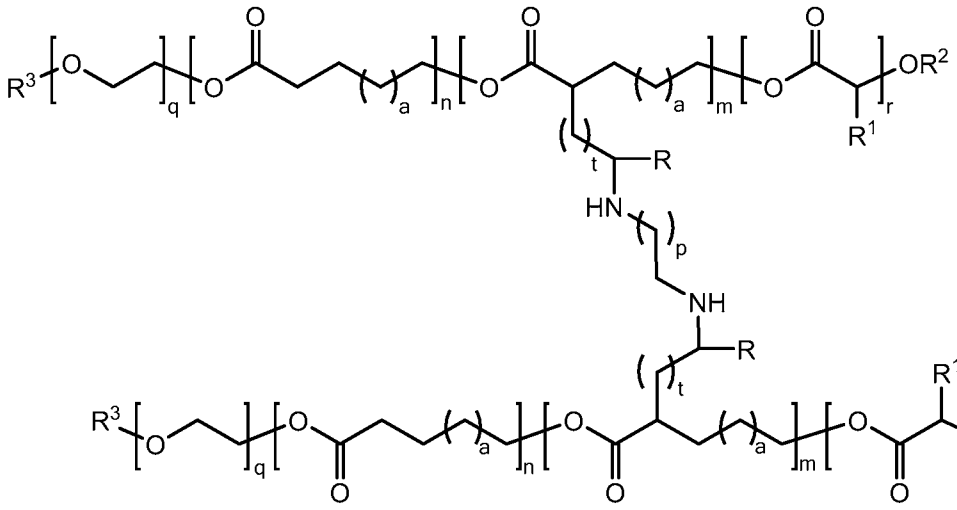
q is independently, at each occurrence, an integer between 0 and 1000, inclusive;

r is independently, at each occurrence, an integer between 0 and 1000, inclusive; and

t is independently, at each occurrence, an integer between 0 and 5, inclusive.

[0029] In another aspect, the present disclosure provides a crosslinked degradable particle, comprising:

a polyester backbone of the Formula VII:



(VII)

wherein:

R is independently, at each occurrence, –H, or $–C_1$-C_6 alkyl

R^1 is independently, at each occurrence, –H, or $–C_1$-C_6 alkyl;

R^2 is independently, at each occurrence, –H, or $–C_1$-C_6 alkyl;

R^3 is independently, at each occurrence, –H, or $–C_1$-C_6 alkyl;

a is 0, 1, or 2;

m is independently, at each occurrence, an integer between 1 and 1000, inclusive;

n is independently, at each occurrence, an integer between 1 and 1000, inclusive;

p is independently, at each occurrence, an integer between 0 and 5, inclusive;

q is independently, at each occurrence, an integer between 0 and 1000, inclusive;

r is independently, at each occurrence, an integer between 0 and 1000, inclusive; and

t is independently, at each occurrence, an integer between 0 and 5, inclusive.

[0030] The crosslinked particles (e.g., macroparticles, microparticles or nanoparticles) of the present disclosure can have uniform size and shape along with other characteristics such as stability. This can allow the crosslinked particles of the present disclosure to be used in medical settings with high reproducibility and reliability. Additional features and advantages of the present disclosure will be apparent to one of skill in the art and are set forth in the Detailed Description, below.

Brief Description of the Figures

[0031] FIG. 1A shows a photo of polycaprolactone (PCL), polyvalerolactone/ polyallylvalerolactone copolymer (PVL-co-PAVL) microparticles at a scale of about 1500 μm.

[0032] FIG. 1B shows photo of PCL, PVL-co-PAVL microparticles at a scale of about 400 μm.

[0033] FIG. 1C shows a photo of PCL, PVL-co-PAVL microparticles at a scale of about 600 μm.

[0034] FIG. 1D shows a photo of PCL, PVL-co-PAVL microparticles at a scale of about 20 μm, along with a size distribution scheme.

[0035] FIG. 2A shows a photo of PVL-co-PAVL microparticles at a scale of about 1500 μm.

[0036] FIG. 2B shows photo of PVL-co-PAVL microparticles at a scale of about 400 μm.

[0037] FIG. 2C shows a photo of PVL-co-PAVL microparticles at a scale of about 600 μm.

[0038] FIG. 2D shows a photo of PVL-co-PAVL microparticles at a scale of about 20 μm, along with a size distribution scheme.

[0039] FIG. 3A shows a schematic of self-assembly of amphiphilic block copolymers into micellar structures.

[0040] FIG. 3B shows a schematic of encapsulation of polymers and crosslinkers of the present disclosure into the lipid phase of a lipid-water emulsion.

[0041] FIG. 4 shows a general schematic for loading drugs into particles of the present disclosure

[0042] FIG. 5 shows a DLS plot of crosslinked mPEG-b-PVL-co-PAVL nanoparticles in water.

[0043] FIG. 6 shows a DLS plot of crosslinked mPEG-b-PVL-co-PAVL nanoparticles in dimethylsulfoxide (DMSO).

[0044] FIG. 7 shows a DLS plot of crosslinked mPEG-b-PVL-co-PAVL nanoparticles in THF.

[0045] FIG. 8 shows a DLS plot of non-crosslinked mPEG-b-PVL-co-PAVL nanoparticles in water.

[0046] FIG. 9A shows a histogram and an image of 25% PVL-co-PAVL microparticles after crosslinking.

[0047] FIG. 9B shows a histogram and microscope image of the same microparticles after a DMSO washing step.

[0048] FIG. 9C shows a histogram and microscope image of the particles after an ethanol washing step.

[0049] FIG. 9D shows a histogram and microscope image of the particles after swelling in THF.

[0050] FIG. 10A shows a ^{1}HNMR spectrum of PVL-co-PAVL polymer.

[0051] FIG. 10B shows a gel permeation chromatography plot of the PVL-co-PAVL polymer backbone comprising 6% PAVL, 10% PAVL, and 25% PAVL.

[0052] FIG. 11A shows a microscope image of mPEG-b-PVL-co-PAVL macroparticles (80:20) at a resolution of about 1 mm.

[0053] FIG. 11B shows a microscope image of mPEG-b-PVL-co-PAVL macroparticles (80:20) at a resolution of about 200 μm.

[0054] FIG. 11C shows a first microscope image of mPEG-b-PVL-co-PAVL macroparticles (80:20) at a resolution of about 10 μm.

[0055] FIG. 11D shows a second microscope image of mPEG-b-PVL-co-PAVL macroparticles (80:20) at a resolution of about 10 μm.

[0056] FIG. 12 shows a microscope micrograph of non-crosslinked microparticles in water.

[0057] FIG. 13 shows the drug loading capacity of macroparticles, according to an embodiment of the disclosure.

[0058] FIG. 14 shows a DSC plot of microparticles loaded with curcumin, paclitaxel, triamcinolone acetonide, triamcinolone hexacetonide, and without drug.

[0059] FIG. 15 shows FTIR spectra of microparticles of the present disclosure loaded with curcumin, paclitaxel, triamcinolone acetonide, triamcinolone hexacetonide, and without drug.

[0060] FIG. 16 shows a microscopic image of microparticle flakes after being dried overnight.

[0061] FIG. 17 shows the release profile of curcumin release from microparticle flakes.

[0062] FIG. 18A shows curcumin-loaded particles dissolved in water containing 1% tween after being dried in THF with 25% PEG as a co-solvent.

[0063] FIG. 18B shows a close-up view of curcumin-loaded particles dissolved in water containing 1% tween after being dried in THF with 25% PEG as a co-solvent.

[0064] FIG. 19A shows a microscope image of microparticle flakes in water after drying with 2.5% PEG as a co-solvent.

[0065] FIG. 19B shows a microscope image of microparticle flakes in THF after drying with 2.5% PEG as a co-solvent.

[0066] FIG. 19C shows a microscope image of microparticle flakes in water after drying with 5% PEG as a co-solvent.

[0067] FIG. 19D shows a microscope image of microparticle flakes in THF after drying with 5% PEG as a co-solvent.

[0068] FIG. 20A shows an aqueous solubility plot of triamcinolone acetonide in the presence of surfactants Tween 80 and SDS.

[0069] FIG. 20B shows an aqueous solubility plot of triamcinolone hexacetonide in the presence of surfactants Tween 80 and SDS.

[0070] FIG. 20C shows an aqueous solubility plot of paclitaxel in the presence of surfactants Tween 80 and SDS.

[0071] FIG. 21 shows a 7-day release profile of curcumin from a macroparticle.

[0072] FIG. 22 shows a 20-day curcumin release profile from a 13-mg and 12-mg macroparticle.

[0073] FIG. 23 shows a 6-day release profile of triamcinolone hexacetonide from two macroparticles.

[0074] FIG. 24 shows a 20-day triamcinolone hexacetonide release profile from a 13.3-mg and 9.2-mg macroparticle.

[0075] FIG. 25 shows a comparison of the release profiles of curcumin, triamcinolone hexacetonide (TAH), triamcinolone acetonide (TAA), and paclitaxel (PTX).

[0076] FIG. 26 shows a microscope micrograph of the photolithography template.

[0077] FIG. 27A shows a gelatin template with raised pegs under a microscope.

[0078] FIG. 27B shows a first microscope image of microparticles prepared by the gelatin hydrogel template method.

[0079] FIG. 27C shows a second microscope image of microparticles prepared by the gelatin hydrogel template method.

[0080] FIG. 28A shows a DSC plot of a control microparticle with no crosslinking.

[0081] FIG. 28B shows a DSC plot of a microparticle with 50% crosslinking. The DSC plot shows about 30% of crystallinity.

[0082] FIG. 28C shows a DSC plot of a microparticle with 100% crosslinking.

[0083] FIG. 29A shows a DSC plot of a control microparticle with no crosslinking.

[0084] FIG. 29B shows a DSC plot of a microparticle with 50% crosslinking. The DSC plot shows less than 1% crystallinity.

[0085] FIG. 29C shows a DSC plot with 100% crosslinking.

Detailed Description of the Invention

[0086] The present disclosure provides crosslinked particles (e.g., microparticles, microparticles or nanoparticles) that can be used in medical applications (e.g., to locally release drugs). In some embodiments, the present disclosure provides microparticles comprising a polyester backbone that can be crosslinked via functional groups disposed along the polyester backbone in the presence of an appropriate crosslinking reagent.

[0087] In some embodiments, the polyester backbones are crosslinked via thioethers. The polyester backbones can be crosslinked via triazoles. The polyester backbones can be crosslinked via amides. The polyester backbones can be crosslinked via amines (e.g., via an amine-epoxide reaction). The polyester backbones can be crosslinked by a tetrazine-trans-cyclooctene reaction. The polyester backbones can be crosslinked by a thiol-norbornene reaction. The polyester backbones can be crosslinked by an amine-carbonyl (e.g., aldehyde or ketone) reductive amination. The particles can be biodegradable.

[0088] The microparticles of the present disclosure can have a diameter between about 1 μm and about 999 μm, including all ranges and subranges therebetween, and more preferably, the microparticles can have a diameter between about 1 μm and about 100 μm, including all ranges and subranges therebetween. In some embodiments, the microparticles of the present disclosure can have a diameter between about 5 μm and about 30 μm, including all ranges and subranges therebetween (e.g., between about 7 μm and about 15 μm or about 10 μm).

[0089] The macroparticles of the present disclosure can have a mean diameter greater than about 1000 μm.

[0090] In some embodiments, the drug dispersed within a microparticle of the disclosure can be triamcinolone, triamcinolone acetonide, triamcinolone hexacetonide, and paclitaxel. In some embodiments other compounds such as curcumin can be dispersed within the particles (for instance, curcumin can be used to more easily visualize release kinetics). In some embodiments, curcumin can be used as a surrogate for a drug. In some embodiments, the drug is covalently bonded to the particle. In some embodiments, the drug is contained within the particle by noncovalent interactions. In some embodiments, the particle releases the drug over a period of at least one week in an aqueous environment (e.g., at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 2 months, at least 3 months, at least 4 months, at least 5 months, or at least 6 months). In some embodiments, the particle degrades as it releases the drug.

[0091] In some embodiments, the polyester backbone comprises polyvalerolactone (PVL), polycaprolactone (PCL), polylactic acid (PLA), polyglycolic acid (PGC), or a combination thereof. In some embodiments, the particle is a macroparticle. In some embodiments, the particle is a microparticle. In some embodiments, the particle is a nanoparticle. In some embodiments, the polyester backbone further comprises polyethylene glycol (PEG). In some embodiments, the polymer backbone is obtained from a monomer residue comprising valerolactone (e.g., polyvalerolactone), caprolactone (e.g., polycaprolactone), lactic acid (e.g., polylactic acid), glycolic acid (e.g., polyglycolic acid), or a combination thereof. In some embodiments, the lactone monomer is selected from the group consisting of lactic acid, glycolic acid, valerolactone, caprolactone, lactide, or a combination thereof.

[0092] In one or more embodiments, any of the valerolactone, caprolactone, lactic acid, lactide, or glycolic acid is functionalized with a functional group. In some embodiments, the functional group can be selected from an allyl group, a propargyl group, or a carboxylic acid group (e.g., the functional groups can be allyl lactide, allyl valerolactone and the like). Alternatively, the functional group can be a trans-cyclooctene, norbornene, or a carbonyl group (e.g., an aldehyde or ketone). Alternatively, the functional group can be a thiol group, an amine, or a tetrazine.

[0093] In one or more embodiments, the polyester and crosslinker are combined in a solvent to form the mixture. In some embodiments of any of the above methods, particles of the

disclosure are made by emulsifying the mixture, wherein the polyester and the crosslinker are in the same phase. In some embodiments, the methods further comprise evaporating at least part of the solvent prior to reacting the functional groups with the crosslinker. In some embodiments, the functional group of the polyester backbone comprises an olefin group (e.g., an allyl group), an alkynyl group (e.g., a propargyl group), an epoxy group, a carboxylic acid group, or a carboxylic acid derivative (e.g., an ester or amide).

[0094] In some embodiments, particles (e.g., microparticles) of the present disclosure can be formed by electrospraying. In some embodiments, particles (e.g., microparticles) of the present disclosure can be formed by spray-drying.

[0095] In some embodiments, the crosslinker comprises a dithiol group. In some embodiments, the dithiol group forms a thioether with an olefin functional group on the polyester backbone. In some embodiments, the crosslinker comprises a diazide. In some embodiments, the diazide forms a triazole with a propargyl functional group on the polyester backbone. In some embodiments, the crosslinker comprises a diamine. In some embodiments, diamine forms a β-hydroxy amine with an epoxide functional group on the polyester backbone. In some embodiments, the diamine forms an amide with a carboxylic acid functional group on the polyester backbone.

[0096] In some embodiments, the step of treating the emulsion comprises heating the emulsion or adding a catalyst (e.g., a cyclization catalyst such as a copper or rhodium salt such as a copper (I) salt). In some embodiments, the catalyst for forming an amide crosslinker is an amide coupling catalyst such as N,N'-dicyclohexylcarbodiimide or diisopropylcarbodiimide. In some embodiments, the polyester backbones comprise polyvalerolactone, polycaprolactone, polylactic acid, polyglycolic acid, or a combination thereof. In some embodiments, the polyester backbones are crosslinked by thioethers, triazoles, or amides. For example, in any of the above-embodiments, the act of combining a polyester with a plurality of functional groups and a crosslinker can further comprise also adding an initiator (e.g., a photoinitiator) and/or a catalyst (e.g., a copper catalyst).

[0097] In some embodiments of any of the above-methods, the solution (e.g., the emulsion in which the particles are formed further comprises an initiator (e.g., a photoinitiator). In some embodiments, the method of treating the solution comprises irradiating the photoinitiator with

ultraviolet light. In some embodiments, a dithiol group forms a thioether with an olefin functional group on the polyester backbone. In some embodiments, the thioether is formed by a radical reaction. In some embodiments, the radical reaction is initiated by a photoinitiator and treatment with ultraviolet light. In some embodiments, the crosslinker comprises a diazide. In some embodiments, the diazide forms a triazole with a propargyl functional group on the polyester backbone. In some embodiments, the triazole is formed in the presence of a copper (I) catalyst.

Definitions

[0098] The articles "a" and "an" are used in this disclosure to refer to one or more than one (i.e., to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

[0099] The term "and/or" is used in this disclosure to mean either "and" or "or" unless indicated otherwise.

[00100] "Alkyl" refers to a straight or branched chain saturated hydrocarbon. C_1-C_6alkyl groups contain 1 to 6 carbon atoms. Examples of a C_1-C_6alkyl group include, but are not limited to, methyl, ethyl, propyl, butyl, pentyl, isopropyl, isobutyl, sec-butyl and tert-butyl, isopentyl and neopentyl.

[00101] The term "treating" with regard to a subject, refers to improving at least one symptom of the subject's disorder. Treating includes curing, improving, or at least partially ameliorating the disorder.

[00102] The term "disorder" is used in this disclosure to mean, and is used interchangeably with, the terms disease, condition, or illness, unless otherwise indicated.

[00103] The term "administer", "administering", or "administration" as used in this disclosure refers to either directly administering a disclosed particle (e.g., a microparticle) or pharmaceutically acceptable salt of the disclosed particle or a composition to a subject.

[00104] As used herein the term "backbone" is understood to mean a polyester chain The polyester backbones of the present disclosure can be crosslinked to form particles such as microparticles or nanoparticles as disclosed herein.

[00105] As used herein, a "particle" is a discrete unit comprising polymer backbones as set forth herein that has been crosslinked. The particle can be a nanoparticle, a microparticle, or a macroparticle. The particle may include a drug dispersed therein.

[00106] A "nanoparticle" is understood as a crosslinked particle of the present disclosure with a diameter of between about 1 nm and about 999 nm, including all size ranges and subranges therebetween.

[00107] A "microparticle" as used herein is understood as a crosslinked particle of the present disclosure with a diameter of between about 1 μm (1,000 nm) and about 999 μm including all size ranges and subranges therebetween. As noted above, the microparticles can have a diameter between about 1 μm and about 100 μm, including all ranges and subranges therebetween. In some embodiments, the microparticles of the present disclosure can have a diameter between about 5 μm and about 30 μm, including all ranges and subranges therebetween (e.g., between about 7 μm and about 15 μm or about 10 μm).

[00108] A "macroparticle" as used herein is understood as a crosslinked particle of the present disclosure with a diameter of between about 1 mm (1,000 μm) and about 100 mm, including all size ranges and subranges therebetween. As used herein, a "macroparticle" can be a device or implant. In some embodiments, a single macroparticle can be visible to the naked eye. In some embodiments, macroparticles are referred to as "cylinders."

[00109] As used herein, a "drug" is any small molecule therapeutic agent. A drug can be, without limitation, a steroid such as triamcinolone, triamcinolone acetonide, triamcinolone hexacetonide, or paclitaxel. A "drug" can also include a visualizing agent such as curcumin.

[00110] A "patient" or "subject" is a mammal, e.g., a human, mouse, rat, guinea pig, dog, cat, horse, cow, pig, or non-human primate, such as a monkey, chimpanzee, baboon, or rhesus.

[00111] Particles of the present disclosure can be used in medical applications. For example, particles can be used to heal a wound (e.g., as antiseptics). A wound is understood as an injury to living tissue. Wounds can be caused by cuts, blows, or impacts. Wounds can also be the result of a surgery. Accordingly, in some embodiments, the compounds of the present disclosure can be used to help heal wounds after a surgery. The particles of the present disclosure can be

injected (e.g., with a syringe). In some embodiments, the particles of the present disclosure are administered during a surgery and remain after the surgery (e.g., for a period of 1-6 months).

[00112] The definition of the crosslinking density of the particle is based on the percentage of the pendant functionality (e.g., allyl, propargyl, or epoxy) of the linear polymer precursor (e.g., polyester) (van der Ende, A.E., et al.. (2008) J. Am Chem. Soc. 130, p. 8706). As used herein, the term "cross-linking density" refers to the proportion of functionalized monomer (e.g., allyl valerolactone) used in preparing a polymer such as a copolymer, expressed as a weight percentage of monomers used. For example, if 4% allylvalerolactone and 96% valerolactone are used (by weight) to prepare a polymer backbone, then the crosslinking density of the resulting particle is understood to be 4%. Actual crosslinking density can be determined by analytical techniques including, but not limited to, infrared spectroscopy, pyrolysis gas chromatography, and nuclear magnetic resonance.

[00113] The crosslinking densities of the particles of the present disclosure can be between 1% and 100%, inclusive. In some embodiments, the crosslinking density is about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, or about 10%.

[00114] As used herein, the term "VL" is understood to mean valerolactone.

Preparation of Microparticles

[00115] Microparticles of the present disclosure can be prepared by dissolution of functionalized polyesters in a solvent along with a crosslinker and subsequent crosslinking of the mixture. The resulting product is a plurality of crosslinked microparticles. As set forth in Examples 3 and 4, microparticles comprising PCL with (polyallylvalerolactone-polyvalerolactone) PAVL-PVL (Example 3) and PAVL-PVL (Example 4) were crosslinked using hexanedithiol in the presence of 2,2-dimethoxy-2-phenylacetophenone (DMPA) by irradiation with ultraviolet (UV) light. The microparticles thus produced (see e.g., FIGs 1A-2D) were in insoluble in dimethyl sulfoxide (DMSO). This demonstrates that the particles produced as described herein are discrete units that are structurally different from the polymeric (e.g., polyester) precursors (or backbones). Without wishing to be bound by theory, crosslinking affords structural integrity to the particles.

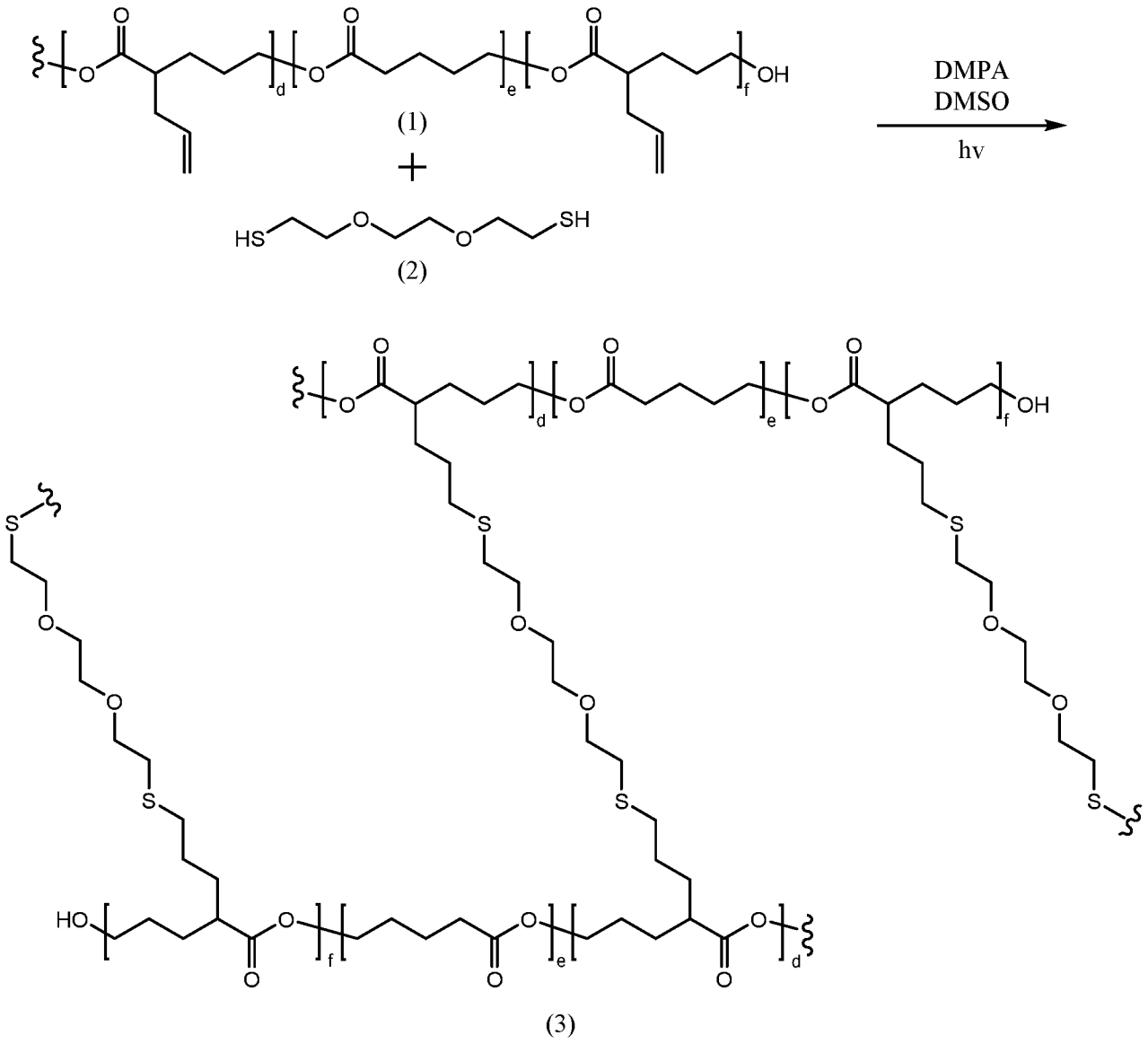
[00116] In contrast to the crosslinked particles, Comparative Examples 3 and 4 demonstrate microparticles that are produced in the absence of a crosslinker. Comparative Examples 3 and 4 combine PCL with PAVL-PVL (Comparative Example 3) and PAVL-PVL (Comparative Example 4) with UV light in the absence of a crosslinker (e.g., hexanedithiol). Because no crosslinking can occur in the absence of a crosslinker, no microparticles were formed. Accordingly, the polyesters remained intact and were soluble in DMSO. Therefore, in some embodiments, it is necessary to crosslink the polyesters described herein in order to form microparticles and in order to ensure desired characteristics such as stability and size.

[00117] Without wishing to be bound by theory, polymer backbones that are incapable of crosslinking (e.g., PLGA polymers) can be dependent upon micelle concentration in order to form. For example, as set forth in FIG. 3A, amphiphilic block copolymers can self-assemble into micellar structures. However, such micelles can fall apart below the critical micelle concentration (CMC).

[00118] In contrast, as set forth in FIG. 3B, compounds of the present disclosure comprise functionalized polymers and reactive crosslinkers and are covalently crosslinked in a particle (e.g., nanoparticle or microparticle) structure. Thus the particles of the present disclosure remain intact regardless of concentration and are not dependent upon the critical micelle concentration.

[00119] According to embodiments of the present disclosure, the microparticles are crosslinked. Schemes 1 through 3 below show general routes to the crosslinked particles of the present disclosure.

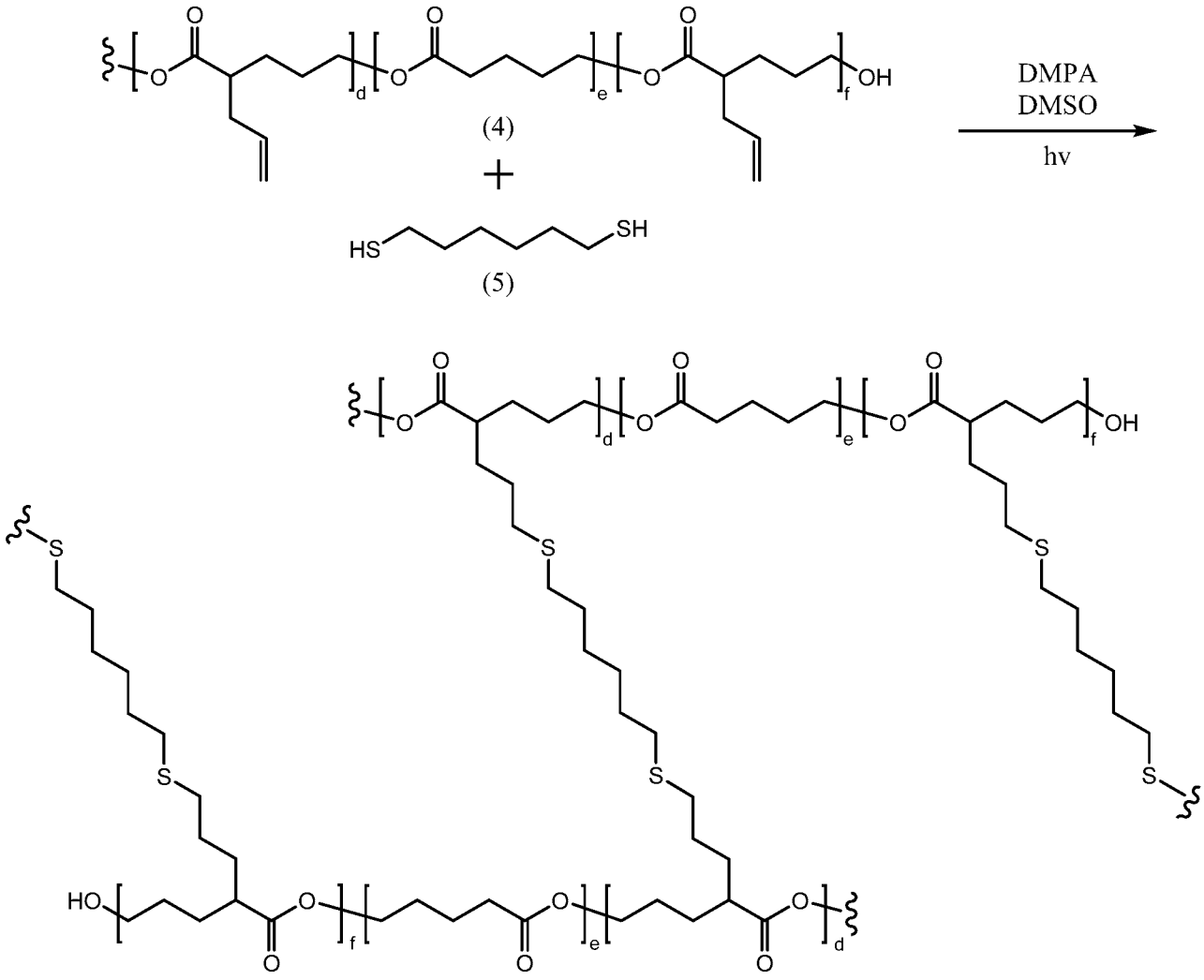
Scheme 1: General Crosslinking Scheme using PAVL-PVL Backbone and 2,2'-(ethane-1,2-diylbis(oxy))bis(ethane-1-thiol) Crosslinker



[00120] As shown in Scheme 1, a polyester comprising polyvalerolactone and polyallylvalerolactone (1) can be crosslinked in using a disulfide (2) in the presence of a radical initiator (e.g., a photoinitiator such as DMPA). The ratio of DMPA per allyl group can be adjusted to control the properties of the resulting microparticle (e.g., to produce more or less crosslinking). For instance, in some embodiments 0.2 equivalents of DMPA per allyl group can be added. In some embodiments, one thiol group in (2) can be added for each allyl group in (1). Upon treatment of the mixture of (1) and (2) with UV light (e.g., 365 nm), the allyl groups can

crosslink with the thiol groups of the crosslinker to produce a crosslinked microparticle (3). As used in Scheme 1, the values for d, e, and f can each independently be any integer between 1 and 1000, inclusive.

Scheme 2: General Crosslinking Scheme using PAVL-PVL Backbone and 1,6-hexanedithiol Crosslinker



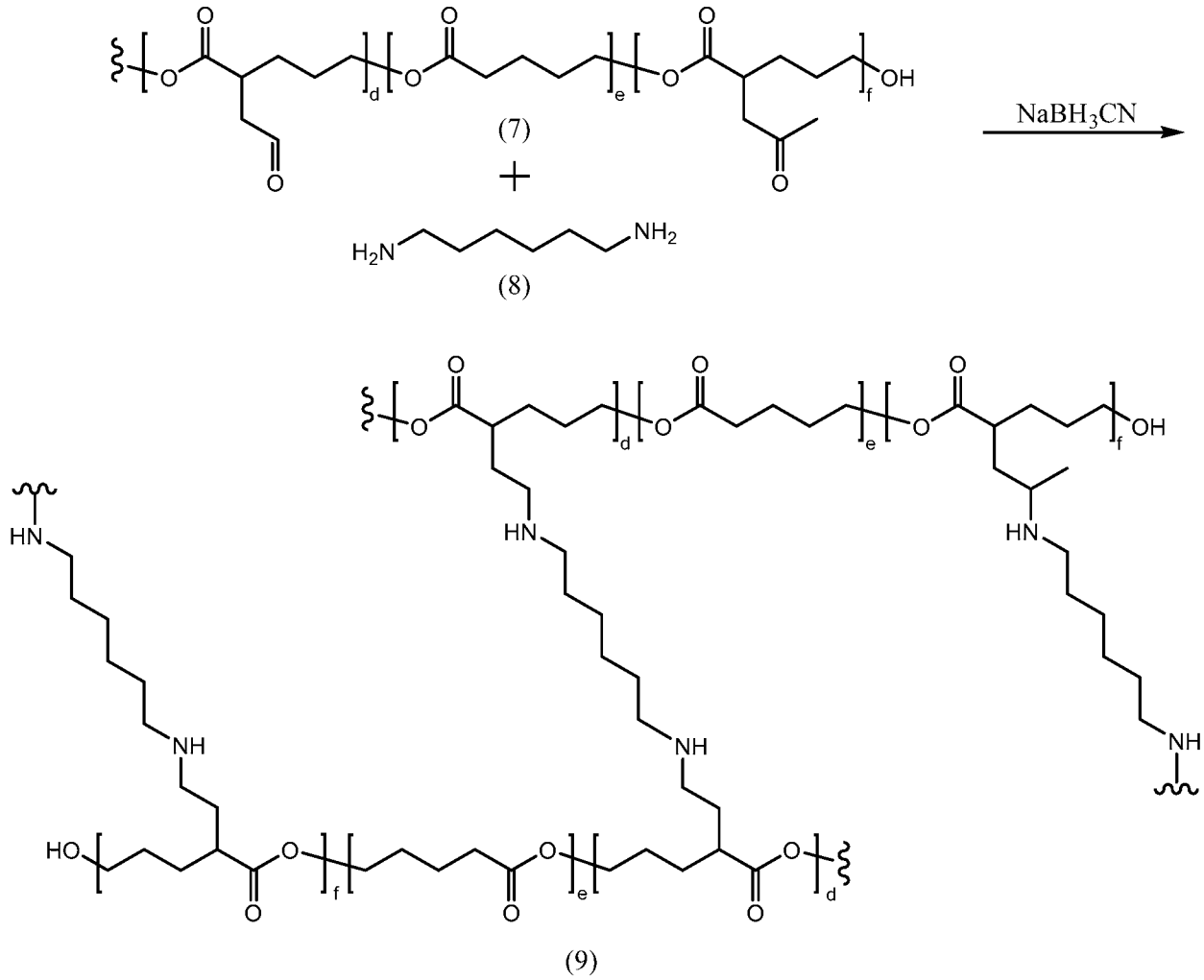
(4) + (5) → (6)

[00121] As shown in Scheme 2, a polyester comprising polyvalerolactone and polyallylvalerolactone (4) can be crosslinked in using a disulfide (5) in the presence of a radical initiator (e.g., a photoinitiator such as DMPA). The ratio of DMPA to allyl groups can be adjusted to control the properties of the resulting microparticle (e.g., to adjust the rate of

crosslinking and to produce more or less crosslinking). For instance, in some embodiments 0.2 equivalents of DMPA per allyl group can be added. In some embodiments, one thiol group in (5) can be added for each allyl group in (4). Upon treatment with UV light (e.g., 365 nm), the allyl groups can crosslink with the thiol groups of the crosslinker to produce a crosslinked microparticle (6). As used in Scheme 2, the values for d, e, and f can each independently be any integer between 1 and 1000, inclusive.

[00122] In some embodiments, crosslinking can take place by the reaction of an amine group with a carbonyl (e.g., a reductive amination). As shown below in Scheme 3, a polymer backbone functionalized with carbonyl groups (e.g., aldehydes or ketones such as methyl ketones) can react with a diamine to form carbon-nitrogen bonds. Such reactions can be facilitated by a reducing agent (e.g., sodium cyanoborohydride), optionally in the presence of an acid (e.g., acetic acid).

Scheme 3 – General Crosslinking Scheme using Carbonyl-Functionalized Backbones and Diamine Crosslinkers



[00123] Scheme 3 shows a reductive amination between a diamine (8) and a polymer backbone that is functionalized with an aldehyde and a methyl ketone (7) to produce a crosslinked polymer (9). One of skill in the art will understand that it is possible to carry out a crosslinking reductive amination using, for instance, only aldehydes, or only ketones (e.g., phenyl ketones, ethyl ketones, and the like), or a mixture of both aldehydes and ketones. As set forth in Scheme 3, the variables d, e, and f can be integers between 1 and 1000, inclusive.

[00124] In some embodiments, the microparticles of the present disclosure can be made from functionalized polymer backbones. That is, as set forth below, the polymer backbones can be functionalized with, for instance, olefin (e.g., allyl), alkynyl (e.g., propargyl), or epoxy groups.

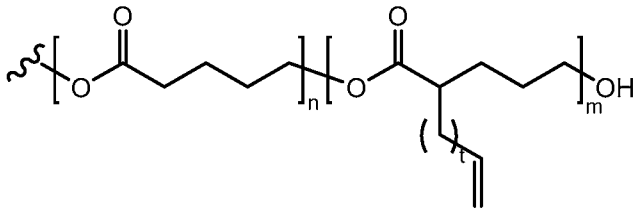
Thus, embodiments the particles of the present disclosure are not made entirely from unfunctionalized poly(lactic-co-glycolic acid) (PLGA), which historically can be difficult to functionalize. However, in some embodiments, unfunctionalized PLGA could be incorporated into portions of a copolymer backbone that also includes other functionalized polymers in the copolymer backbone.

[00125] Functionalization of the polymers of the present disclosure can enable one of skill in the art to customize the features of the particles. For example, as set forth below, the adjustment of the ratios and types of crosslinker and polymer can allow for alterations in, e.g., porosity, drug loading and release, and rates of degradation.

Polyesters

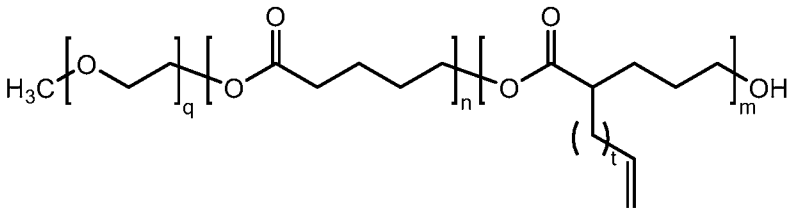
[00126] A variety of different polyester backbones can be used to form particles of the present disclosure. For example, in some embodiments the polyester backbones are made from polycaprolactone (PCL). In some embodiments, the polyester backbones are made from polyvalerolactone (PVL). In some embodiments, the PCL or PVL can be functionalized with an allyl group to produce polyallylcaprolactone (PACL) or polyallylvalerolactone (PAVL). In some embodiments, polyesters of the present disclosure are copolymers comprising two or more different monomers. For example, polyesters can comprise PVL and PAVL; PCL and PACL; PVL and PACL; or PCL and PAVL. In some embodiments, polyesters of the present disclosure can further comprise polylactic acid and/or polyglycolic acid. In some embodiments, any of the polyvalerolactone, polycaprolactone, polylactic acid, or polyglycolic acid can be functionalized with a functional group. For example, any of the polyvalerolactone, polycaprolactone, polylactic acid, or polyglycolic acid can further include an ally group, a propargyl group, or a carboxylic acid (or carboxylic acid derivative) disposed along the polymer backbone. The functional group can be used to crosslink the polymer backbone with another polymer backbone. In some embodiments, the copolymers of the disclosure can be block copolymers or random copolymers.

[00127] For instance, in one embodiment, the polyester backbone can comprise a copolymer of polyvalerolactone and polyallylvalerolactone (PVL-co-PAVL):



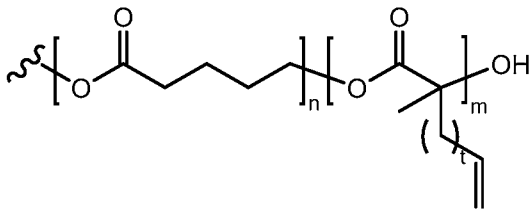
The values of m and n are integers and can each independently fall between about 1 and 1,000. For instance, when n is about 48 and m is about 15, the molecular weight is about 7,000 g/mol. When n is about 128 and m is about 14, the molecular weight is about 14,760 g/mol.

[00128] In another embodiment, the polyester backbone can comprise a stabilizer (e.g., a PEG stabilizer). For example, a polyester backbone can comprise mPEG2k-b-PVL-co-PAVL:



The values of m, n and q are each integers and can each independently fall between about 1 and 1,000. For example when q is about 50, n is about 40, and m is about 9, the molecular weight of the polyester is about 7,500 g/mol.

[00129] In another embodiment, the polyester backbone can comprise polyallyl lactide. The polyallyl lactide can be formed from polymerization of allyl lactide. For example, a polyester backbone can comprise a copolymer of polyvalerolactone and polyallyllactide (PVL-co-PAL):



[00130] The polyesters of the present disclosure can be prepared using a variety of different suitable monomers. For example, valerolactone can be used to prepare polyvalerolactone, and allylvalerolactone can be used to prepare polyallylvalerolactone. Similarly, caprolactone can be used to prepare polycaprolactone, and allylcaprolactone can be used to prepare polyallylcaprolactone. In some embodiments, lactic acid, glycolic acid, allyl lactide, and

combinations thereof can be used as monomers to prepare the polyesters disclosed herein. One of skill in the art will readily understand how to select an appropriate monomer to arrive at a desired polyester backbone.

[00131] In any of the embodiments disclosed herein, the polyesters of the present disclosure can further comprise polyethyleneglycol (PEG). In some embodiments, the PEG can connect two different sections of polyester. That is, the PEG can be dispersed between ester-containing portions of the polyester backbone. Alternatively, in some embodiments, the PEG can be attached at the end of the polymer (i.e., the PEG can comprise a terminal portion of the polymer). Thus, in some embodiments, the PEG is found primarily towards the outside of the microparticles.

[00132] In some embodiments, crosslinked polymers of the present disclosure can further include additional polymers entangled therein. In some embodiments, compositions of the present disclosure can include PVL and/or PAVL polymer backbones crosslinked together. In some embodiments, the present disclosure includes PVL and/or PAVL polymer backbones crosslinked together with PCL entangled therein. In some embodiments, the present disclosure can include PVL and/or PAVL polymerized onto PCL backbones, or PVL and or PAVL portions crosslinked together. In some embodiments, the present disclosure can include PVL and/or PAVL and PEG polymer backbones crosslinked together.

Crosslinkers

[00133] The present disclosure provides for a number of different crosslinkers and crosslinking strategies that can be used to crosslink and form the microparticles described herein. In one embodiment, crosslinking can take place in the presence of a radical initiator (e.g., a photoinitiator). In some embodiments, the crosslinking reaction can be a radical thiol-ene reaction. For example, as set forth in Examples 3 and 4, a photoinitiator (i.e., 2,2-dimethoxy-2-phenylacetophenone) can be used to crosslink a hexanedithiol crosslinker with the allyl functional groups present on a PAVL-PVL polymer backbone. One of skill in the art will recognize that a photoinitiator can be used create radicals (e.g., in the presence of UV light). In some embodiments, photoinitiators do not require heat to produce radicals. The radicals thus created can initiate a thiol-ene chain reaction between the thiols on the hexanedithiol with the olefin functionality (e.g., of the ally group) of PAVL to crosslink the polyester backbones and

produce particles (e.g., microparticles or nanoparticles). One of skill in the art will appreciate that additional radical initiators can be used to initiate a crosslinking reaction such as the thiol-ene reaction. For example, other radical initiators can include, without limitation, thermal initiators, halogens such as chlorine, bromine, and iodine, azo compounds such as azobisisobutyronitrile (AIBN), and organic peroxides such as di-tert-butyl peroxide and benzoyl peroxide.

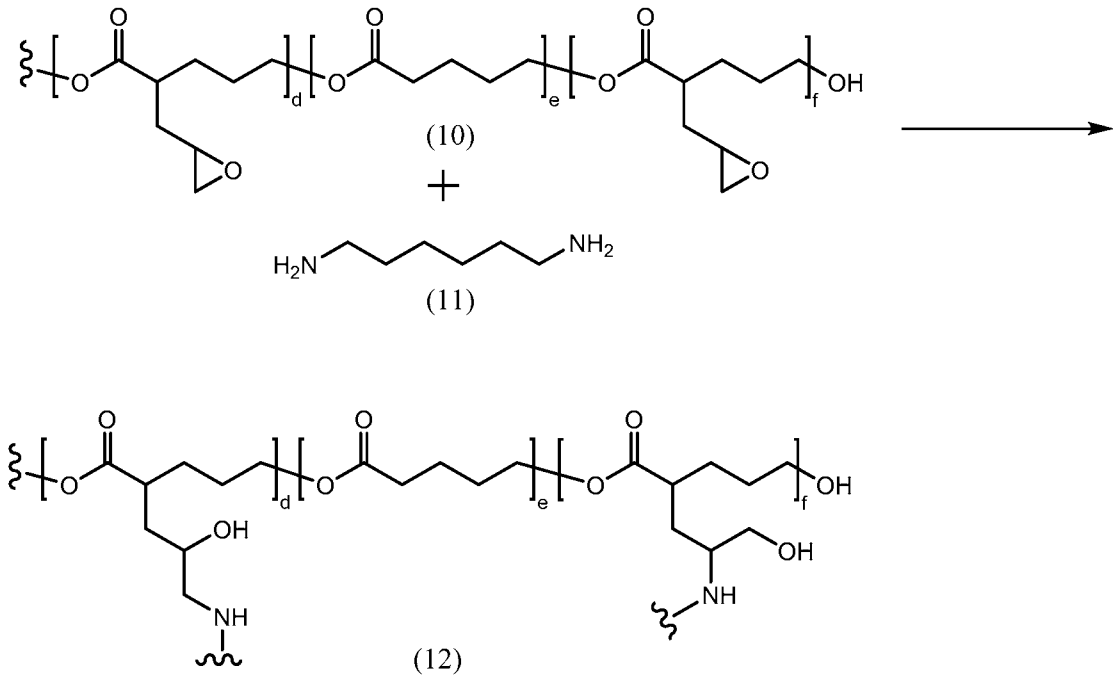
[00134] In some embodiments, the radical initiator can be a drug itself. For instance, using a drug that can form radicals to initiate a crosslinking chain reaction can simultaneously lead to the creation of crosslinked particles (e.g., microparticles) as well as ensure that the drug is dispersed within the particles. In some embodiments, a drug can be an initiator for crosslinking of the polymer backbones (e.g., polyester backbone) to form a particle of the present disclosure. Additionally, the radical initiators of the present disclosure need not be photoinitiators. In some embodiments, the radical initiators used herein can create radicals, for instance, thermally (e.g., upon heating). The amount of time necessary to crosslink polyesters using UV exposure can be, for instance, between about 1 and about 60 minutes. For example, an emulsion of the present disclosure can be exposed to UV light for about 1, about 5, about 10, about 15, about 20, about 25, about 30, about 35, about 40, about 45, about 50, or about 60 minutes.

[00135] Additionally, crosslinking can take place via the formation of a triazole from the reaction between an alkyne group and an azide group. For example, polyesters of the present disclosure can be functionalized with an alkynyl group (e.g., a propargyl group). The alkynyl group can react in the presence of a diazide (e.g., 1,6-hexanediazide). The alkynyl groups on the polyester chains can react to form triazoles with the crosslinkers (e.g., via the azide-alkyne Huisgen cycloaddition), thus creating particles (e.g., microparticles). One of skill in the art will understand that this reaction can be carried out in the presence of a catalyst. For instance, the cycloaddition reaction can be carried out in the presence of a copper (I) salt (e.g., cuprous bromide or cuprous iodide). In some embodiments, the reaction can be carried out in the presence of a copper (II) salt (e.g., copper (II) sulfate) and a reducing agent (e.g. sodium ascorbate) to produce copper (I) in situ. In some embodiments, the cycloaddition reaction takes place in the absence of a catalyst. For example, in some embodiments, the cycloaddition reaction can take place upon heating the mixture.

[00136] In some embodiments, crosslinking can take place via the formation of amide bonds (–C(O)NR–). For example, in some embodiments crosslinking can be effected by amide formation between a polyester of the disclosure that has been functionalized with a carboxylic acid group (or a carboxylic acid derivative) and a diamine (e.g., 1,6 hexanediamine). The amide formation can take place in the presence of a peptide coupling catalyst such as N,N'-Dicyclohexylcarbodiimide ("DCC"), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate ("HBTU"), or 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate ("HATU"). In some embodiments, the amide coupling reagent can be added after the carboxylic acid group and the diamine are dissolved in the same phase. One of skill in the art will further recognize that it is possible to form amide linkages in the absence of a peptide coupling reagent. For example, amide bonds can be formed by heating a mixture of carboxylic acid groups (e.g., in the presence of an acid). Alternatively, amide bonds can be formed between amines and carboxylic acid derivatives. For example, a crosslinking amide bond can be formed by treatment of an ester or non-crosslinked amide with a crosslinking amine group.

[00137] In some embodiments, crosslinking can take place via the formation of a β-hydroxy amine. For example, crosslinking can take place between an epoxide group disposed along a polyester backbone as described herein and an amine moiety. The diamines can react with the epoxides (e.g., nucleophilic attack) to form carbon-nitrogen bonds. One of skill in the art will understand that the regiochemistry of the β-hydroxy amine-forming reaction can be controlled by the reaction conditions (e.g., use of acid or basic catalysis). For example, one can influence whether a monosubstituted epoxide opens at the terminal position by using basic catalysis. Thus, as shown in Scheme 4, below, one of skill in the art will understand that multiple outcomes of amine-epoxy reaction are possible in the reaction between an epoxide-functionalized backbone (10) and a diamine (11) to arrive at a crosslinked particle (12):

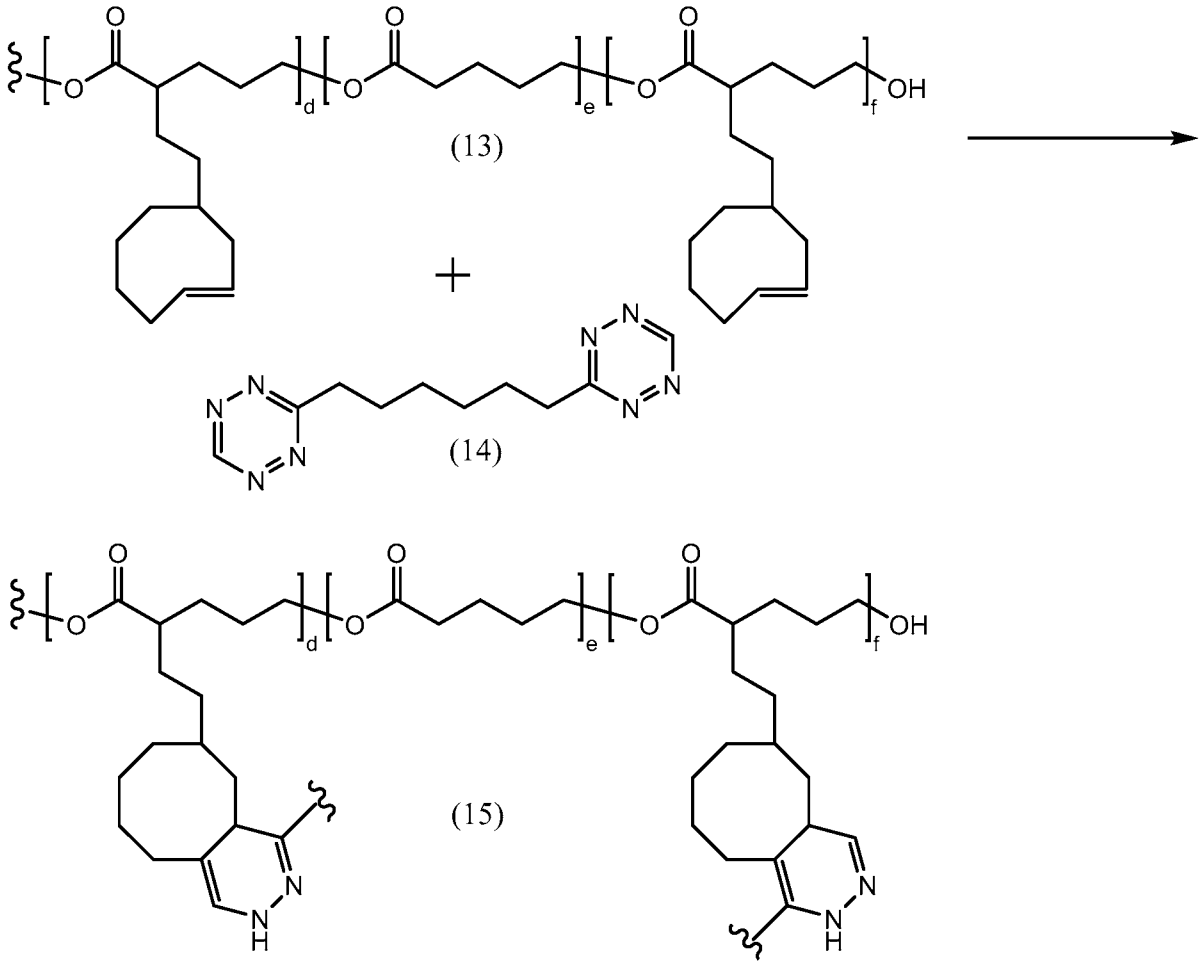
Scheme 4 – Possible Regiochemistries of Crosslinking Reaction of Amines with Epoxy Groups



[00138] In some embodiments, the nucleophile can be a molecule wherein the nucleophilic site has an atom with an additional lone pair of atoms alpha to the nucleophilic atom (e.g., can be an "alpha effect" nucleophile). For example, the nucleophilic portion of the crosslinker can be a hydrazine, a peroxide, or a hydroxylamine.

[00139] In some embodiments, particles (e.g., microparticles) of the present disclosure can be crosslinked by a reaction between a tetrazine and a *trans*-cyclooctene. For example, crosslinking can take place as set forth in Scheme 5, below. One of skill in the art will understand that a variety of different regiochemistries is possible with a tetrazine-*trans*-cyclooctene reaction.

Scheme 5 – Exemplary Crosslinking Reaction Between *trans*-Cyclooctene and Tetrazine

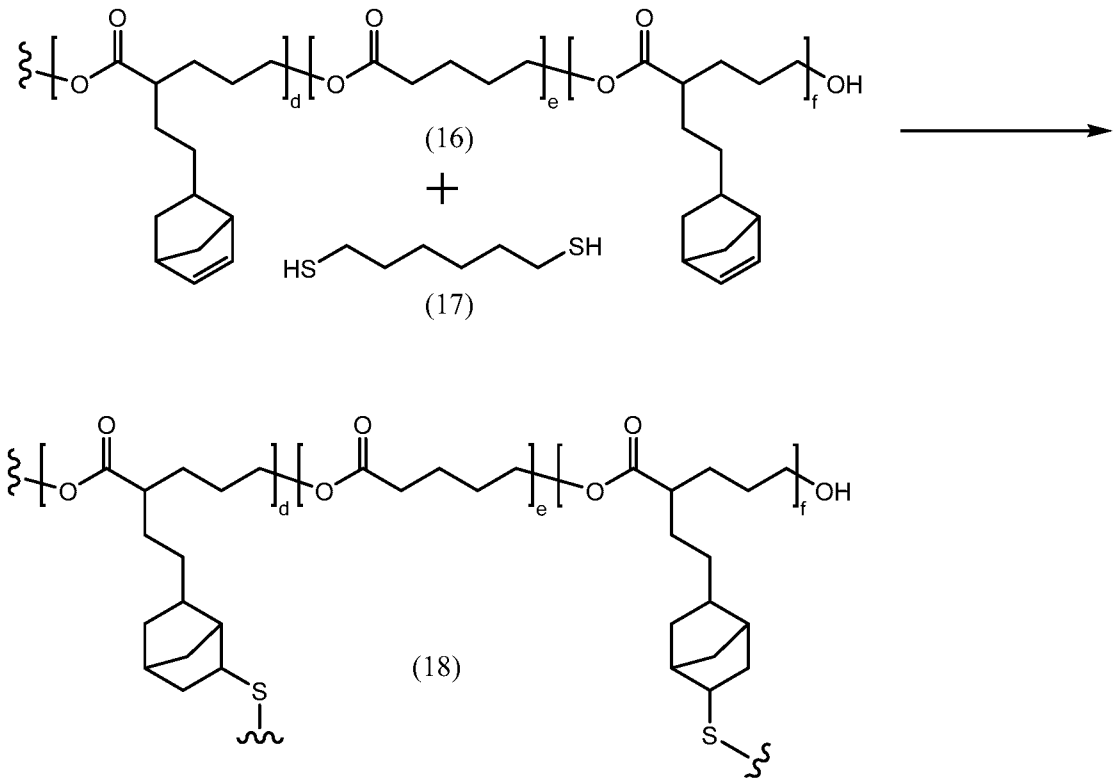


[00140] As set forth in Scheme 5, treatment of a *trans*-cyclooctene functionalized backbone (13) can be crosslinked with a ditetrazine (14). The tetrazine group can react with the *trans*-olefin of the cyclooctene group (e.g., a Diels-Alder cycloaddition followed by elimination of nitrogen gas). As set forth above in Scheme 5, the regiochemistry of tetrazine addition can vary. The flexibility in regiochemical crosslinking is also shown in Formula V. One of skill in the art will understand that Formula V shows that the crosslinking reaction is not limited to a specific regiochemistry (e.g., the *trans*-cyclooctene can be attached to the polymer backbone at different positions than the position shown).

[00141] In some embodiments, particles (e.g., microparticles) of the present disclosure can be crosslinked by a reaction between a thiol and a norbornene. For example, crosslinking can take place as set forth in Scheme 6, below. One of skill in the art will understand that a variety of

different regiochemistries is possible with a thiol-norbornene reaction, and the present disclosure is not limited to a specific regiochemistry.

Scheme 6 – Possible Regiochemistries of Crosslinking Reaction of Norbornene with Thiol Groups



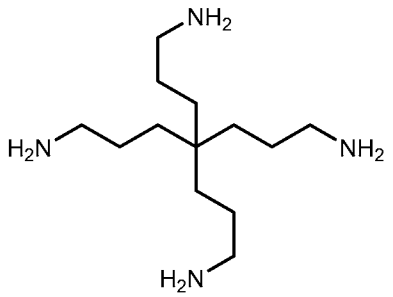
[00142] As set forth in Scheme 6, treatment of a norbornane-functionalized backbone (16) can be crosslinked with a dithiol (17) in the presence of ultraviolet light to form a crosslinked particle (18). In some embodiments, a photoinitiator can be added. The thiol group can react with the olefin of the norbornyl group to form sulfur-carbon bonds (e.g., by radical addition). As set forth above in Scheme 6, the regiochemistry of thiol addition can vary. The flexibility in regiochemical crosslinking is also shown in Formula VI. One of skill in the art will understand that Formula VI shows that the norbornyl group can be connected to the polymer backbone and crosslinked via a dithiol with a variety of different crosslinking regiochemistries, and the present disclosure is not limited to a specific regiochemistry.

[00143] One of skill in the art will understand that the above schemes are illustrative of the present invention and are not to be construed as limiting. For example, one of skill in the art will

readily understand that any of the functional groups described above (e.g., norbornene groups, *trans*-cyclooctene groups, tetrazine groups) can be substituted without deviating from the spirit of the present disclosure. For example, any of the functional groups set forth above can have, for example, a methyl substituent.

[00144] One of skill in the art will understand that it is possible to switch the nature of the functional groups and crosslinkers disclosed herein to achieve similar results as disclosed herein. That is, one of skill in the art will understand that it is possible, for example, to employ functional groups disposed along the polyester backbone to crosslink with diolefins (e.g., 1,5-hexadiene) and achieve similar results.

[00145] In some embodiments, crosslinkers can have two functional groups (i.e., the crosslinkers can be linear and have a functional group at each end). Examples of such bifunctional crosslinkers are 1,6-hexanedithiol. In some embodiments, crosslinkers can be multifunctional (e.g., can have more than two functional groups). For example, a tetrafunctional crosslinker can have the structure of 4,4-bis(3-aminopropyl)heptane-1,7-diamine:



[00146] One of skill in the art will understand that such a tetrafunctional crosslinker can be used, for instance, in the presence of epoxy-functionalized polymer backbones. Additionally, one of skill in the art will understand that the amine functionalities can be replaced with thiol groups to enable a tetrafunctional crosslinker in a thiol-ene reaction.

[00147] Additionally, one of skill in the art will understand that it is possible to use other chemical reactions (e.g., robust chemical reactions such as "click" reactions) to form crosslinks as described herein.

[00148] As used herein, crosslinkers of the present disclosure can comprise polymer (e.g., polyester, polycarbonate backbones). In other words, the crosslinker can comprise a polymer

with functional groups disposed thereon that are capable of reacting with the functional groups of another polymer. For example, a polyester backbone comprising a plurality of allyl groups disposed thereon can be crosslinked by a polyester polymer comprising a plurality of free thiol groups disposed thereon. In some embodiments, the crosslinking polymer can comprise a plurality of monomer units (e.g., 100 or more, 200 or more, 300 or more, or 1000 or more monomer units). In some embodiments, the monomer units can be functionalized or unfunctionalized valerolactone units.

Size Control Techniques

[00149] The present disclosure provides for the preparation of particles of controllable size. In some embodiments, the particles can be microparticles or nanoparticles. For example, the particles described herein can have diameters between about 1 and 999 μm, including all ranges and subranges therebetween (e.g., between about 5 and about 500 μm; or about 10 μm; about 20 μm; about 50 μm; about 100 μm; or about 200 μm).

[00150] Size optimization or size control can be accomplished by a number of different methods described herein. For example, in some embodiments, the polymers and crosslinkers described herein can be dissolved in a non-aqueous (e.g., organic) solvent. The mixture of the polymers and crosslinkers (and, optionally, initiators or catalysts) can be emulsified with an aqueous phase (e.g., water optionally comprising an emulsifying agent such as polyvinylalcohol, PVA, or PEG). The emulsion parameters can be used to control the resulting particle size. That is, in some embodiments, the particle precursors (e.g., polymers, crosslinking agents and initiators) can be dissolved within droplets of the non-aqueous solvent of the emulsion. The crosslinking reaction can then take place while the particle precursors are dissolved in the non-aqueous solvent of the emulsion. In other words, the emulsion (i.e., the non-aqueous phase), can act as a mold or cast to allow uniformly dispersed microparticles. In some embodiments, the crosslinking can take place within the emulsion (i.e., the non-aqueous phase). For example, an emulsion comprising non-aqueous droplets with the particular precursors (e.g., polyester backbone and crosslinker) dissolved therein can be irradiated. In some embodiments, all of the components of the reaction are water-insoluble and therefore dissolve in the non-aqueous droplets of the emulsion.

[00151] Accordingly, in some embodiments, the size of the microparticles is a function of the size of the droplets (e.g., microdroplets) of the non-aqueous solvent. Thus, in some embodiments, the speed of stirring or agitation of the emulsion can be used to control the size of the non-aqueous droplets and thus the size of the resulting microparticles. In some embodiments, sonication (e.g., by probe tip or horn) can be used to control the size of the non-aqueous droplets and thus the size of the resulting microparticles.

[00152] Thus, in some embodiments, polymer precursors (e.g., PCL) can be added at high concentrations (e.g., greater than 50 mg/mL). In some embodiments, the speed of the emulsion process can be adjusted between about 10,000 rpm and 22,000 rpm. For example, the speed of the emulsion process can be about 10,000 rpm, about 11,000 rpm, about 12,000 rpm, about 13,000 rpm, about 14,000 rpm, about 15,000 rpm, about 16,000 rpm, about 17,000 rpm, about 18,000 rpm, about 19,000 rpm, about 20,000 rpm, about 21,000 rpm, or about 22,000 rpm. In some embodiments, the percentage of surfactant (e.g., polyvinyl alcohol, polyvinylpyrollidone or polyethylene glycol) in the aqueous phase can also be used to control the droplet size (and thus the size of the resulting particles). For example, the viscosity of the aqueous phase can be controlled by the amount of polyvinyl alcohol. In some embodiments, the percentage of polyvinyl alcohol can be between about 5% (wt) and about 20% (wt). For example, the percentage of polyvinyl alcohol can be about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, or about 20% by weight. Similarly, in some embodiments the molecular weight of the surfactant (e.g., polyvinyl alcohol, polyvinylpyrollidone or polyethylene glycol) can be used to control the droplet size (and thus the size of the resulting particles).

[00153] The ratio of aqueous solvent to non-aqueous solvent can also be used to control the size of the particles. For example, in some embodiments, between about 1 and 100 mL of aqueous solvent is used (e.g., about 1, about 5, about 10, or about 15 mL of aqueous solvent). In some embodiments, between about 1 and about 10 mL of non-aqueous solvent is used (e.g., about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9 or about 10 mL of non-aqueous solvent is used). In some embodiments, the ratio of aqueous to non-aqueous solvent is between about 1:1 to about 10:1.

[00154] After crosslinking the particles in the non-aqueous phase, the solvent (e.g., the non-aqueous solvent, the aqueous solvent, or both) can be removed. In some embodiments, removal of the solvent includes exposing the emulsion to a gas stream (e.g., an N_2 stream). The gas stream can last for a number of hours (e.g., about 1 hour, about 3 hours, about 6 hours, about 12 hours, or about 24 hours).

[00155] In another embodiment, the microparticles and macroparticles of the present disclosure can be controlled by photolithography. As set forth in Example 12, templates were formed by creating pegs of uniform size and shape which were used to create wells that are likewise of uniform size and shape. Polyesters and crosslinkers were dissolved in the wells and crosslinked to created microparticles and macroparticles of uniform size. The resulting particles can then be removed from the wells and used. In some embodiments, the molded solution can also contain a filler (e.g., a plasticizer). In some embodiments, the filler can be used to control the porosity of the resulting particles.

[00156] In another embodiment, the size of the particles (e.g., microparticles or nanoparticles) can be controlled by milling of a corresponding macroparticle. For example, in some embodiments, the crosslinking reactions of the present disclosure can be performed in a single phase (i.e., not an emulsion) to create a macroscopic particle (e.g, a particle with a mass of >10 mg). The resulting macroparticle can then be milled (e.g., crushed) to create a plurality of nanoparticles or microparticles.

Anti-Aggregation techniques

[00157] In some embodiments, particles of the present disclosure can comprise PEG polymers attached to the polyester particle backbone. In some embodiments, the PEG polymers can be attached such that they are disposed toward the outside of the particle. For example, the PEG polymers can be attached at the terminal portion of the polyester particle backbones.

[00158] In some embodiments, attachment of PEG polymers can help to reduce aggregation of the particles of the present disclosure. In some embodiments, other polymers such as polyvinylpyrrolidone or pluronics can be used in place of PEG to help prevent aggregation. Also, attachment of PEG polymers can make the particles more hydrophilic and help facilitate drug loading. For example, a PVL-co-PAVL microparticle was prepared according to the

methods disclosed herein. Without wishing to be bound by theory, the resulting particles were hydrophobic and demonstrated some aggregation. In some embodiments, it could be difficult to load drugs into the resulting particles because the particles were non-porous and hydrophobic.

[00159] In some embodiments, attachment of PEG polymers can be accomplished by using a hydroxy-PEG molecule as an initiator for a polymerization reaction (e.g., as an initiator for polyester formation). For example, a multi-arm PEG such as a PEG dendrimer or a six-arm, hydroxy terminated PEG can be used as a polymerization initiator.

[00160] In contrast, preparation of particles comprising mPEG-2K-PVL-co-PAVL (i.e., particles wherein PEG was disposed on the outside of the particle) demonstrated greater hydrophilicity, less aggregation, and easier drug loading. In some embodiments, at least about 2.5% PEG can be used (e.g., as a co-solvent) to reduce aggregation of drug particles (e.g., at least about 2.5%, at least about 5%, or at least about 10%). For example, FIG. 18A shows curcumin-loaded particles dissolved in water containing 1% tween after being dried in THF with 25% PEG as a co-solvent. Also, FIG. 18B shows a close-up view of curcumin-loaded particles dissolved in water containing 1% tween after being dried in THF with 25% PEG as a co-solvent. Without wishing to be bound by theory, the results suggest that dissolving in water comprising a surfactant can help reduce clumping of the particles.

Drug Loading and Release

[00161] In some embodiments, drugs can be loaded into the particles of the present disclosure by soaking the particles in a solvent (e.g., water, tetrahydrofuran (THF) or dimethylsulfoxide (DMSO)) that contains the drug. In some embodiments, the drug can be a small molecule, including, but not limited to, triamcinolone, triamcinolone hexacetonide, paclitaxel. Other drugs include, but are not limited to, bimatoprost, travaprost, brimonidine, camptothecin, tamoxifen, quercetin, thiostrepton, temozolamide, trametinib, seliciclib, fN'LFN'YK, GCGGGDHGVSSGV, hepatocyte growth factor (HGF), and bone morphogenetic protein 2 (BMP2).

[00162] In some embodiments, the drugs released from particles of the present disclosure can be hydrophobic. In some embodiments, particle loading with such hydrophobic drugs and subsequent release from the particles can facilitate the administration of such hydrophobic drugs

(e.g., *in vivo*). FIG. 13 gives loading capacities of macroparticles of the present disclosure for the drugs curcumin (as a visible surrogate for a drug), paclitaxel, triamcinolone acetonide, and triamcinolone hexacetonide.

[00163] In some embodiments, the particles (e.g., microparticles such as 10 μm microparticles) can provide sustained release (e.g., about 3 months of sustained release of a drug (e.g., triamcinolone hexacetonide) in a relevant animal model.

[00164] FIG. 4 shows a schematic of the method for loading drugs into particles of the present disclosure. As set forth in FIG. 4, particles are suspended in an organic solvent containing a drug. The resulting mixture is stirred, and the drug can incorporate into the porous regions of the particles. After purification, the drugs can be lyophilized and stored until use.

[00165] In some embodiments, the loading procedure can affect the amount of drug that is absorbed into a particle of the present disclosure. For example, as set forth in Examples 7 and 8, 25 mg of 75:25 (mPEG-PVL-PAVL:PVL-PAVL) particles were swollen overnight with 2 mg/mL triamcinolone hexacetonide in THF. However, without wishing to be bound by theory, slow addition of greater volumes of water can facilitate greater uptake of triamcinolone hexacetonide by allowing the drug to preferentially partition into the particles. As set forth in Examples 7 and 8, slow addition of water enabled 67% loading efficiency. Additional parameters, in addition to the rate of water addition, that can affect the loading of a drug into a particle of the present disclosure are, for instance, the solvent in which the drug is dissolved, the time that the particles soak with the drug, and the volume of water used. Other parameters include the pH and the ionic strength of the solvent. For example, protic organic solvents such as methanol or ethanol can be used in place of water to facilitate loading of drug into a particle of the present disclosure.

[00166] Without wishing to be bound by theory, soaking the particles of the present disclosure, (e.g., in THF, in the presence of a drug) can cause the particles to swell. For example, Example 5 shows that particles of the present disclosure can change in size (e.g., can swell) depending on the solvent in which they are placed. FIG. 5 shows a histogram of crosslinked mPEG-b-(PVL-coPAVL) microparticles demonstrating that had an average diameter of about 79 nm when placed in water. In some embodiments, the same particles swelled to a diameter of about 85 nm when soaked in dimethylsulfoxide (DMSO) as set forth in FIG. 6. The

particles swelled to a diameter of about 208 nm when soaked in THF, as set forth in FIG. 7. In some embodiments, the difference in volume of a particle can range by a factor of 5-20. For example, a particle soaked in THF can be about 2x as large, about 3x as large, about 4x as large, about 5x as large, about 6x as large, about 7x as large, about 8x as large, about 9x as large, about 10x as large, about 11x as large, about 12x as large, about 13x as large, about 14x as large, about 15x as large, about 16x as large, about 17x as large, about 18x as large, about 19x as large, or about 20x as large, as a particle soaked in water. For comparison, FIG. 8 sets forth a histogram of non-crosslinked mPEG-b-PVL-co-PAVL microparticles after soaking in water.

[00167] Additionally, FIG. 9 sets forth the swelling of particles that have been suspended in THF. FIG. 9A shows a histogram and an image of microparticles after crosslinking. and FIG. 9B and FIG. 9C show histograms and images of microparticles after a DMSO washing step and an ethanol washing step, respectively. FIG. 9D shows images and a histogram of particles soaked in THF. As set forth in FIG. 9D, the THF-soaked particles can be larger than the particles soaked in other solvents such as water or ethanol.

[00168] The release of drugs from particles of the present disclosure can be dependent upon the crosslinking density of the particles. For example, high crosslinking density can lead to slower drug release as high crosslinking density can lead to slower hydrolysis and thus slower degradation of the particles.

[00169] The release of drugs from particles of the present disclosure can be dependent upon the density of the particles. For instance, in some embodiments increasing the length of the crosslinker can decrease the density of the particle and allow for faster release of drug from a given particle.

[00170] In some embodiments, the particles disclosed herein display low crystallinity. Without wishing to be bound by theory, the low crystallinity can be advantageous for diffusion-mediated release. FIGs. 28 and 29 shows that microparticles of the present disclosure have low crystallinity at high crosslinking density.

Examples

[00171] The disclosure is further illustrated by the following examples and synthesis examples, which are not to be construed as limiting this disclosure in scope or spirit to the

specific procedures herein described. It is to be understood that the examples are provided to illustrate certain embodiments and that no limitation to the scope of the disclosure is intended thereby. It is to be further understood that resort may be had to various other embodiments, modifications, and equivalents thereof which may suggest themselves to those skilled in the art without departing from the spirit of the present disclosure and/or scope of the appended claims.

HPLC Methods

[00172] Unless otherwise indicated, quantitation of drug products was carried out using HPLC methods. Calibration curves for drugs used herein (e.g., triamcinolone, triamcinolone hexacetonide, triamcinolone acetonide, paclitaxel, and curcumin) were prepared by injecting known concentrations of the drugs and measuring the area under the curve at each concentration. Analyses were carried out using an Agilent Zorbax Eclipse XDB-C18 column (150 × 4.6 mm i.d.) with a 12.5 x 4.6 mm guard column. The parameters for each drug are given below in Table 1

Table 1 – Calibration Parameters for Drug Concentrations

Drug	Injection Volume	Retention time	Flow Rate	Detection wavelength	Mobile Phase	Cal. Slope	R^2
Triamcinolone hexacetonide	20 µL	3 min	1.2 mL/min	240 nm	MeOH: H_2O 90:10	Y=57.882x	0.9999
Paclitaxel	20 µL	7.8 min	1 mL/min	227 nm	MeOH: H_2O 50:50	Y=73.156x	0.9998
Curcumin	20 µL	4.45 min	1 mL/min	420 nm	ACN: H_2O:AcOH 55:45:0.1	Y=338.71x	0.9996

Example 1 – Preparation of PVL-co-PAVL copolymer

[00173] Benzyl alcohol (60 µl), valerolactone (8 mL) and allylvalerolactone (2 mL) were dissolved in toluene (20 mL) and triazabicyclodecene (catalyst) was added 2% mol : monomer and stirred at room temperature for 4 hours. FIG. 10 shows a ^{1}HNMR spectrum of PVL-co-PAVL polymer with a molecular weight of 17200 g/mol (i.e., about 128 units of valerolactone and about 14 units of allylvalerolactone). The number average molecular weight of the polymer was about 12,200 g/mol, with a peak molecular weight of about 14100 g/mol. The polydispersity index was bout 1.41. The melting temperature was about 35 °C. The temperature of recovery

was about 11 °C. FIG. 10B shows a gel permeation chromatography plot of the PVL-co-PAVL nanoparticles.

[00174] The mixture was subjected to gel permeation chromatography. The weight average molecular weight was about 17,200 g/mol.

Example 2 – Preparation of Polyvalerolactone/Polyallyl Lactic Acid (PVL-co-PAL)

[00175] Allyl lactide is prepared according the method disclosed in U.S. Patent No. 8,758,828 to Markland, et. al. Benzyl alcohol, valerolactone and allyl lactide are dissolved in triazabicyclodecene and stirred at room temperature for 4 hours. The resulting polymer is isolated and used for crosslinking microparticles.

Example 3 – Preparation of Crosslinked Microparticles Comprising Polycaprolactone and Polyallylvalerolactone

[00176] Polycaprolactone homopolymer (PCL; 50 mg; 50 kDa; 1 mmol), polyvalerolactone (PVL; 50 mg) and polyallylvalerolactone (PAVL; 50 mg (6700 g/mol; 19% allylvalerolactone and 81% valerolactone)) and hexanedithiol (1 –SH group per alkene) were dissolved in 1 mL dichloromethane. 2,2-Dimethoxy-2-phenylacetophenone (DMPA; 3.4 mg; 0.2 equivalents per alkene) was added and the solution was added dropwise to 20 mL of water containing 5% polyvinyl alcohol. The mixture was homogenized with stirring (i.e., a Polytron ® mechanical homogenizer at 22,000 rpm) for five minutes. The homogenized mixture was irradiated at 365 nm – 4 mW under stirring for 30 minutes.

[00177] The mixture was stirred for 3 hours to allow the dichloromethane to evaporate. The mixture was then centrifuged at 4000 rpm at 10 °C for 10 minutes. The aqueous solution containing polyvinyl alcohol was poured off and the particles were rinsed with distilled water. The particles were then centrifuged and rinsed with water as above an additional three times.

[00178] The particles were then dispersed in DMSO and centrifuged at 4000 rpm at 20 °C for ten minutes. The DMSO was poured off and the process was repeated another two times. The resulting crosslinked particles were swollen and semi-transparent and did not dissolve in DMSO.

[00179] FIG. 1A shows a photo of a PCL-co-PAVL copolymer at a scale of about 1500 μm produced by the above-method. FIGs. 1B, 1C, and 1D show photos of a PCL-co- PAVL/PVL

copolymer produced by the above-method at a scale of 400 µm, 600 µm, and 20 µm, respectively. The particles comprised between 0.01% and 20% polyallylvalerolactone (PAVL), with the remainder comprising polycaprolactone (PCL) and polyvalerolactone (PVL).

Comparative Example 3 – Attempted Preparation of Non-Crosslinked Microparticles Comprising Polycaprolactone and Polyallylvalerolactone

[00180] Polycaprolactone homopolymer (PCL; 50 mg; 50 kDa; 1 mmol) and polyallylvalerolactone (PVL-co-PAVL; 50 mg) were dissolved in 1 mL dichloromethane. The solution was added dropwise to 20 mL of water containing 5% polyvinyl alcohol. The mixture was homogenized with stirring (i.e., a Polytron ® mechanical homogenizer at 22,000 rpm) for five minutes. The homogenized mixture was irradiated at 365 nm – 4 mW under stirring for 30 minutes. No crosslinker or DMPA was added.

[00181] The mixture was stirred for 3 hours to allow the dichloromethane to evaporate. The mixture was then centrifuged at 4000 rpm at 10 °C for 10 minutes. The aqueous solution containing polyvinyl alcohol was poured off and the particles were rinsed with distilled water. The particles were then centrifuged and rinsed with water as above an additional three times.

[00182] The mixture was then dispersed in DMSO and centrifuged at 4000 rpm at 20 °C for ten minutes. The DMSO was poured off and the process was repeated another two times. Although particles were formed, the particle precursors dissolved in DMSO and were not recovered. This example was performed as a control experiment and the results demonstrate that crosslinking is necessary to produce microparticles of the present disclosure.

Example 4 – Preparation of Crosslinked Microparticles Comprising Polyallylvalerolactone

[00183] Polyallylvalerolactone (PAVL; 100 mg (6700 g/mol; 19% allylvalerolactone and 81% valerolactone)) and hexanedithiol (1 –SH group per alkene) were dissolved in 1 mL dichloromethane. 2,2-Dimethoxy-2-phenylacetophenone (DMPA; 0.2 equivalents per alkene) was added and the solution was added dropwise to 20 mL of water containing 5% polyvinyl alcohol. The mixture was homogenized with stirring (i.e., a Polytron ® mechanical homogenizer at 22,000 rpm) for five minutes. The homogenized mixture was irradiated at 365 nm – 4 mW under stirring for 30 minutes.

[00184] The mixture was stirred for 3 hours to allow the dichloromethane to evaporate. The mixture was then centrifuged at 4000 rpm at 10 °C for 10 minutes. The aqueous solution containing polyvinyl alcohol was poured off and the particles were rinsed with distilled water. The particles were then centrifuged and rinsed with water as above an additional three times.

[00185] The particles were then dispersed in DMSO and centrifuged at 4000 rpm at 20 °C for ten minutes. The DMSO was poured off and the process was repeated another two times. The resulting crosslinked particles were swollen and semi-transparent and did not dissolve in DMSO.

[00186] FIG. 2A shows a photo of a PVL-co-PAVL copolymer at a scale of about 1500 μm produced by the above-method. FIGs. 2B, 2C, and 2D show photos of a PVL-co- PAVL copolymer produced by the above-method at a scale of 400 μm, 600 μm, and 20 μm, respectively.

Comparative Example 4 – Attempted Preparation of Non-Crosslinked Microparticles Comprising Polyallylvalerolactone

[00187] Polyallylvalerolactone (PAVL; 100 mg) was dissolved in 1 mL dichloromethane. The solution was added dropwise to 20 mL of water containing 5% polyvinyl alcohol. The mixture was homogenized with stirring (i.e., a Polytron ® mechanical homogenizer at 22,000 rpm) for five minutes. No DMPA or crosslinker was added. The homogenized mixture was irradiated at 365 nm – 4 mW under stirring for 30 minutes.

[00188] The mixture was stirred for 3 hours to allow the dichloromethane to evaporate. The mixture was then centrifuged at 4000 rpm at 10 °C for 10 minutes. The aqueous solution containing polyvinyl alcohol was poured off and the particles were rinsed with distilled water. The particles were then centrifuged and rinsed with water as above an additional three times.

[00189] The mixture was then dispersed in DMSO and centrifuged at 4000 rpm at 20 °C for ten minutes. The DMSO was poured off and the process was repeated another two times. Although particles were formed, the particle precursors dissolved in DMSO and were not recovered. This example was performed as a control experiment and the results demonstrate that crosslinking is necessary to produce microparticles of the present disclosure.

Example 5 – Preparation of Crosslinked Microparticles Comprising Polyvalerolactone, Polyallylvalerolactone, and PEG

[00190] 50 mg of mPEG-PVL-PAVL (6.0×10^{-5} mol allyl), 5 mg DMPA (0.25 eq/allyl) and 4.4 μL 1,6-hexanedithiol (0.5 eq/allyl) were dissolved in 3 mL THF. The polymer solution in THF was added dropwise with stirring to 10 mL deionized water in a 20-mL glass vial. The solvent was evaporated for about 18 hours and then the solution was irradiated with UV light (365 nm) for five minutes. The resulting microparticles were characterized via dynamic light scattering (DLS).

[00191] FIG. 5 shows a DLS plot of the crosslinked particles in water. As shown, the particles are about 100 nm in diameter. Table 2 below shows the results of the DLS analysis.

Table 2 – DLS Analysis of Crosslinked mPEG-b-(PVL-coPAVL) Microparticles in Water

Cumulant Results		Distribution Results			
Z-average (nm)	78.65		Size (d) (nm)	% Int	σ
Pd index	0.140	Peak 1	90.69	97.9	30.10
Polydispersity (nm)	29.4	Peak 2	26.81	2.1	4.420
% Polydispersity	37.4	Peak 3	0.000	0.0	0.000
Derived kcps	48,863.4				

[00192] FIG. 6 shows a DLS plot of the crosslinked particles in DMSO. As shown, the particles are about 100 nm in diameter. Table 3 below shows the results of the DLS analysis.

Table 3 – DLS Analysis of Crosslinked mPEG-b-(PVL-coPAVL) Microparticles in DMSO

Cumulant Results		Distribution Results			
Z-average (nm)	85.22		Size (d) (nm)	% Int	σ
Pd index	0.077	Peak 1	91.61	100.0	24.28
Polydispersity (nm)	23.6	Peak 2	0.000	0.0	0.000
% Polydispersity	27.7	Peak 3	0.000	0.0	0.000
Derived kcps	3,424.2				

[00193] FIG. 7 shows a DLS plot of the crosslinked particles in THF. As shown, the particles are between about 100 nm and 1000 nm in diameter. Table 4 below shows the results of the DLS analysis.

Table 4 – DLS Analysis of Crosslinked mPEG-b-(PVL-coPAVL) Microparticles in THF

Cumulant Results		Distribution Results				
Z-average (nm)	208.4		Size (d) (nm)	% Int	σ	%Pd
Pd index	0.171	Peak 1	236.4	100.0	84.76	35.9
Polydispersity (nm)	86.1	Peak 2	0.000	0.0	0.000	0
% Polydispersity	41.3	Peak 3	0.000	0.0	0.000	0
Derived kcps	19181.1					

[00194] FIG. 11A shows a microscope image of mPEG-b-PAVL-co-PVL macroparticles (80:20) produced by this method at a resolution of about 1 mm.

[00195] FIG. 11B shows a microscope image of mPEG-b-PAVL-co-PVL macroparticles (80:20) produced by this method at a resolution of about 200 μm.

[00196] FIG. 11C shows a first microscope image of mPEG-b-PAVL-co-PVL macroparticles (80:20) produced by this method at a resolution of about 10 μm.

[00197] FIG. 11D shows a second microscope image of mPEG-b-PAVL-co-PVL macroparticles (80:20) produced by this method at a resolution of about 10 μm.

Example 6 – Preparation of Non-Crosslinked Nanoparticles Comprising Polyvalerolactone, Polyallylvalerolactone, and PEG

[00198] 50 mg of mPEG-PVL-PAVL (6.0×10^{-5} mol allyl) and 4.4 μL 1,6-hexanedithiol (0.5 eq/allyl) were dissolved in 3 mL THF. The polymer solution in THF was added dropwise with stirring to 10 mL deionized water in a 20-mL glass vial. No photoinitiator was added, and the emulsion was irradiated with UV light (365 nm) for five minutes as a control measure. The solvent was evaporated for about 18 hours, and the resulting micelles were characterized via dynamic light scattering.

[00199] FIG. 8 shows a DLS image of non-crosslinked microparticles produced as in the method above in water, and FIG. 12 shows a DLS plot of non-crosslinked particles in water. As shown, the particles are about 100 nm in diameter. Table 5 below shows the results of the DLS analysis. Without wishing to be bound by theory, because the particles were not crosslinked, they re-dissolved in organic solvent.

[00200] Table 5 – DLS Analysis of Non-Crosslinked mPEG-b-(PVL-coPAVL) Microparticles in Water

Cumulant Results		Distribution Results			
Z-average (nm)	80.89		Size (d) (nm)	% Int	σ
Pd index	0.173	Peak 1	94.69	100.0	32.66
Polydispersity (nm)	33.6	Peak 2	0.000	0.0	0.000
% Polydispersity	41.6	Peak 3	0.000	0.0	0.000
Derived kcps	44486.7				

Example 7 – Loading of Microparticles with Triamcinolone Hexacetonide

[00201] 25 mg of 75:25 (mPEG-PVL-PAVL:PVL-PAVL) particles were swollen overnight with 2 mg/mL triamcinolone hexacetonide in THF. 10 mL water including 0.1% tween was then added dropwise. The resulting mixture was centrifuged, the supernatant was collected, and the addition of 10 mL water including 0.1% tween was added dropwise again (2x; 30 mL total).

[00202] After the first centrifugation, it was observed that the particles did not easily resuspended in 10 mL water containing 0.1% tween. Without wishing to be bound by theory, this may be due to the fact that the triamcinolone hexacetonide crystallized on the surface of the particles. Without wishing to be bound by theory, this may be due to the relatively fast addition of water and the limited solubility of triamcinolone hexacetonide, which caused it to crystallize. Also without wishing to be bound by theory, the release profile showed relatively rapid release from the particles, likely a result of the surface-crystallized drug re-dissolving in solution.

Example 8 – Loading of Particles with Triamcinolone Hexacetonide with Slow Addition of Water

[00203] 15-mg macroparticles were placed in 0.5mL of THF containing 15 mg of drug. After 2 hours of swelling, the cylinders were washed with fresh THF and dried at room temperature for 24 hours.

[00204] 40 mg of microparticles were swollen in 0.5 mL of tetrahydrofuran containing 10 mg of drug. Slow addition of water was used in some embodiments for the addition to microparticles.

[00205] The loading efficiency, which included surface-bound drug or free drug in solution, was 67%. Upon suspending the particles in dissolution media, 20% of the triamcinolone hexacetonide was released within an hour, and 30% was released within 2 hours.

[00206] Without wishing to be bound by theory, very slow addition of larger volumes of water can give triamcinolone hexacetonide the opportunity to preferentially partition into the macroparticles. Accordingly, FIG. 13 shows the loading capacity of the 15-mg macroparticles of the present disclosure with curcumin (CCM), triamcinolone hexacetonide (TAH), triamcinolone acetonide (TAA), and paclitaxel (PTX).

[00207] FIG. 14 shows differential scanning calorimetry plots of macroparticles loaded with curcumin (CCM), triamcinolone hexacetonide (TAH), triamcinolone acetonide (TAA), and paclitaxel (PTX) and without drugs. FIG. 15 shows FTIR spectra of microparticles loaded with curcumin (CCM), triamcinolone hexacetonide (TAH), triamcinolone acetonide (TAA), and paclitaxel (PTX) and without drugs.

Example 9 – Formation of Microparticle Flakes

[00208] Crosslinked microparticles (15 mg) were loaded with 2.5 mg curcumin by overnight soaking in THF followed by the slow addition of 50 mL PBS containing 0.1% Tween. The microparticles were rinsed with THF to remove free curcumin and dried overnight.

[00209] It was observed that microparticles thus produced formed "flakes" that could not be re-suspended in THF or PBS buffer solution upon drying. Microscope images of the flakes are

shown in FIG. 16 after being dried overnight, and FIG. 17 shows a release profile of curcumin from microscopic flakes. The flakes could not be re-suspended in PBS buffer.

[00210] The release profile of curcumin of microparticle flakes produced by the method described above. The release profile is further quantified in Table 6, below.

Table 6 – Release Profile of Microparticle Flakes

	AUC	Conc (μg/mL)	Dilution	Final Conc (mg/mL)	Efficiency	% Loading
Initial Release	489.8	1.259093597	251.8187193	0.251818719	1.134190112	1.937067072
				Total (μg curcumin)	% retention in flakes	
Extraction After 48 H	2782	7.151487108	143.0297422	143.0297422	56.79869334	

[00211] As shown in Table 6 above, 51% of curcumin was released after 48 hours, and 57% was recovered in post-release extraction of the flakes.

[00212] In order to address the difficulties re-suspending the microparticle flakes, particles were dried with 25% PEG_{400} as a co-solvent. Particles dried in PEG, included those that had been loaded with curcumin, could be re-suspended in water with Tween or THF. FIGs. 18A and 18B show microscope images of microparticles of the invention after being dried with 25% PEG_{400} as a co-solvent. FIG. 19A shows a microscope image of microparticle flakes in water after drying with 2.5% PEG_{400} as a co-solvent. FIG. 19B shows a microscope image of microparticle flakes in THF after drying with 2.5% PEG_{400} as a co-solvent. FIG. 19C shows a microscope image of microparticle flakes in water after drying with 5% PEG_{400} as a co-solvent. FIG. 19D shows a microscope image of microparticle flakes in THF after drying with 5% PEG_{400} as a co-solvent. FIGs 18 and 19 demonstrate that as little as 2.5% PEG_{400} was capable of re-suspending microparticle flakes.

[00213] FIG. 9A shows a histogram and a optical microscope image of 25% PVL-co-PAVL microparticles after crosslinking. The average diameter was 6.8 μm ± 2.5 nm. FIG. 9B shows a histogram and OM image of the same microparticles after a DMSO washing step (average diameter 6.4 μm ± 1.8 nm) and FIG. 9C shows a histogram and OM image of the particles after an ethanol washing step (average diameter 8 μm ± 2.5nm). FIG. 9D shows a histogram and OM image of the particles after swelling in THF, after which the average diameter was 11.1 μm ± 4.5

nm. The results show that in some embodiments, suspending the particles in THF causes the particles to swell.

Example 10 – Aqueous drug solubility

[00214] Triamcinolone acetonide, triamcinolone hexacetonide, and paclitaxel were dissolved in water with varying concentrations of surfactants as co-solvents. Sodium dodecyl sulfate (SDS) is an anionic surfactant with a critical micelle concentration (CDC) of 8.2 mM. The hydrophobic lipophilic balance (HLB) is 40. Tween 80 is a non-ionic surfactant with a critical micelle concentration (CMC) of 0.012 mM, and a hydrophobic lipophilic balance (HLB) of 15.

[00215] FIG. 20 shows that certain drugs can by hydrophobic, and can require addition of surfactants (e.g. sodium dodecyl sulfate and Tween 80) to dissolve in water. FIG. 20A shows an aqueous solubility plot of triamcinolone acetonide in the presence of surfactants Tween 80 and SDS. FIG. 20B shows an aqueous solubility plot of triamcinolone hexacetonide in the presence of surfactants Tween 80 and SDS. FIG. 20C shows an aqueous solubility plot of paclitaxel in the presence of surfactants Tween 80 and SDS.

Example 11 – Preliminary Drug Release from Crosslinked Macroparticles

[00216] A crosslinked macroparticle weighing about 15 mg comprising PVL-co-PAVL (MW = 14760 g/mol, 13% AVL, 87% VL)was loaded with 2.5 mg paclitaxel by overnight soaking in THF followed by the slow addition of 50 mL PBS containing 0.1% Tween.

[00217] The macroparticles were suspended in PBS (0.1% Tween) and the release rate was observed. The macroparticles released 5% of the paclitaxel after 3 hours at room temperature and about 5% after 24 hours at room temperature. The loading capacity was found to be 1.7% w/w, and the loading efficiency was 30%.

[00218] A second cylinder (was loaded with curcumin and dissolved in THF. The amount of drug in the cylinder was 1.176 mg (9.64% capacity). A release profile is shown in FIG. 21. FIG. 21 shows that almost all of the curcumin is released after about eight days. Without wishing to be bound by theory, it is proposed that mechanical agitation (e.g., stirring with a stir bar) can affect the release parameters of particles of the present disclosure, causing faster release.

[00219] FIG. 22 shows a 20-day curcumin release profile from a 13-mg and 12-mg macroparticle.

[00220] Two cylinders (were loaded with triamcinolone hexacetonide and dissolved in THF. The amount of drug in the first cylinder (labelled with a circle) was 1.118 mg (9.12% capacity), and the amount of drug in the second cylinder (labelled with an "X") was 0.901 (11.651% capacity). A release profile of both cylinders is shown in FIG. 23. FIG. 23 shows that the release profile for both cylinders is very similar, and that about 60% of total drug is released after about 6 days.

[00221] FIG. 24 shows a 20-day triamcinolone hexacetonide release profile from a 13.3-mg and 9.2-mg macroparticle.

[00222] FIG. 25 shows a comparison of the release profiles of curcumin, triamcinolone hexacetonide (TAH), triamcinolone acetonide (TAA), and paclitaxel (PTX).

Example 12 – Photolithography of microparticles

[00223] Microparticles were fabricated with a silicon master template with 10 μm cylindrical pegs which serve as the inverse for a degradable gelatin template (i.e., the pegs can control the size of the wells. Wells on a gelatin template were filled with polymer solution, crosslinked, and harvested. The resulting particles had a homogenous size distribution. FIG. 26 shows an example micrograph of the photolithography template (G. Acharyo; Journal of Controlled Release 141; 2010; pp. 314-319).

Example 13 – Gelatin Hydrogel Template Method for Photolithography

Step 1 – Preparation of Template

[00224] 5 mL of warm 30% (w/v) gelatin solution was poured over a pegged silicon template. The solution and template were cooled in a refrigerator for five minutes. The template was peeled away from the gelatin mold to produce a gelatin mold with individual wells.

Step 2 – Preparation of Microparticles

[00225] 100 μL of 20% PAVL-PVL in dichloromethane was spread on the template along with 1,6-hexanedithiol and 20% DPMA (per allyl group). The template and polymer mixture was covered with a glass slide and irradiated with UV light (365 nm) for ten minutes over ice.

The glass slide was removed and the solvent was evaporated. The template was dissolved in water and the microparticles were collected by centrifugation.

[00226] FIG. 27A shows a gelatin template with pegs under a microscope. FIGs. 27B and 27C show microscope images of microparticles prepared by the above-method.

Example 14 – Stability and Characterization of Microparticles.

[00227] Particles of the present disclosure were evaluated using differential scanning calorimetry (DSC). The particles comprised PVL-co-PAVL (MW = 6700 g/mol, 19% AVL, 81%VL). FIG. 28 shows DSC plots of microparticles with different degrees of crosslinking. The DSC plots measured the enthalpy of melting ($\Delta°H_m$) of particles freeze dried for four days. FIG. 28A shows a DSC plot of a control microparticle with no crosslinking and shows relatively high crystallinity. FIG. 28B shows a DSC plot of a microparticle with 50% crosslinking. The DSC plot shows relatively low crystallinity. FIG. 28C shows a DSC plot of a microparticle with 100% crosslinking. The DSC plot shows even lower crystallinity than the 50% crosslinked particles.

[00228] Similarly, FIG. 29 shows DSC plots of microparticles with different degrees of crosslinking. The DSC plots measured the enthalpy of melting ($\Delta°H_m$) of particles freeze dried for four days. FIG. 29A shows a DSC plot of a control microparticle with no crosslinking (i.e., just the polymer backbone is analyzed). FIG. 29B shows a DSC plot of a microparticle with 50% crosslinking. The DSC plot shows low crystallinity. FIG. 29C shows a DSC plot with 100% crosslinking. The DSC plot shows low crystallinity. Without wishing to be bound by theory, the low crystallinity of the drug can help facilitate diffusion-mediated release.

[00229] The middle trace shows a trace of 10% PAVL microparticles. The number average molecular weight (Mn) was 12,000 and the weight average molecular weight (Mw) was 17,500. The polydispersity index (PDI) was 1.45. The particles were found to be semi-crystalline and the melting temperature was found to be between about 25-35 °C.

[00230] The top trace shows a trace of 8% PAVL microparticles. The number average molecular weight (Mn) was 32,700 and the weight average molecular weight (Mw) was 50,000. The polydispersity index (PDI) was 1.55. The particles were found to be an amorphous rubber.

Example 15 – Efficacy of Particles Against Tumors in Mice

[00231] Nude mice were implanted in hind limb with GL261 glioma cells and were treated with fluorescently labeled GIRLRG peptide and daily radiation of 3 Gy for 3 days. Mice were similarly treated with systemic taxol, taxol-loaded, control peptide particles, taxol-loaded targeted microparticles, and naked particles.

Example 16 – Preparation of Particles by Crosslinking with Tetrazine-*Trans*-Cyclooctene

[00232] Polyvalerolactone (PVL; 50 mg) and poly(*trans*-cyclooctene)valerolactone (P^tCOVL; 50 mg (6700 g/mol; 19% (*trans*-cyclooctene)valerolactone and 81% valerolactone)) and hexanedi-tetrazine (1 tetrazine group per *trans*-cyclooctene) are dissolved in 1 mL dichloromethane. The solution is added dropwise to 20 mL of water containing 5% polyvinyl alcohol. The mixture is homogenized with stirring (i.e., a Polytron ® mechanical homogenizer at 22,000 rpm) for five minutes. The homogenized mixture is stirred for about an additional 12-48 hours.

[00233] The mixture is then centrifuged at 4000 rpm at 10 °C for 10 minutes. The aqueous solution containing polyvinyl alcohol is poured off and the particles are rinsed with distilled water. The particles are then centrifuged and rinsed with water as above an additional three times.

Example 17 – Formation of Microparticles by Electrospray

[00234] Polyallylvalerolactone (PAVL; 100 mg (6700 g/mol; 19% allylvalerolactone and 81% valerolactone)) and hexanedithiol (1 –SH group per alkene) are dissolved in 1 mL dichloromethane. 2,2-Dimethoxy-2-phenylacetophenone (DMPA; 0.2 equivalents per alkene) is added and the solution is sprayed on to a 20 mL water bath containing 5% polyvinyl alcohol using an electrosprayer. The electrosprayed droplets and the homogenized mixture are irradiated at 365 nm – 4 mW under stirring for 30 minutes.

[00235] The mixture is stirred for 3 hours to allow the dichloromethane to evaporate. The mixture is then centrifuged at 4000 rpm at 10 °C for 10 minutes. The aqueous solution containing polyvinyl alcohol is poured off and the particles are rinsed with distilled water. The particles are then centrifuged and rinsed with water as above an additional three times.

[00236] The particles are then dispersed in DMSO and centrifuged at 4000 rpm at 20 °C for ten minutes. The DMSO is poured off and the process is repeated another two times.

Example 18 – Formation of Microparticles by Spray Drying

[00237] Polyallylvalerolactone (PAVL; 100 mg (6700 g/mol; 19% allylvalerolactone and 81% valerolactone)) and hexanedithiol (1 –SH group per alkene) are dissolved in 1 mL dichloromethane. 2,2-Dimethoxy-2-phenylacetophenone (DMPA; 0.2 equivalents per alkene) is added and the solution is sprayed on to a 20 mL water bath containing 5% polyvinyl alcohol using a spray dryer. The spray-dried droplets and the homogenized mixture are irradiated at 365 nm – 4 mW under stirring for 30 minutes.

[00238] The mixture is stirred for 3 hours to allow the dichloromethane to evaporate. The mixture is then centrifuged at 4000 rpm at 10 °C for 10 minutes. The aqueous solution containing polyvinyl alcohol is poured off and the particles are rinsed with distilled water. The particles are then centrifuged and rinsed with water as above an additional three times.

[00239] The particles are then dispersed in DMSO and centrifuged at 4000 rpm at 20 °C for ten minutes. The DMSO is poured off and the process is repeated another two times.

Equivalents

[00240] While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and other variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

Claims:

1. A crosslinked degradable particle, comprising:

a plurality of polyester backbones, wherein the plurality of polyester backbones are crosslinked via thioethers , triazoles, or amides; and

a drug dispersed within the crosslinked degradable particle.

2. The crosslinked particle of claim 1, wherein the polyester backbones are crosslinked via thioethers.

3. The crosslinked particle of claim 1, wherein the polyester backbones are crosslinked via triazoles.

4. The crosslinked particle of claim 1, wherein the polyester backbones are crosslinked via amides.

5. The crosslinked particle of claim 1, wherein the particle is biodegradable.

6. The crosslinked particle of claim 1, wherein the particle has a diameter between about 1 μm and about 100 μm.

7. The crosslinked particle of claim 6, wherein the particle has a diameter between about 5 μm and about 20 μm.

8. The crosslinked particle of claim 7, wherein the particle has a diameter between about 7 μm and about 15 μm.

9. The crosslinked particle of claim 8, wherein the particle has a diameter of about 10 μm.

10. The crosslinked particle of claim 1, wherein the drug is selected from the group consisting of triamcinolone, triamcinolone acetonide, triamcinolone hexacetonide, and paclitaxel.

11. The crosslinked particle of claim 1, wherein the drug is covalently bonded to the particle.

12. The crosslinked particle of claim 1, wherein the drug is contained within the particle by noncovalent interactions.

13. The crosslinked particle of claim 1, wherein the particle releases the drug over a period of at least one month in an aqueous environment.

14. The crosslinked particle of claim 1, wherein the particle degrades as it releases the drug.

15. The crosslinked particle of claim 1, wherein the polyester backbone comprises polyvalerolactone, polycaprolactone, polylactic acid, polyglycolic acid, or a combination thereof.

16. The crosslinked particle of claim 1, wherein the particle is a microparticle.

17. The crosslinked particle of claim 1, wherein the particle is a nanoparticle.

18. The crosslinked particle of claim 1, wherein the polyester backbone further comprises polyethylene glycol.

19. A crosslinked degradable particle, comprising:

a plurality of polymer backbones obtained from lactone monomer residues, wherein the plurality of polymer backbones are crosslinked via thioethers , triazoles, or amides; and

a drug dispersed within the crosslinked degradable particle, wherein the crosslinked degradable particle has a nominal diameter between 1 μm and 100 μm.

20. The crosslinked particle of claim 19, wherein the polyester backbones are crosslinked via thioethers.

21. The crosslinked particle of claim 19, wherein the polyester backbones are crosslinked via triazoles.

22. The crosslinked particle of claim 19, wherein the polyester backbones are crosslinked via amides.

23. The crosslinked particle of claim 19, wherein the particle is biodegradable.

24. The crosslinked particle of claim 19, wherein the particle has a diameter between about 5 μm and about 20 μm.

25. The crosslinked particle of claim 24, wherein the particle has a diameter between about 7 μm and about 15 μm.

26. The crosslinked particle of claim 25, wherein the particle has a diameter of about 10 μm.

27. The crosslinked particle of claim 19, wherein the drug is selected from the group consisting of triamcinolone, triamcinolone acetonide, triamcinolone hexacetonide, and paclitaxel.

28. The crosslinked particle of claim 19, wherein the drug is covalently bonded to the particle.

29. The crosslinked particle of claim 19, wherein the drug is contained within the particle by noncovalent interactions.

30. The crosslinked particle of claim 19, wherein the particle releases the drug over a period of at least one month in an aqueous environment.

31. The crosslinked particle of claim 19, wherein the particle degrades as it releases the drug.

32. The crosslinked particle of claim 19, wherein the polymer backbone is obtained from valerolactone, caprolactone, lactic acid, glycolic acid, or a combination thereof.

33. The crosslinked particle of claim 19, wherein the particle is a microparticle.

34. The crosslinked particle of claim 19, wherein the particle is a nanoparticle.

35. The crosslinked particle of claim 19, wherein the polymer backbones further comprise polyethylene glycol.

36. A crosslinked degradable particle, comprising:

a plurality of polymer backbones obtained from lactone monomer residues, wherein the plurality of polymer backbones are crosslinked via thioethers, triazoles, or amides; and

a drug dispersed within the crosslinked degradable particle, wherein the crosslinked degradable particle has a nominal diameter between 1 micron and 100 microns.

37. The crosslinked particle of claim 36, wherein the polymer backbones are crosslinked via thioethers.

38. The crosslinked particle of claim 36, wherein the polymer backbones are crosslinked via triazoles.

39. The crosslinked particle of claim 36, wherein the polymer backbones are crosslinked via amides.

40. The crosslinked particle of claim 36, wherein the particle is biodegradable.

41. The crosslinked particle of claim 40, wherein the particle has a diameter between about 5 μm and about 20 μm.

42. The crosslinked particle of claim 41, wherein the particle has a diameter between about 7 μm and about 15 μm.

43. The crosslinked particle of claim 42, wherein the particle has a diameter of about 10 μm.

44. The crosslinked particle of claim 36, wherein the drug is selected from the group consisting of triamcinolone, triamcinolone acetonide, triamcinolone hexacetonide, and paclitaxel.

45. The crosslinked particle of claim 36, wherein the drug is covalently bonded to the particle.

46. The crosslinked particle of claim 36, wherein the drug is contained within the particle by noncovalent interactions.

47. The crosslinked particle of claim 36, wherein the particle releases the drug over a period of at least one month in an aqueous environment.

48. The crosslinked particle of claim 36, wherein the particle degrades as it releases the drug.

49. The crosslinked particle of claim 36, wherein the lactone monomer is selected from the group consisting of lactic acid, glycolic acid, valerolactone, caprolactone, lactide, or a combination thereof.

50. The crosslinked particle of claim 49, wherein any of the valerolactone, caprolactone, lactic acid, lactide, or glycolic acid is functionalized with a functional group selected from an allyl group, a propargyl group, or a carboxylic acid group.

51. The crosslinked particle of claim 36, wherein the polymer backbone further comprises polyethylene glycol.

52. The crosslinked particle of claim 36, wherein the particle is a microparticle.

53. The crosslinked particle of claim 36, wherein the particle is a nanoparticle.

54. A method of preparing a crosslinked degradable particle, comprising:

combining a polyester containing a plurality of functional groups and a crosslinker to form a mixture; and

reacting the functional groups with crosslinkers to form a crosslinked degradable particle.

55. The method of claim 54, wherein the polyester and crosslinker are combined in a solvent to form the mixture.

56. The method of claim 54, further comprising emulsifying the mixture, wherein the polyester and the crosslinker are in the same phase.

57. The method of claim 54, further comprising evaporating at least part of the solvent after reacting the functional groups with the crosslinker.

58. The method of claim 54, wherein the functional group comprises an olefin group.

59. The method of claim 58, wherein the olefin group is an allyl group.

60. The method of claim 54, wherein the functional group comprises a propargyl group.

61. The method of claim 54, wherein the functional group comprises an epoxy group.

62. The method of claim 54, wherein the functional group comprises a carboxylic acid group.

63. The method of claim 54, wherein the crosslinker comprises a dithiol group.

64. The method of claim 63, wherein the dithiol group forms a thioether with an olefin functional group on the polyester backbone.

65. The method of claim 54, wherein the crosslinker comprises a diazide.

66. The method of claim 65, wherein the diazide forms a triazole with a propargyl functional group on the polyester backbone.

67. The method of claim 54, wherein the crosslinker comprises a diamine.

68. The method of claim 67, wherein the diamine forms a β-hydroxy amine with an epoxide functional group on the polyester backbone.

69. The method of claim 67, wherein the diamine forms an amide with a carboxylic acid functional group on the polyester backbone.

70. The method of claim 54, wherein the particle is biodegradable.

71. The method of claim 54, wherein the particle has a diameter between about 1 μm and about 100 μm.

72. The method of claim 71, wherein the particle has a diameter between about 5 μm and about 20 μm.

73. The method of claim 72, wherein the particle has a diameter between about 7 μm and about 15 μm.

74. The method of claim 73, wherein the particle has a diameter of about 10 μm.

75. The method of claim 54, wherein the particle further comprises a drug dispersed therein.

76. The method of claim 75, wherein the drug is selected from the group consisting of triamcinolone, triamcinolone acetonide, triamcinolone hexacetonide, and paclitaxel.

77. The method of claim 75, wherein the drug is covalently bonded to the particle.

78. The method of claim 75, wherein the drug is contained within the particle by noncovalent interactions.

79. The method of claim 75, wherein the particle degrades as it releases the drug.

80. The method of claim 54, wherein the polyester comprises polyvalerolactone, polycaprolactone, polylactic acid, polyglycolic acid, or a combination thereof.

81. The method of claim 54, wherein the polyester further comprises polyethylene glycol.

82. The method of claim 54, wherein the particle is a microparticle.

83. The method of claim 54, wherein the particle is a nanoparticle.

84. A method of preparing a crosslinked degradable particle, comprising:

dissolving a polyester containing a plurality of allyl groups, a dithiol, and a photoinitiator in at least one solvent to form a solution;

emulsifying the solution in an aqueous phase to form an emulsion;

irradiating the emulsion with UV light to react the dithiol with two of the allyl groups to form a crosslink; and

evaporating at least a portion of the solvent from the emulsion.

85. A method of preparing a crosslinked degradable particle, comprising:

dissolving a polyester containing a plurality of propargyl groups and a diazide in at least one solvent to form a solution;

emulsifying the solution in an aqueous phase to form an emulsion;

treating the emulsion to react the diazide with two of the propargyl groups to form a crosslink; and

evaporating at least a portion of the solvent from the emulsion .

86. The method of claim 82, wherein the step of treating the emulsion comprises heating the emulsion or adding a catalyst.

87. The method of claim 83, wherein the catalyst is a copper (I) salt.

88. A method of preparing a crosslinked degradable particle, comprising:

dissolving a polyester containing a plurality of epoxide groups and a diamine in at least one solvent to form a solution;

emulsifying the solution in an aqueous phase to form an emulsion;

allowing the diamine to react with the epoxide groups to form a crosslink; and

evaporating at least a portion of the solvent from the emulsion .

89. A method of preparing a crosslinked degradable particle, comprising:

dissolving a polyester containing a plurality of carboxylic acid groups and a diamine in at least one solvent to form a solution;

emulsifying the solution in an aqueous phase to form an emulsion;

treating the emulsion to react diamine to react with the carboxylic acid groups to form a crosslink; and

evaporating at least a portion of the solvent from the emulsion .

90. The method of claim 86, wherein the method of treating the emulsion comprises adding a catalyst.

91. The method of claim 87, wherein the catalyst is N,N'-Dicyclohexylcarbodiimide or diisopropylcarbodiimide.

92. A method of reducing aggregation of a plurality of crosslinked degradable particles, comprising attaching a plurality of polyethylene glycol chains to an exterior of the plurality of crosslinked degradable particles.

93. The method of claim 89, wherein the particles comprise polyester backbones.

94. The method of claim 90, wherein the polyester backbones comprise polyvalerolactone, polycaprolactone, polylactic acid, polyglycolic acid, or a combination thereof.

95. The method of claim 90, wherein the polyester backbones are crosslinked by thioethers.

96. The method of claim 90, wherein the polyester backbones are crosslinked by triazoles.

97. The method of claim 90, wherein the polyester backbones are crosslinked by amides.

98. The method of claim 89, wherein the particle is biodegradable.

99. The method of claim 89, wherein the particles have a diameter between about 1 μm and about 100 μm.

100. The method of claim 96, wherein the particle has a diameter between about 5 μm and about 20 μm.

101. The method of claim 97, wherein the particle has a diameter between about 7 μm and about 15 μm.

102. The method of claim 98, wherein the particle has a diameter of about 10 μm.

103. The method of claim 89, wherein the crosslinked particles further comprise a drug.

104. The method of claim 100, wherein the drug is selected from the group consisting of triamcinolone, triamcinolone acetonide, triamcinolone hexacetonide, and paclitaxel.

105. The method of claim 100, wherein the drug is covalently bonded to the particle.

106. The method of claim 100, wherein the drug is contained within the particle by noncovalent interactions.

107. The method of claim 100, wherein the particle releases the drug over a period of at least one month in an aqueous environment.

108. The method of claim 89, wherein the particle degrades as it releases the drug.

109. The method of claim 89, wherein the particle is a microparticle.

110. The method of claim 89, wherein the particle is a nanoparticle.

111. A method of dispersing a drug within a crosslinked degradable particle, comprising: swelling the crosslinked degradable particle with a solvent to form a swollen crosslinked degradable particle, wherein the solvent further comprises a drug dispersed therein; and

removing the crosslinked degradable particles from the solvent.

112. The method of claim 111, wherein the polymer backbones are crosslinked via thioethers.

113. The method of claim 111, wherein the polymer backbones are crosslinked via triazoles.

114. The method of claim 111, wherein the polymer backbones are crosslinked via amides.

115. The method of claim 111, wherein the particle is biodegradable.

116. The method of claim 111, wherein the particle has a diameter between about 1 μm and about 100 μm.

117. The method of claim 116, wherein the particle has a diameter between about 5 μm and about 20 μm.

118. The method of claim 117, wherein the particle has a diameter between about 7 μm and about 15 μm.

119. The method of claim 118, wherein the particle has a diameter of about 10 μm.

120. The method of claim 111, wherein the drug is selected from the group consisting of triamcinolone, triamcinolone acetonide, triamcinolone hexacetonide, and paclitaxel.

121. The method of claim 111, wherein the drug is contained within the particle by noncovalent interactions.

122. The method of claim 111, wherein the particle releases the drug over a period of at least one month in an aqueous environment.

123. The method of claim 122, wherein the particle degrades as it releases the drug.

124. The method of claim 111, wherein the polyester backbone comprises polyvalerolactone, polycaprolactone, polylactic acid, polyglycolic acid, or a combination thereof.

125. The method of claim 111, wherein any of the polyvalerolactone, polycaprolactone, polylactic acid, or polyglycolic acid is functionalized with a functional group selected from an allyl group, a propargyl group, or a carboxylic acid group.

126. The method of claim 111, wherein the polyester backbone further comprises polyethylene glycol.

127. The method of claim 111, wherein the solvent further comprises a surfactant.

128. The method of claim 111, wherein the particle is a microparticle.

129. The method of claim 111, wherein the particle is a nanoparticle.

130. A method of preparing a crosslinked degradable implant, comprising:

dissolving a polyester containing a plurality of functional groups and a crosslinker in at least one solvent to form a solution;

treating the solution to react the crosslinker with two of the functional groups to form a crosslink;

wherein the crosslinked degradable implant has a diameter of at least about 1 millimeter.

131. The method of claim 130, wherein the polyester comprises polyvalerolactone, polycaprolactone, polylactic acid, polyglycolic acid, or a combination thereof.

132. The method of claim 130, wherein the functional group comprises an olefin group.

133. The method of claim 132, wherein the olefin group is an allyl group.

134. The method of claim 130, wherein the functional group comprises a propargyl group.

135. The method of claim 130, wherein the functional group comprises an epoxy group.

136. The method of claim 130, wherein the functional group comprises a carboxylic acid group.

137. The method of claim 130, wherein the crosslinker comprises a dithiol group.

138. The method of claim 137, wherein the dithiol group forms a thioether with an olefin functional group on the polyester backbone.

139. The method of claim 130, wherein the solution further comprises an initiator.

140. The method of claim 139, wherein the initiator is a photoinitiator.

141. The method of claim 140, wherein treating the solution comprises irradiating the photoinitiator with ultraviolet light.

142. The method of claim 127, wherein the crosslinker comprises a diazide.

143. The method of claim 136, wherein the diazide forms a triazole with a propargyl functional group on the polyester backbone.

144. The method of claim 130, wherein treating the solution comprises adding a cyclization catalyst.

145. The method of claim 144, wherein the catalyst is a copper salt.

146. The method of claim 130, wherein the crosslinker comprises a diamine.

147. The method of claim 146, wherein the diamine forms a β-hydroxy amine with an epoxide functional group on the polyester backbone.

148. The method of claim 146, wherein the diamine forms an amide with a carboxylic acid functional group on the polyester backbone.

149. The method of claim 130 wherein treating the solution comprises adding an amide coupling catalyst to the solution.

150. The method of claim 149, wherein the amide coupling catalyst is dicyclohexylcarbodiimide or diisopropylcarbodiimide.

151. The method of claim 130, wherein the implant is biodegradable.

152. The method of claim 130, wherein the implant further comprises a drug dispersed therein.

153. The method of claim 130, wherein the drug is selected from the group consisting of triamcinolone, triamcinolone acetonide, triamcinolone hexacetonide, and paclitaxel.

154. The method of claim 130, wherein the drug is covalently bonded to the implant.

155. The method of claim 130, wherein the drug is contained within the implant by noncovalent interactions.

156. The method of claim 142, wherein the implant releases the drug over a period of at least one month in an aqueous environment.

157. The method of claim 156, wherein the implant degrades as it releases the drug.

158. The method of claim 130, wherein the polyester backbone comprises polyvalerolactone, polycaprolactone, polylactic acid, polyglycolic acid, or a combination thereof.

159. The method of claim 130, wherein the polyester backbone further comprises polyethylene glycol.

160. A method of controlling an average size of a distribution of crosslinked degradable particles, comprising:

preparing a plurality of molds of uniform size and shape;

combining a polyester containing a plurality of functional groups and a crosslinker to form a mixture;

dispersing the mixture within the molds; and

treating the mixture to react the crosslinker with two of the functional groups to form a crosslink.

161. The method of claim 160, wherein the polyester comprises polyvalerolactone, polycaprolactone, polylactic acid, polyglycolic acid, or a combination thereof.

162. The method of claim 160, wherein the functional group comprises an olefin group.

163. The method of claim 152, wherein the olefin group is an allyl group.

164. The method of claim 160, wherein the functional group comprises a propargyl group.

165. The method of claim 160, wherein the functional group comprises an epoxy group.

166. The method of claim 160, wherein the functional group comprises a carboxylic acid group.

167. The method of claim 160, wherein the crosslinker comprises a dithiol group.

168. The method of claim 167, wherein the dithiol group forms a thioether with an olefin functional group on the polyester backbone.

169. The method of claim 160, wherein the crosslinker comprises a diazide.

170. The method of claim 169, wherein the diazide forms a triazole with a propargyl functional group on the polyester backbone.

171. The method of claim 160, wherein the crosslinker comprises a diamine.

172. The method of claim 171 wherein the diamine forms a β-hydroxy amine with an epoxide functional group on the polyester backbone.

173. The method of claim 171, wherein the diamine forms an amide with a carboxylic acid functional group on the polyester backbone.

174. The method of claim 160, wherein the particle is biodegradable.

175. The method of claim 160, wherein the particle has a diameter between about 1 μm and about 100 μm.

176. The method of claim 175, wherein the particle has a diameter between about 5 μm and about 20 μm.

177. The method of claim 176, wherein the particle has a diameter between about 7 μm and about 15 μm.

178. The method of claim 177, wherein the particle has a diameter of about 10 μm.

179. The method of claim 160, wherein the particle further comprises a drug dispersed therein.

180. The method of claim 179, wherein the drug is selected from the group consisting of triamcinolone, triamcinolone acetonide, triamcinolone hexacetonide, and paclitaxel.

181. The method of claim 179, wherein the drug is covalently bonded to the particle.

182. The method of claim 179, wherein the drug is contained within the particle by noncovalent interactions.

183. The method of claim 179, wherein the particle releases the drug over a period of at least one month in an aqueous environment.

184. The method of claim 179, wherein the particle degrades as it releases the drug.

185. The method of claim 160, wherein the polyester backbone further comprises polyethylene glycol.

186. The method of claim 160, wherein the particle is a microparticle.

187. The method of claim 160, wherein the particle is a nanoparticle.

188. A method of controlling an average size of a distribution of crosslinked degradable particles, comprising:

combining a polyester containing a plurality of functional groups and a crosslinker in at least one nonaqueous solvent to form an emulsion wherein the nonaqueous solvent comprises droplets of uniform size,

wherein the polyester and crosslinker, are dissolved in the nonaqueous solvent droplets; and

treating the emulsion to react the crosslinker with two of the functional groups to form a crosslink, wherein the particles are crosslinked while dissolved in the nonaqueous solvent.

189. The method of claim 188, wherein the polyester comprises polyvalerolactone, polycaprolactone, polylactic acid, polyglycolic acid, or a combination thereof.

190. The method of claim 188, wherein the functional group comprises an olefin group.

191. The method of claim 190, wherein the olefin group is an allyl group.

192. The method of claim 188, wherein the functional group comprises a propargyl group.

193. The method of claim 188, wherein the functional group comprises an epoxy group.

194. The method of claim 188, wherein the functional group comprises a carboxylic acid group.

195. The method of claim 188, wherein the crosslinker comprises a dithiol group.

196. The method of claim 188, wherein the dithiol group forms a thioether with an olefin functional group on the polyester backbone.

197. The method of claim 188, wherein the solution further comprises an initiator.

198. The method of claim 197, wherein the initiator is a photoinitiator.

199. The method of claim 198, wherein treating the solution comprises irradiating the photoinitiator with ultraviolet light.

200. The method of claim 188, wherein the crosslinker comprises a diazide.

201. The method of claim 200 wherein the diazide forms a triazole with a propargyl functional group on the polyester backbone.

202. The method of claim 201, wherein treating the solution comprises adding a cyclization catalyst.

203. The method of claim 202, wherein the catalyst is a copper salt.

204. The method of claim 188, wherein the crosslinker comprises a diamine.

205. The method of claim 203 wherein the diamine forms a β-hydroxy amine with an epoxide functional group on the polyester backbone.

206. The method of claim 204, wherein the diamine forms an amide with a carboxylic acid functional group on the polyester backbone.

207. The method of claim 206, wherein treating the solution comprises adding an amide coupling catalyst to the solution.

208. The method of claim 207, wherein the amide coupling catalyst is dicyclohexylcarbodiimide or diisopropylcarbodiimide.

209. The method of claim 188, wherein the particle is biodegradable.

210. The method of claim 188, wherein the particle has a diameter between about 1 μm and about 100 μm.

211. The method of claim 210 wherein the particle has a diameter between about 5 μm and about 20 μm.211161, wherein the particle has a diameter between about 7 μm and about 15 μm.

212. The method of claim 212 wherein the particle has a diameter of about 10 μm.

213. The method of claim 188, wherein the particle further comprises a drug dispersed therein.

214. The method of claim 213, wherein the drug is selected from the group consisting of triamcinolone, triamcinolone acetonide, triamcinolone hexacetonide, and paclitaxel.

215. The method of claim 213, wherein the drug is covalently bonded to the particle.

216. The method of claim 213, wherein the drug is contained within the particle by noncovalent interactions.

217. The method of claim 213, wherein the particle releases the drug over a period of at least one month in an aqueous environment.

218. The method of claim 213, wherein the particle degrades as it releases the drug.

219. The method of claim 188, wherein the polyester backbone further comprises polyethylene glycol.

220. A method of treating a disease, comprising:

administering to a subject in need thereof a therapeutically effective amount of the crosslinked degradable particle of claim 1 containing the drug.

221. A crosslinked degradable particle, formed by:

forming a polyester containing a plurality of functional groups and a crosslinker to form a mixture; and

reacting the functional groups with crosslinkers to form a crosslinked degradable particle.

222. The particle of claim 221, wherein the polyester is formed from monomers selected from lactic acid residues, glycolic acid residues, valerolactone residues, caprolactone residues, lactide residues, or a combination thereof.

223. The crosslinked particle of claim 221, wherein the functional group comprises an olefin group.

224. The crosslinked particle of claim 223, wherein the olefin group is an allyl group.

225. The crosslinked particle of claim 221, wherein the functional group comprises a propargyl group.

226. The crosslinked particle of claim 221, wherein the functional group comprises an epoxy group.

227. The crosslinked particle of claim 221, wherein the functional group comprises a carboxylic acid group.

228. The crosslinked particle of claim 221, wherein the crosslinker comprises a dithiol group.

229. The crosslinked particle of claim 228, wherein the dithiol group forms a thioether with an olefin functional group on the polyester backbone.

230. The crosslinked particle of claim 229, wherein the thioether is formed by a radical reaction.

231. The crosslinked particle of claim 230, wherein the radical reaction is initiated by a photoinitiator and treatment with ultraviolet light.

232. The crosslinked particle of claim 221, wherein the crosslinker comprises a diazide.

233. The crosslinked particle of claim 232, wherein the diazide forms a triazole with a propargyl functional group on the polyester backbone.

234. The crosslinked particle of claim 233, wherein the triazole is formed in the presence of a copper (I) catalyst.

235. The crosslinked particle of claim 221, wherein the crosslinker comprises a diamine.

236. The crosslinked particle of claim 235, wherein the diamine forms a β-hydroxy amine with an epoxide functional group on the polyester backbone.

237. The crosslinked particle of claim 235, wherein the diamine forms an amide with a carboxylic acid functional group on the polyester backbone.

238. The crosslinked particle of claim 237, wherein the amide is formed in the presence of an amide coupling catalyst.

239. The crosslinked particle of claim 238, wherein the amide coupling catalyst is selected from dicyclohexylcarbodiimide or diisopropylcarbodiimide

240. The crosslinked particle of claim 221, wherein the particle is biodegradable.

241. The crosslinked particle of claim 221, wherein the particle has a diameter between about 1 μm and about 100 μm.

242. The crosslinked particle of claim 241, wherein the particle has a diameter between about 5 μm and about 20 μm.

243. The crosslinked particle of claim 242, wherein the particle has a diameter between about 7 μm and about 15 μm.

244. The crosslinked particle of claim 243, wherein the particle has a diameter of about 10 μm.

245. The crosslinked particle of claim 221, wherein the particle further comprises a drug dispersed therein.

246. The crosslinked particle of claim 245, wherein the drug is selected from the group consisting of triamcinolone, triamcinolone acetonide, triamcinolone hexacetonide, and paclitaxel.

247. The crosslinked particle of claim 245, wherein the drug is covalently bonded to the particle.

248. The crosslinked particle of claim 245, wherein the drug is contained within the particle by noncovalent interactions.

249. The crosslinked particle of claim 245, wherein the particle degrades as it releases the drug.

250. The crosslinked particle of claim 221, wherein the polyester comprises polyvalerolactone, polycaprolactone, polylactic acid, polyglycolic acid, or a combination thereof.

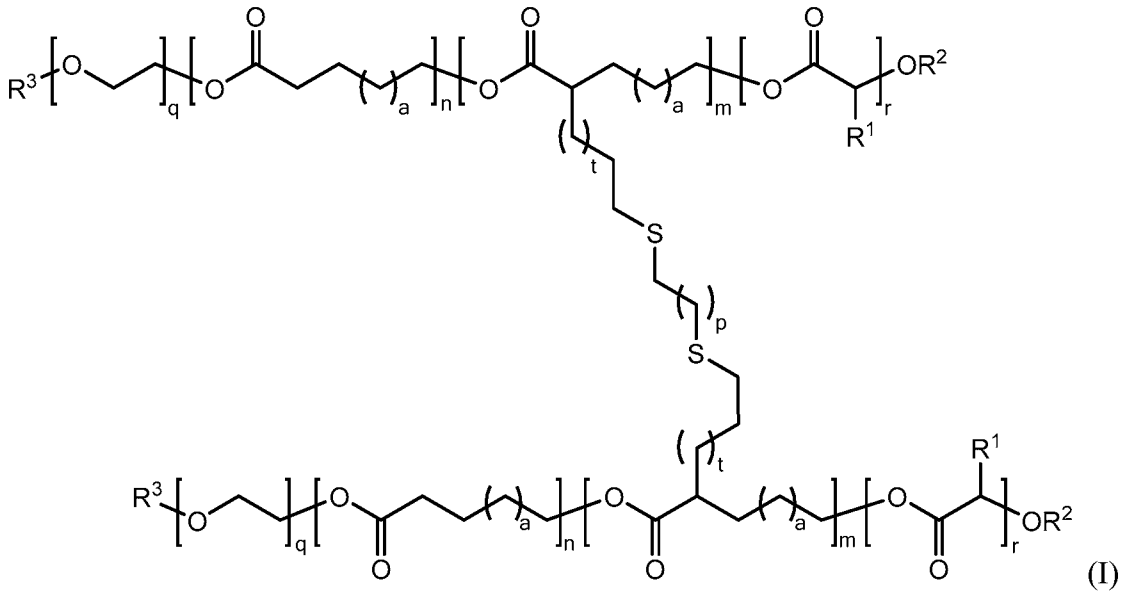
251. The crosslinked particle of claim 221, wherein the polyester further comprises polyethylene glycol.

252. The crosslinked particle of claim 221, wherein the particle is a microparticle.

253. The crosslinked particle of claim 221, wherein the particle is a nanoparticle.

254. A crosslinked degradable particle, comprising:

a polyester backbone of the Formula I:



(I)

wherein:

R^1 is independently, at each occurrence, –H, or $–C_1$-C_6 alkyl;

R^2 is independently, at each occurrence, –H, or $–C_1$-C_6 alkyl;

R^3 is independently, at each occurrence, –H, or $–C_1$-C_6 alkyl;

a is 0, 1, or 2;

m is independently, at each occurrence, an integer between 1 and 100, inclusive;

n is independently, at each occurrence, an integer between 1 and 100, inclusive;

p is independently, at each occurrence, an integer between 0 and 5, inclusive;

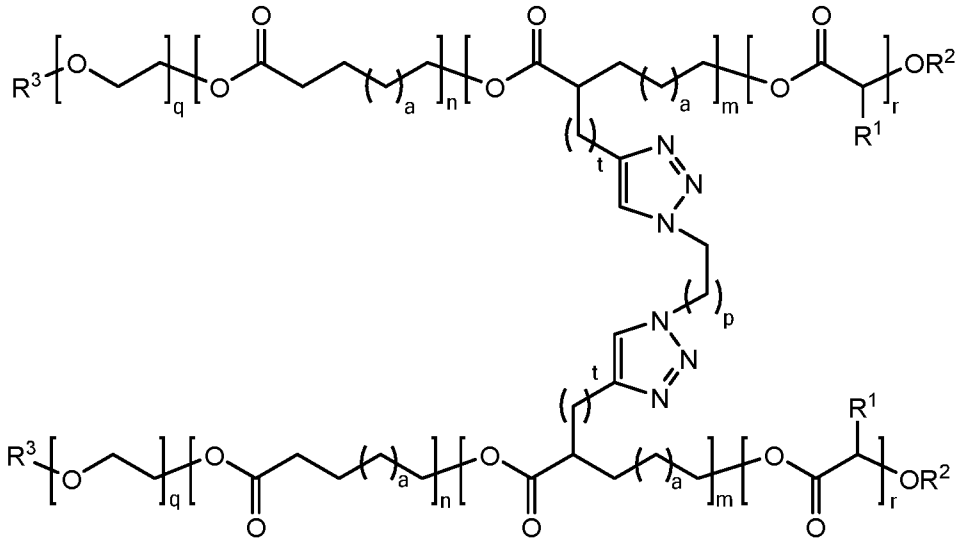
q is independently, at each occurrence, an integer between 0 and 100, inclusive;

r is independently, at each occurrence, an integer between 0 and 100, inclusive; and

t is independently, at each occurrence, an integer between 0 and 5, inclusive.

255. A crosslinked degradable particle, comprising:

a polyester backbone of the Formula II:



(II)

wherein:

R^1 is independently, at each occurrence, –H, or $–C_1$-C_6 alkyl;

R^2 is independently, at each occurrence, –H, or $–C_1$-C_6 alkyl;

R^3 is independently, at each occurrence, –H, or $–C_1$-C_6 alkyl;

a is 0, 1, or 2;

m is independently, at each occurrence, an integer between 1 and 100, inclusive;

n is independently, at each occurrence, an integer between 1 and 100, inclusive;

p is independently, at each occurrence, an integer between 0 and 5, inclusive;

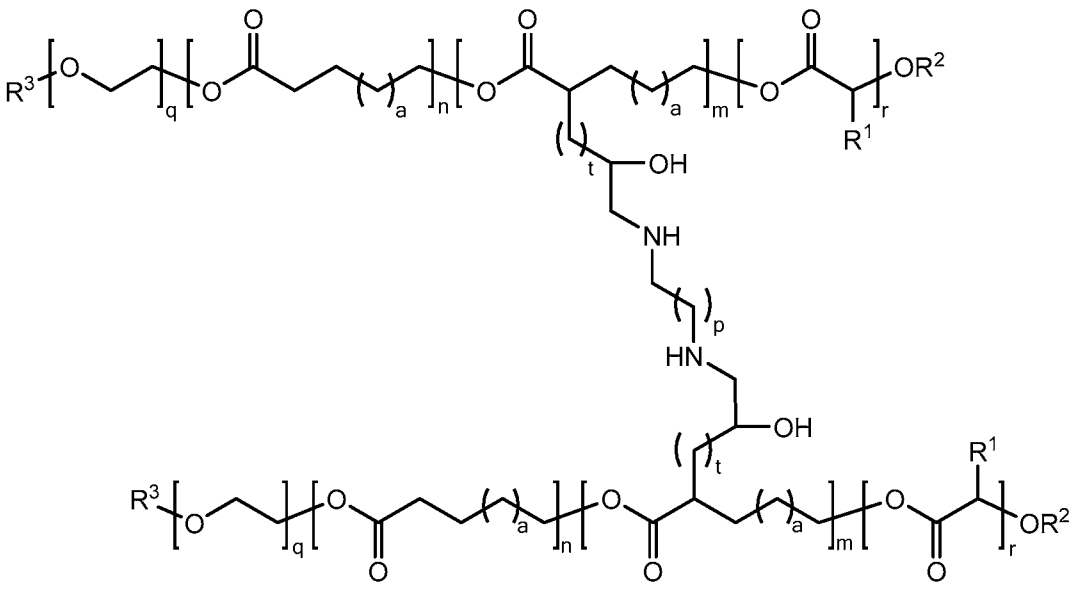
q is independently, at each occurrence, an integer between 0 and 100, inclusive;

r is independently, at each occurrence, an integer between 0 and 100, inclusive; and

t is independently, at each occurrence, an integer between 0 and 5, inclusive.

256. A crosslinked degradable particle, comprising:

a polyester backbone of the Formula III:



(III)

wherein:

R^1 is independently, at each occurrence, –H, or $–C_1$-C_6 alkyl;

R^2 is independently, at each occurrence, –H, or $–C_1$-C_6 alkyl;

R^3 is independently, at each occurrence, –H, or $–C_1$-C_6 alkyl;

a is 0, 1, or 2;

m is independently, at each occurrence, an integer between 1 and 100, inclusive;

n is independently, at each occurrence, an integer between 1 and 100, inclusive;

p is independently, at each occurrence, an integer between 0 and 5, inclusive;

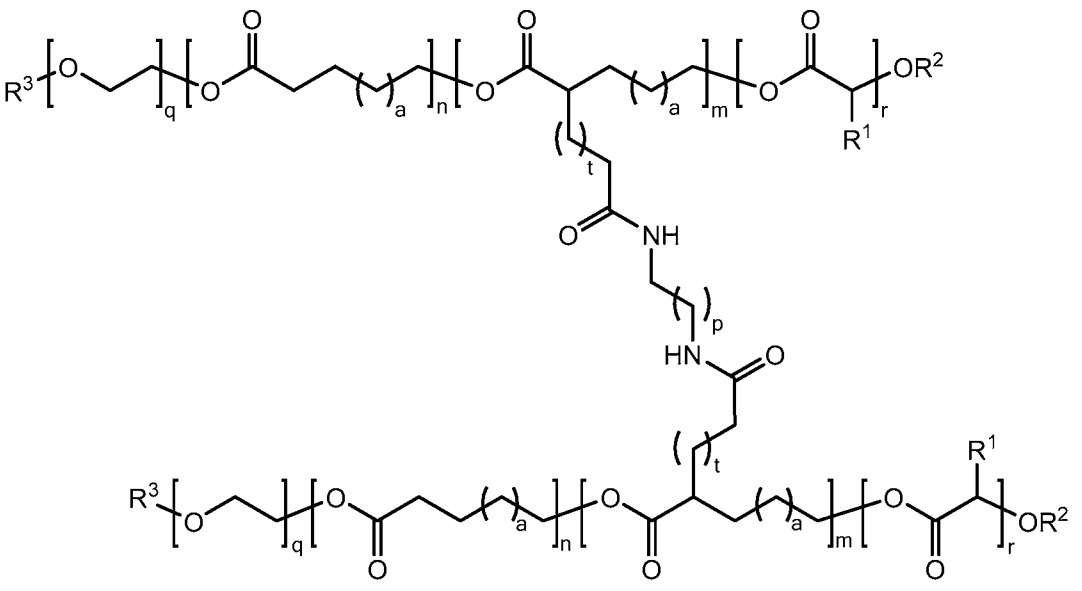
q is independently, at each occurrence, an integer between 0 and 100, inclusive;

r is independently, at each occurrence, an integer between 0 and 100, inclusive; and

t is independently, at each occurrence, an integer between 0 and 5, inclusive.

257. A crosslinked degradable particle, comprising:

a polyester backbone of the Formula IV:



(IV)

wherein:

R^1 is independently, at each occurrence, –H, or $–C_1$-C_6 alkyl;

R^2 is independently, at each occurrence, –H, or $–C_1$-C_6 alkyl;

R^3 is independently, at each occurrence, –H, or $–C_1$-C_6 alkyl;

a is 0, 1, or 2;

m is independently, at each occurrence, an integer between 1 and 100, inclusive;

n is independently, at each occurrence, an integer between 1 and 100, inclusive;

p is independently, at each occurrence, an integer between 0 and 5, inclusive;

q is independently, at each occurrence, an integer between 0 and 100, inclusive;

r is independently, at each occurrence, an integer between 0 and 100, inclusive; and

t is independently, at each occurrence, an integer between 0 and 5, inclusive.

FIG. 1A

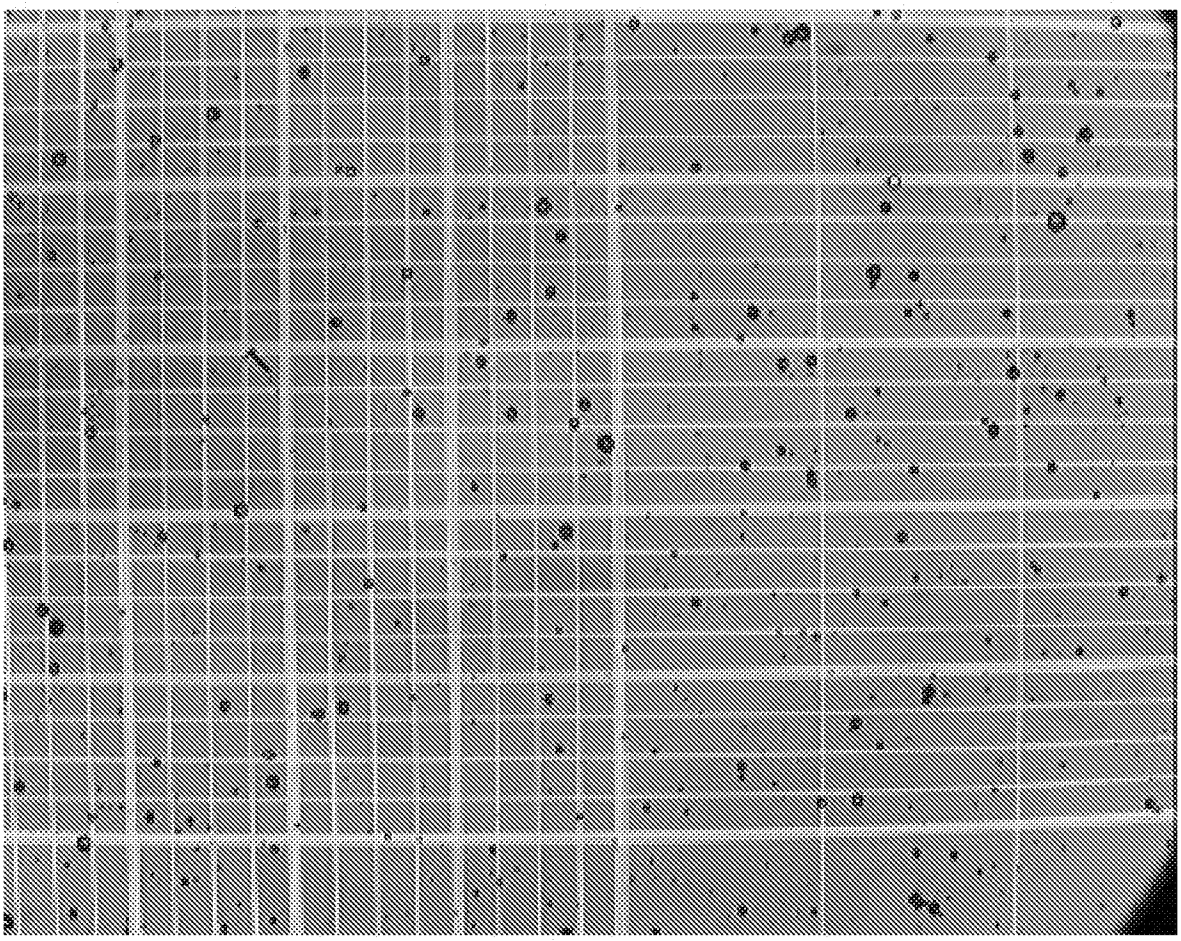


FIG. 1B

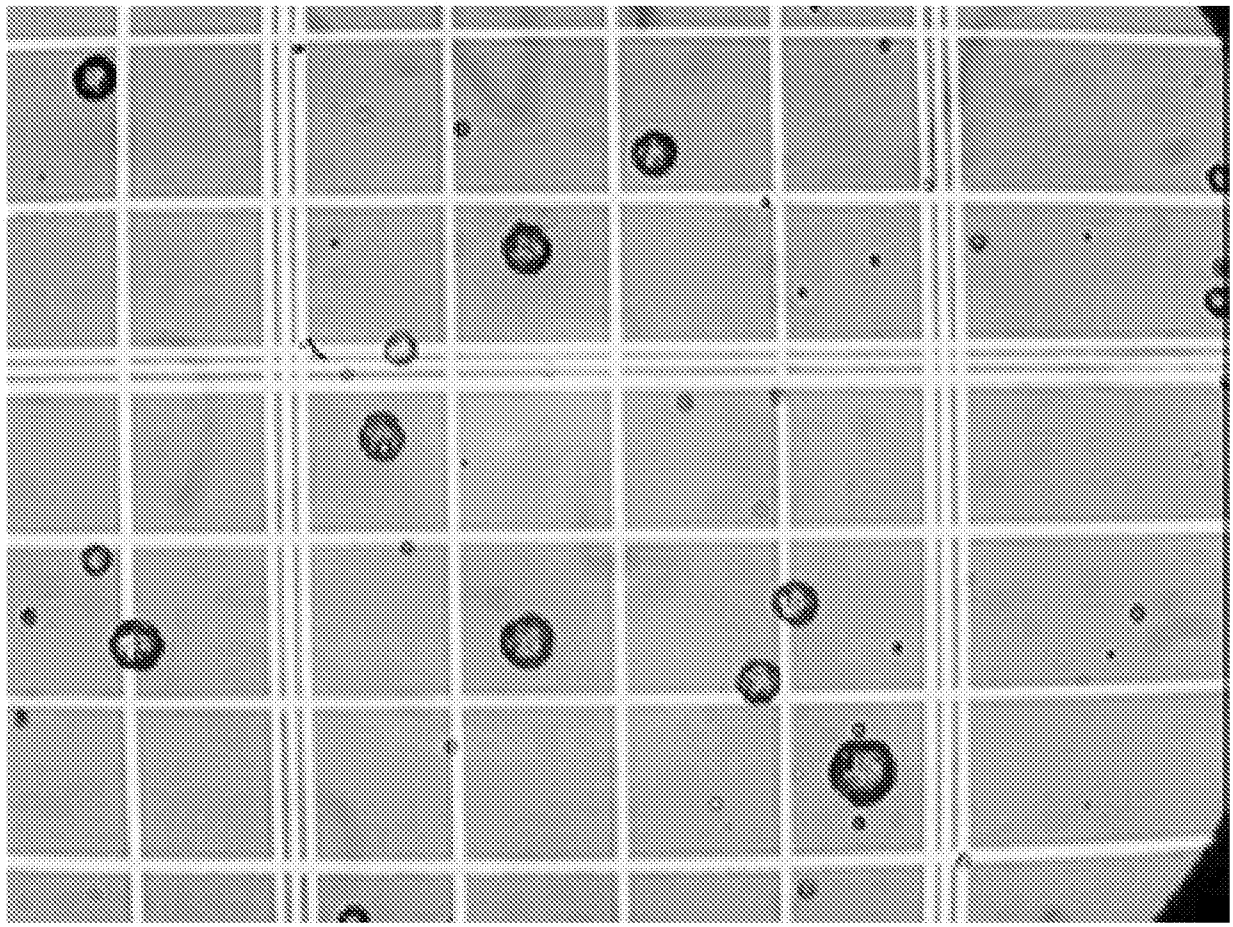


FIG. 1C

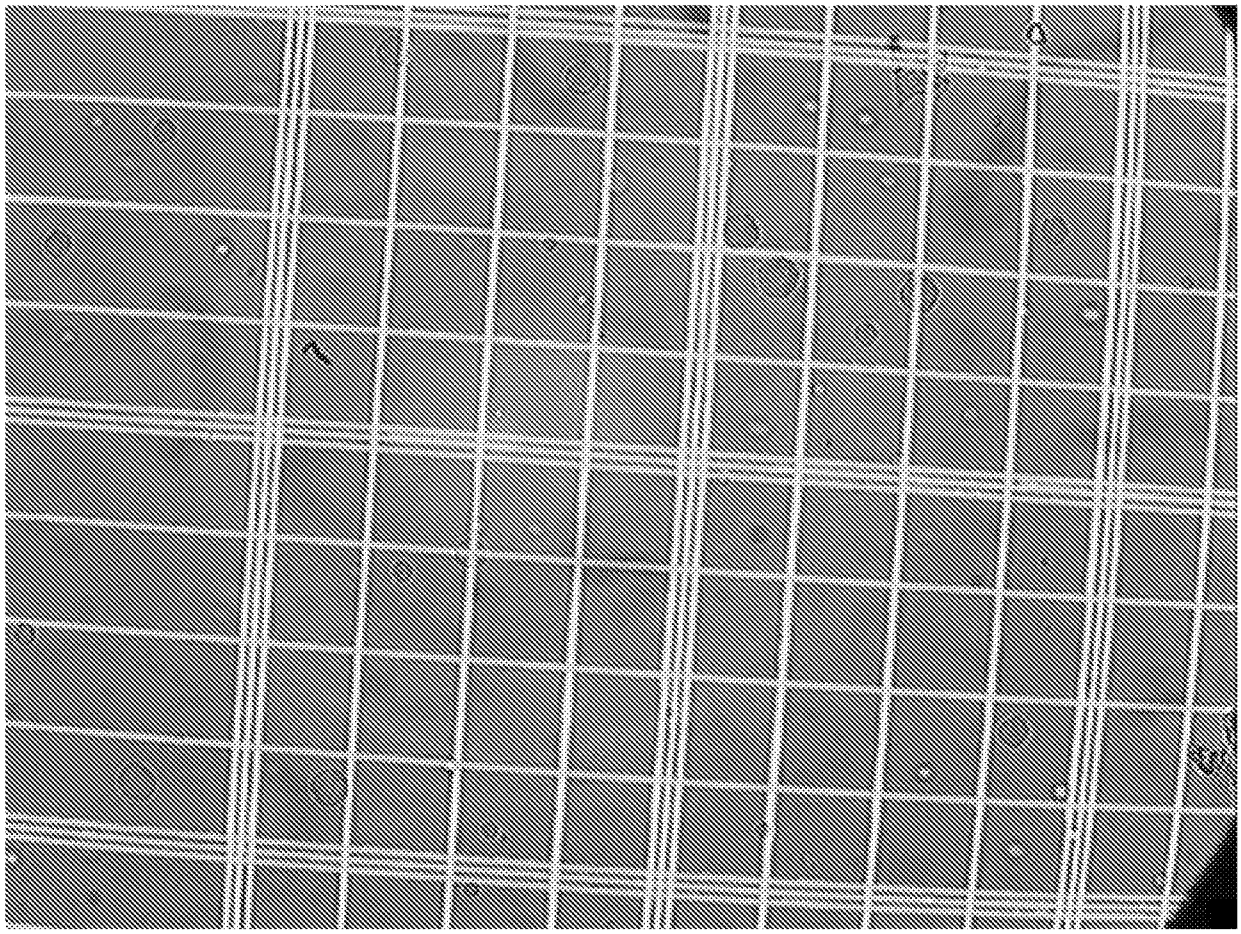


FIG. 1D

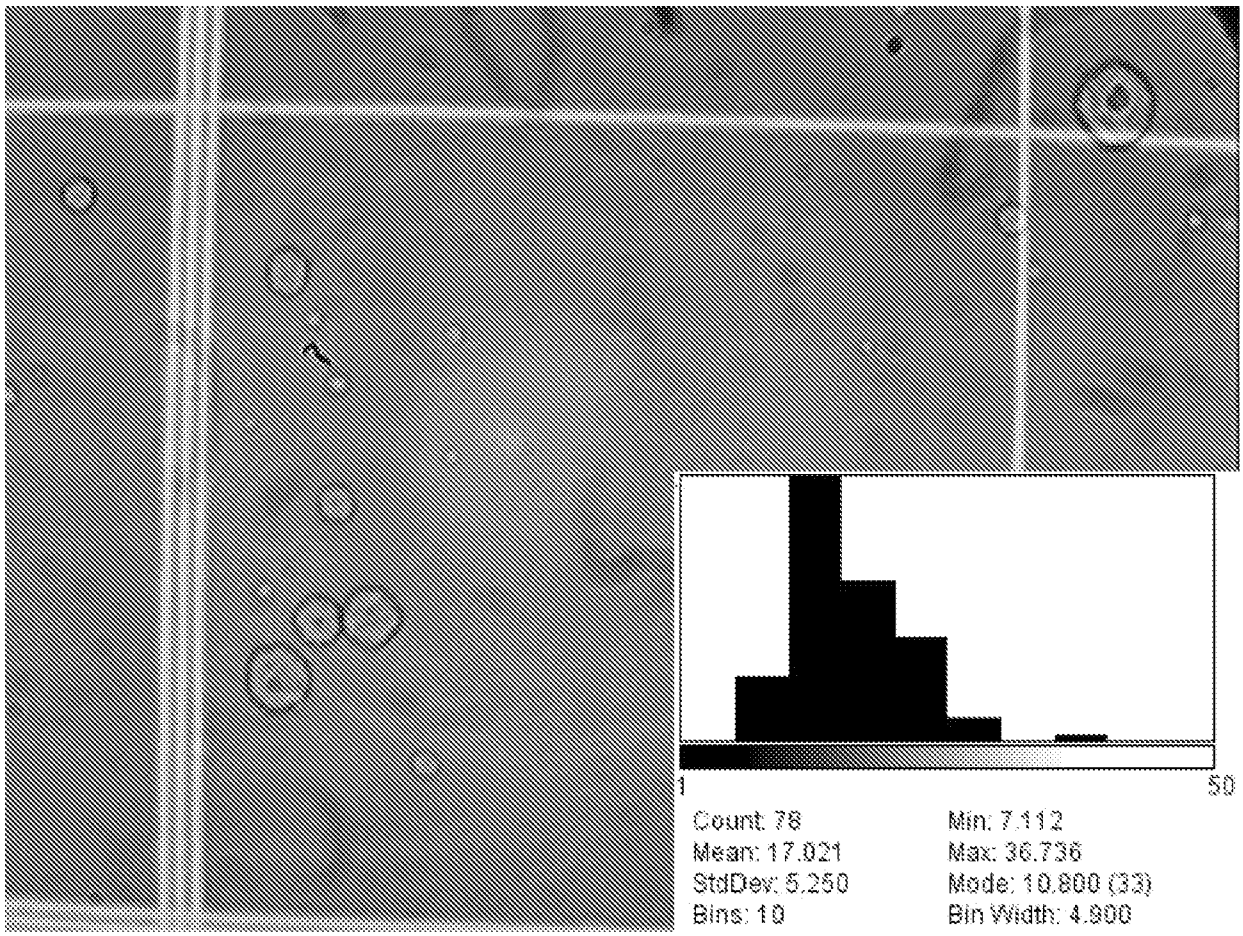

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Max: 36.736
Mode: 10.800 (33)
Bin Width: 4.900

FIG. 2A

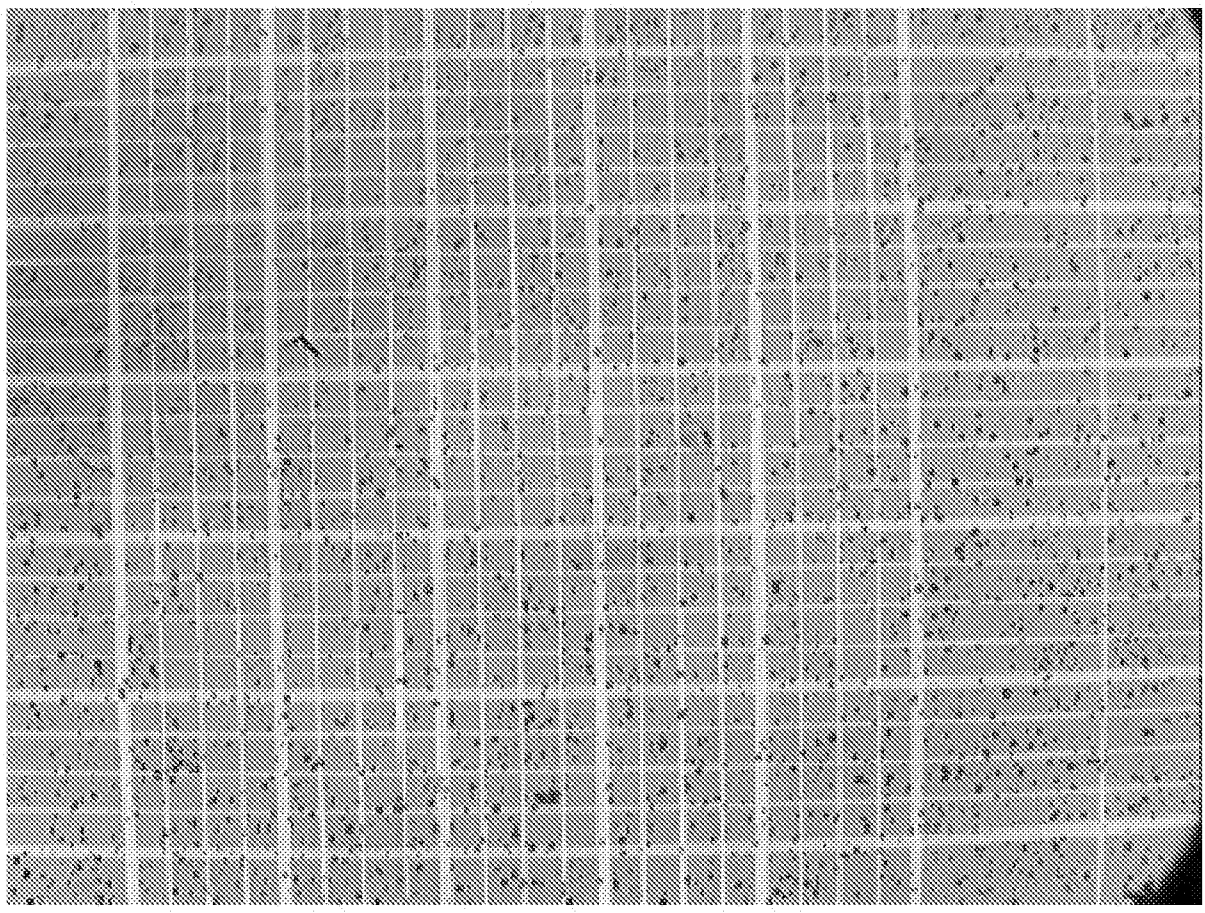


FIG. 2B

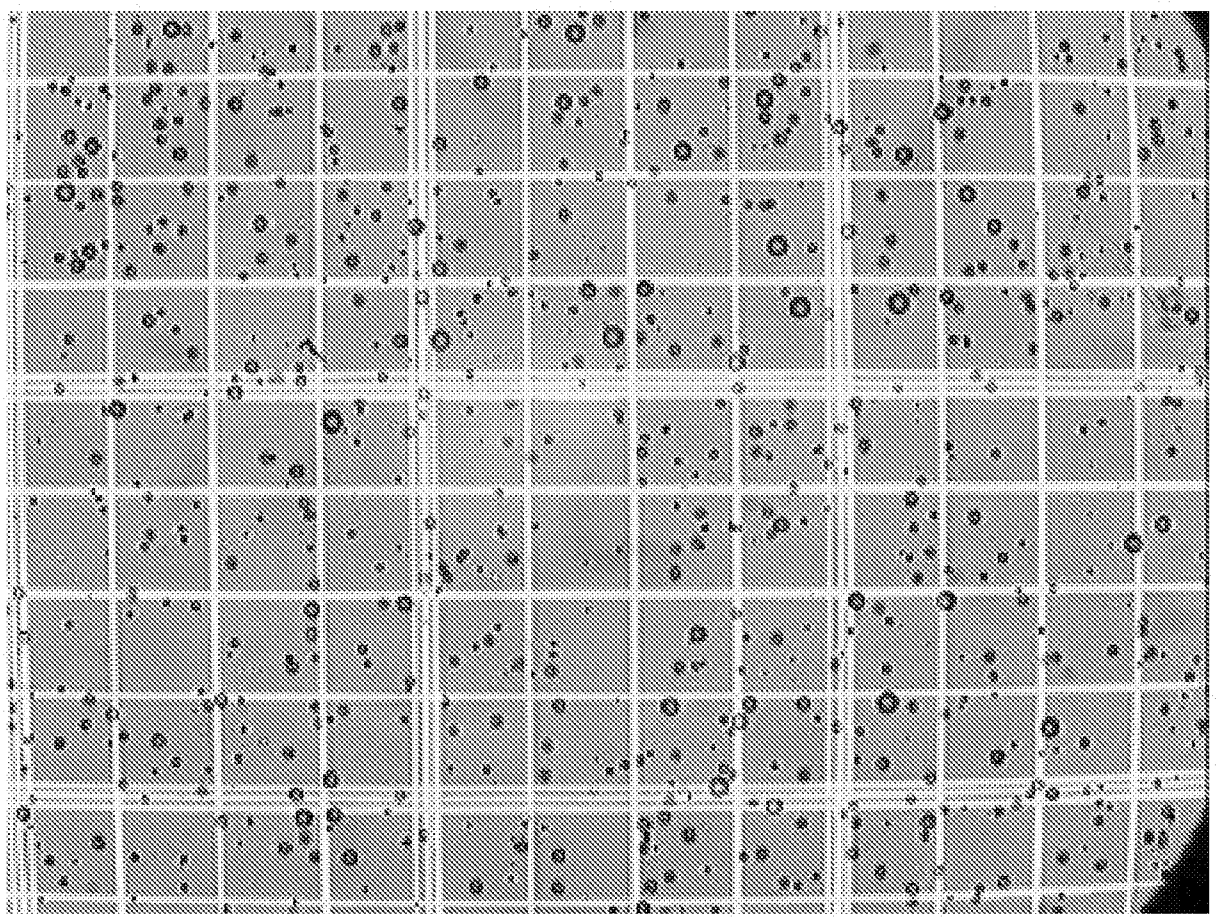


FIG. 2C

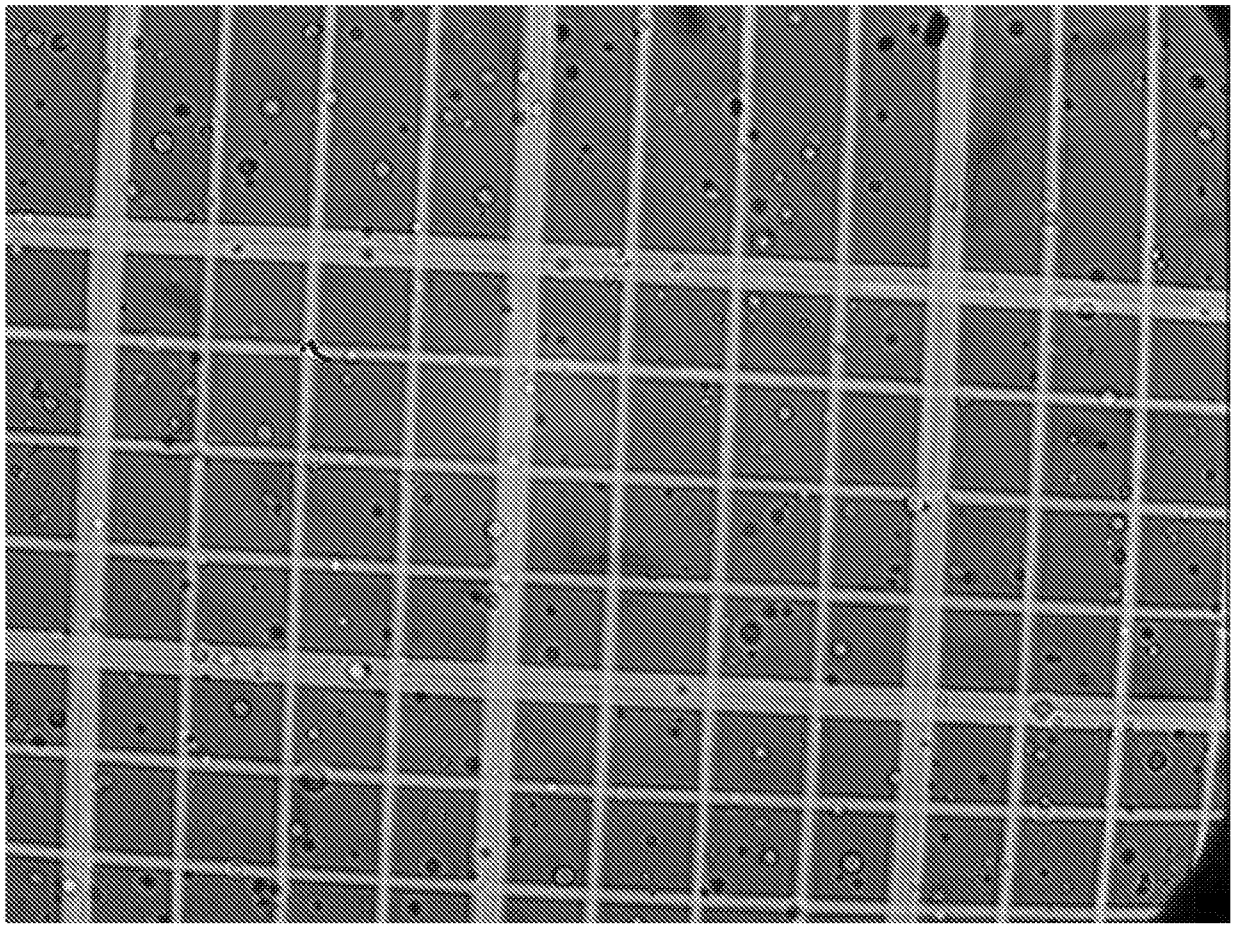


FIG. 2D

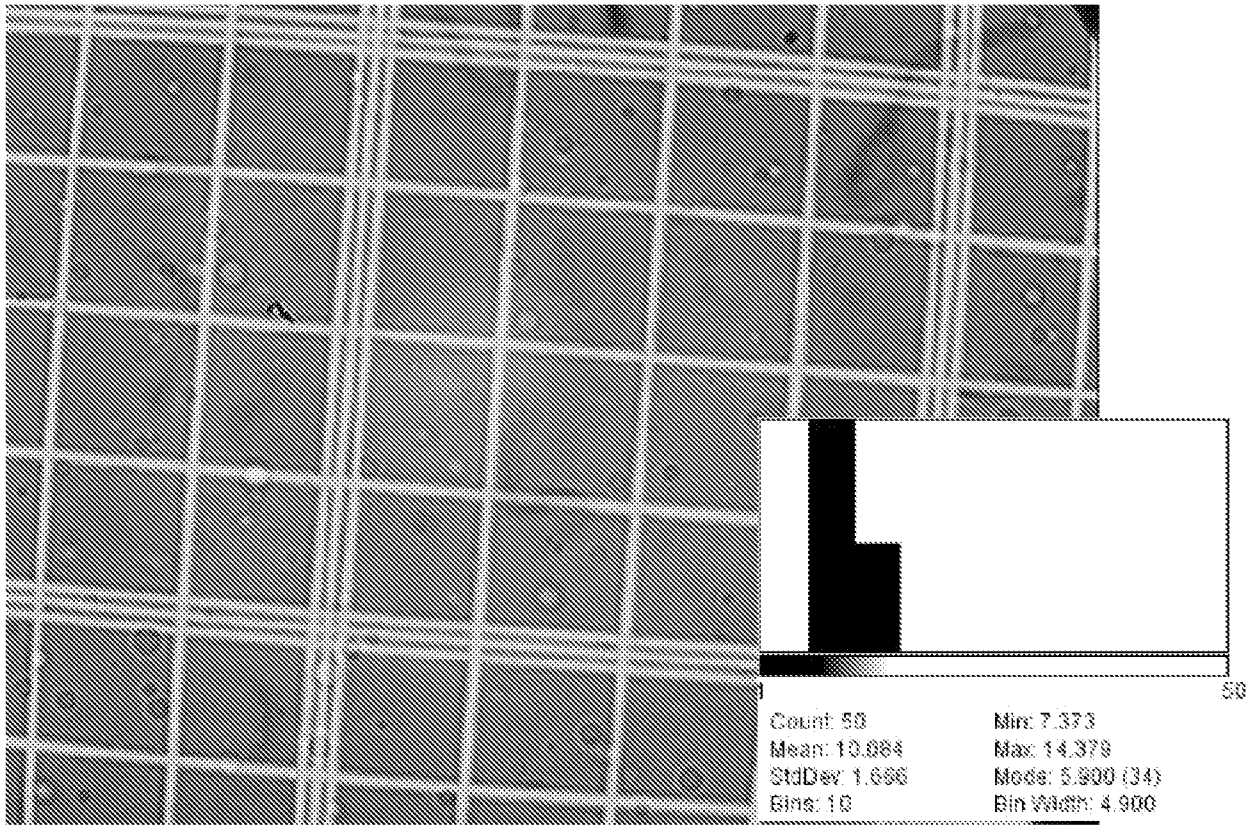

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Count: 50
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Min: 7.373
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Bin Width: 4.900

FIG. 3A

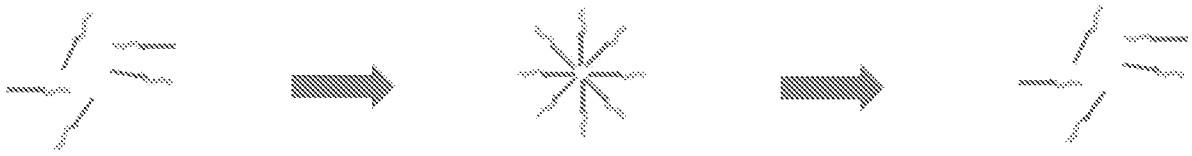


FIG. 3B

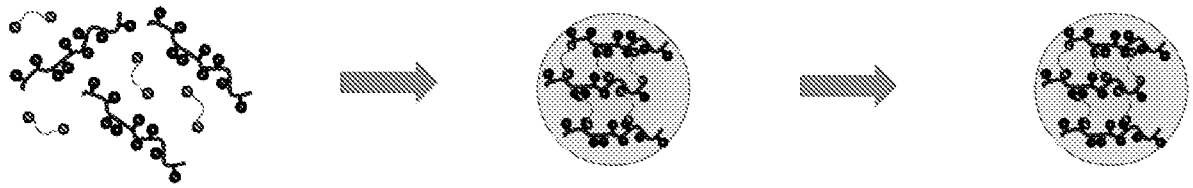


FIG. 4

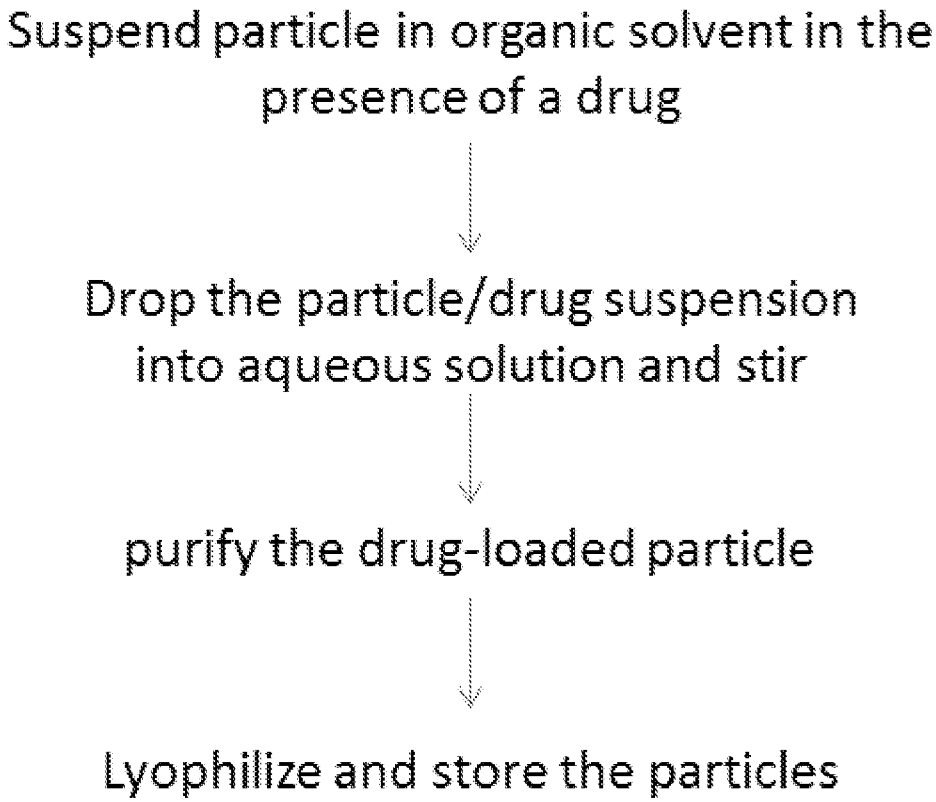

Suspend particle in organic solvent in the presence of a drug
Drop the particle/drug suspension into aqueous solution and stir
purify the drug-loaded particle
Lyophilize and store the particles

FIG. 5

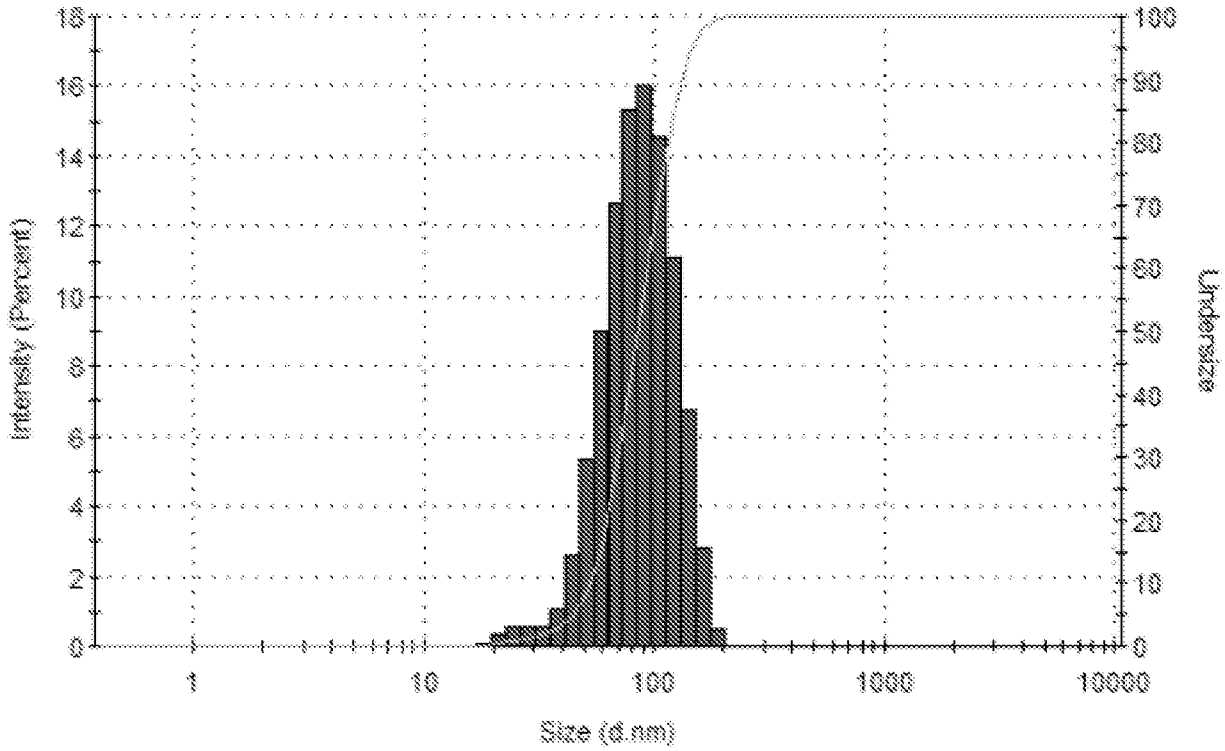

Intensity (Percent)
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Size (d.nm)
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8
10
12
14
16
18
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30
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50
60
70
80
90
100
1
10
100
1000
10000

FIG. 6

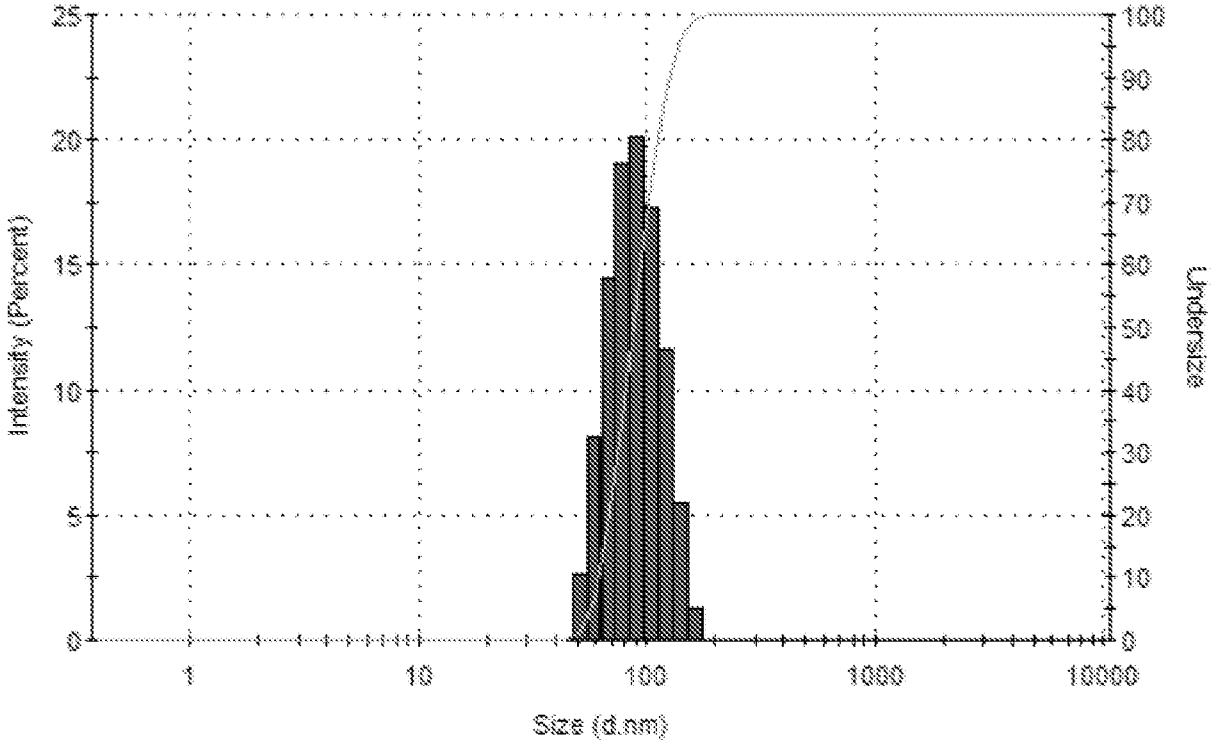

Intensity (Percent)
Undersize
Size (d.nm)
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10
15
20
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10
20
30
40
50
60
70
80
90
100
1
10
100
1000
10000

FIG. 7

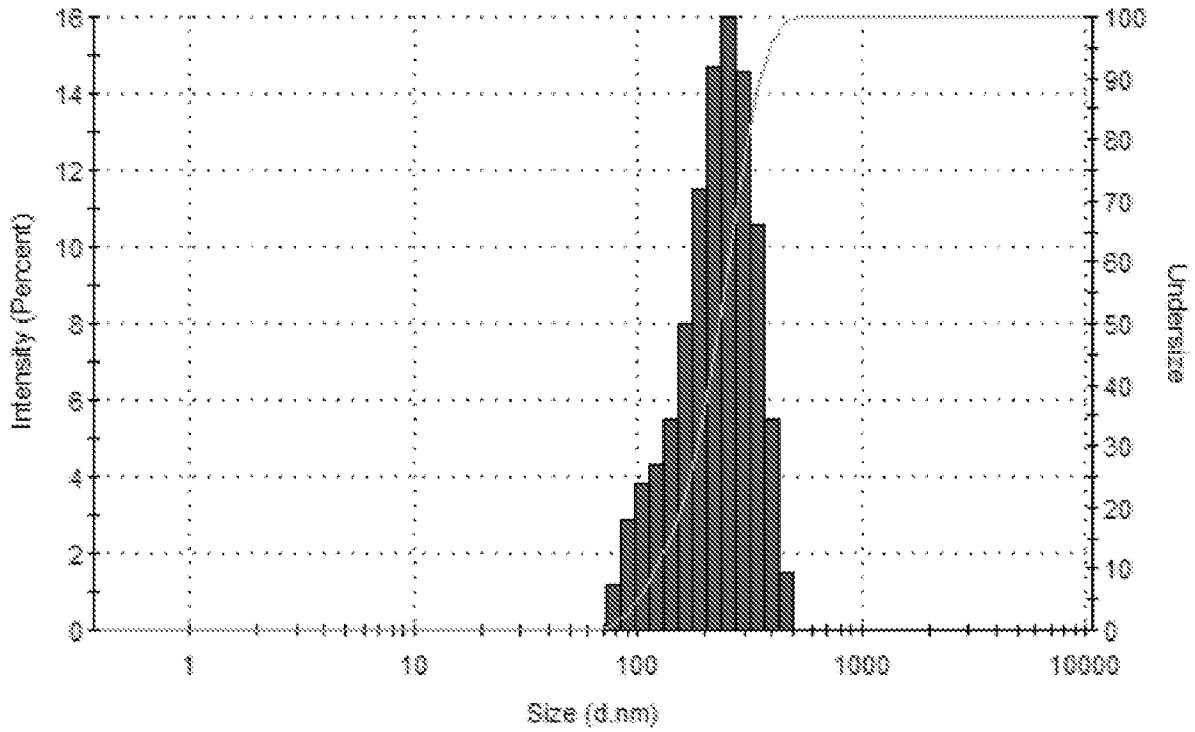

Intensity (Percent)
Undersize
Size (d.nm)
0
2
4
6
8
10
12
14
16
0
10
20
30
40
50
60
70
80
90
100
1
10
100
1000
10000

FIG. 8

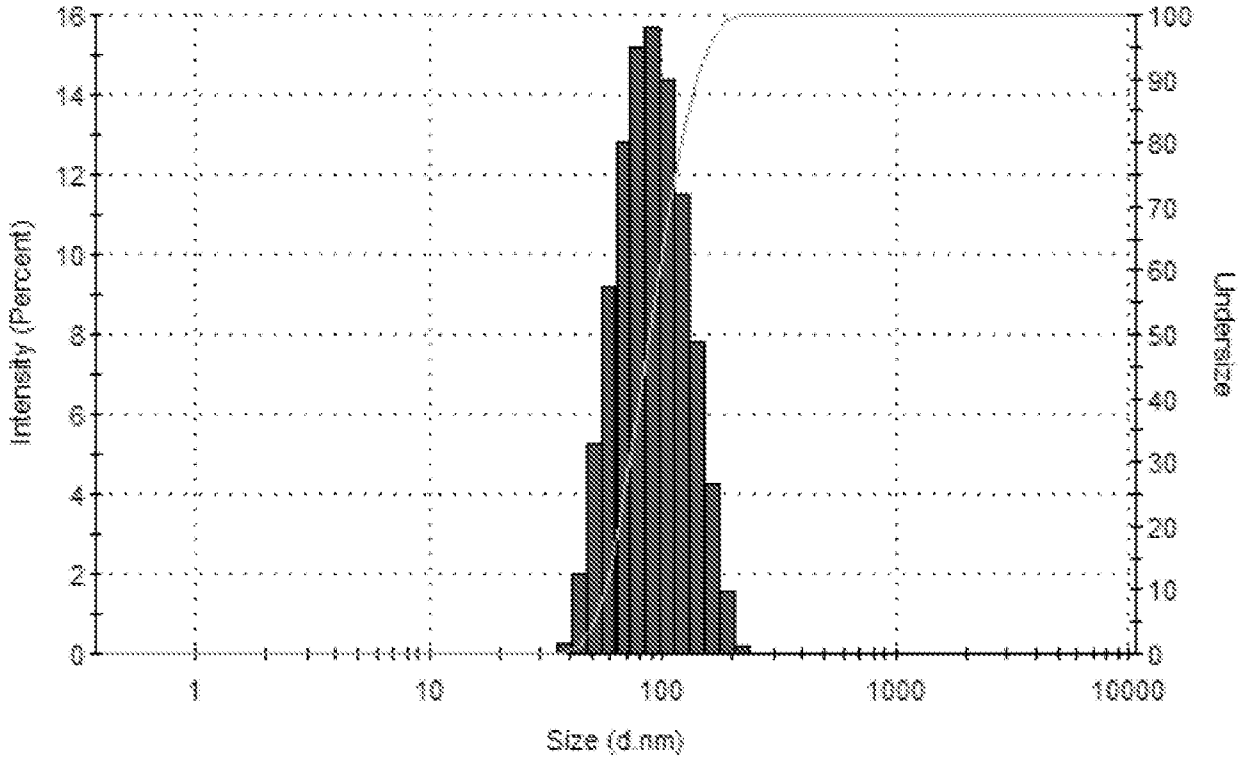

Intensity (Percent)
Undersize
Size (d.nm)
0
2
4
6
8
10
12
14
16
18
0
10
20
30
40
50
60
70
80
90
100
1
10
100
1000
10000

FIG. 9A

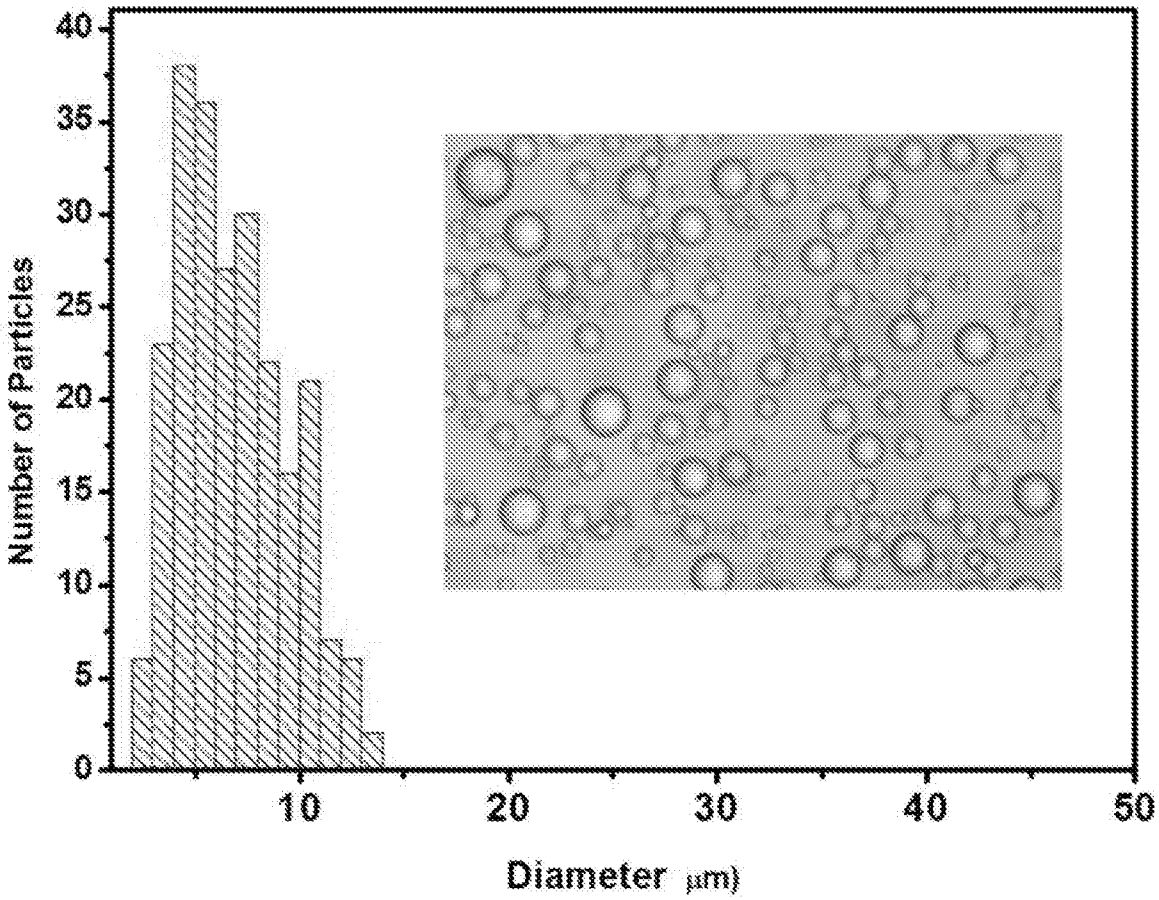

Number of Particles
0
5
10
15
20
25
30
35
40
10
20
30
40
50
Diameter (μm)

FIG. 9B

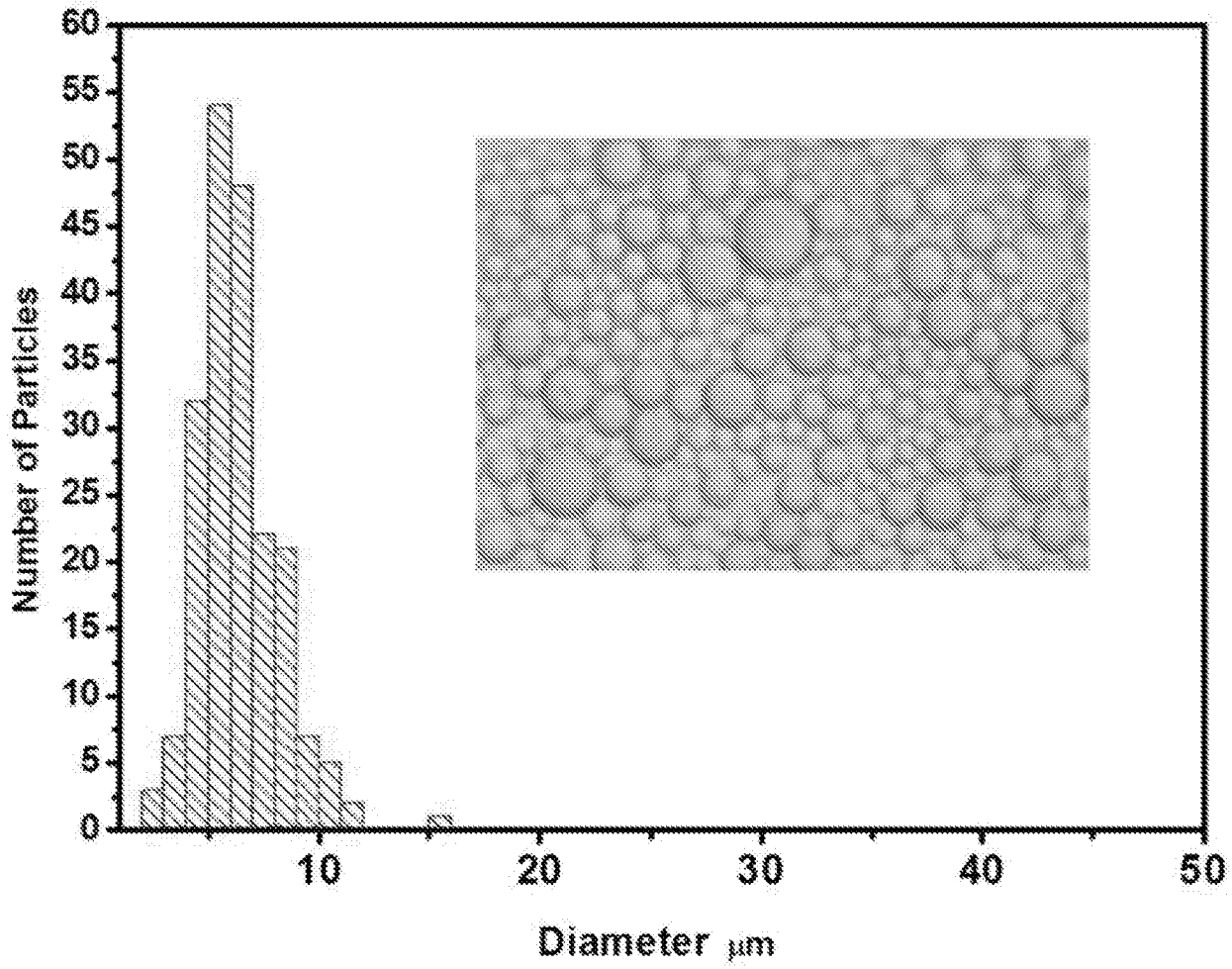

Number of Particles
0
5
10
15
20
25
30
35
40
45
50
55
60
10
20
30
40
50
Diameter μm

FIG. 9C

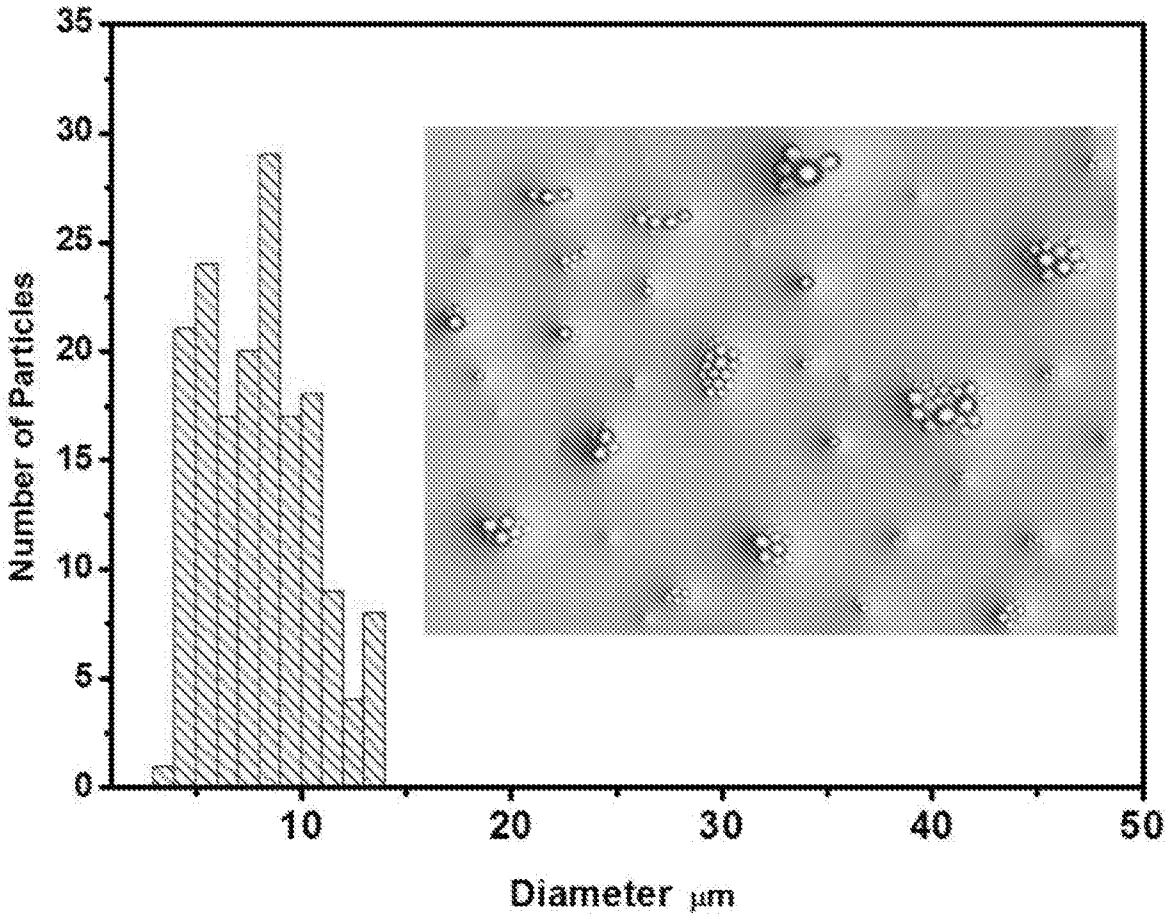

Number of Particles
0
5
10
15
20
25
30
35
10
20
30
40
50
Diameter μm

FIG. 9D

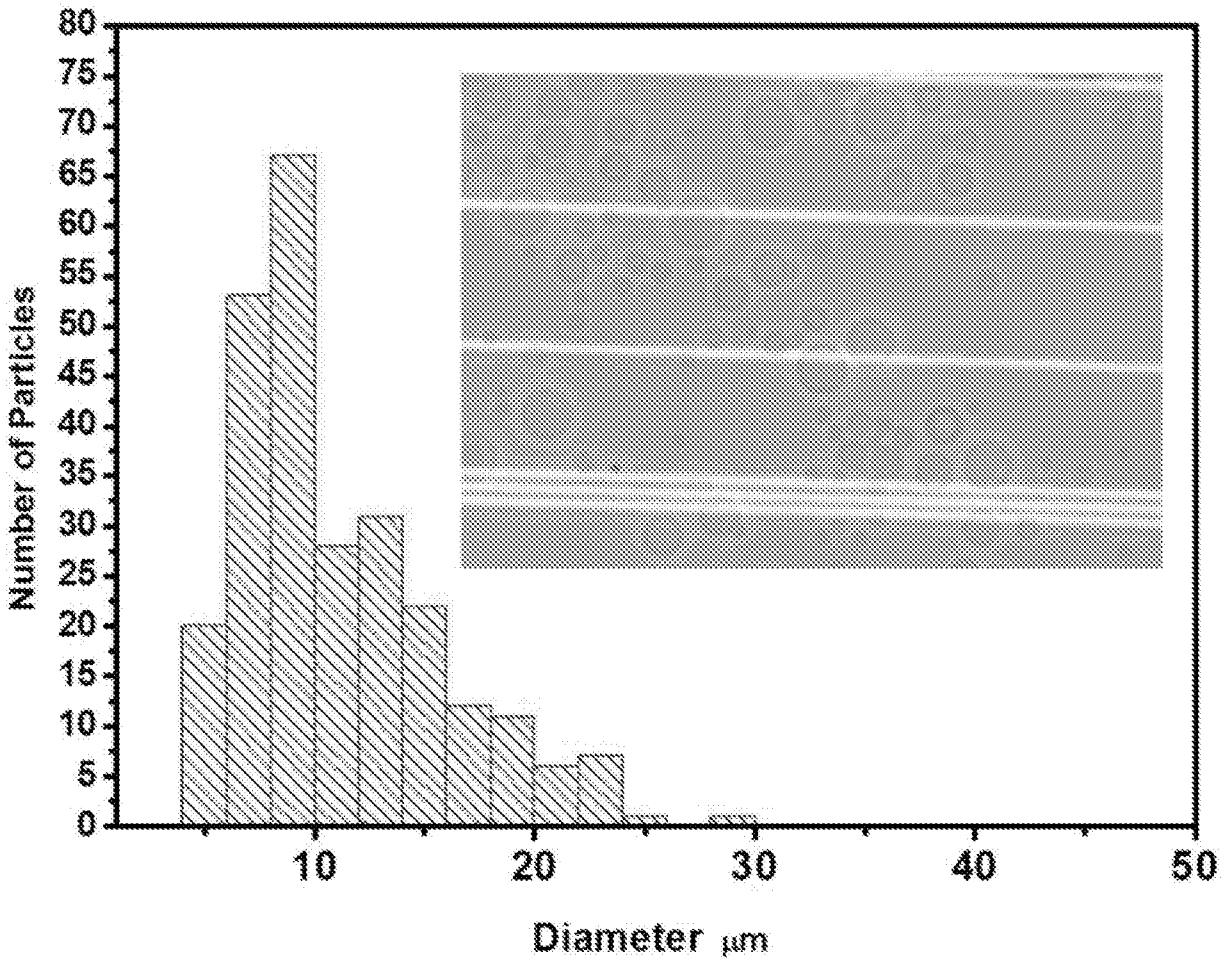

Number of Particles
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
10
20
30
40
50
Diameter μm

FIG. 10A

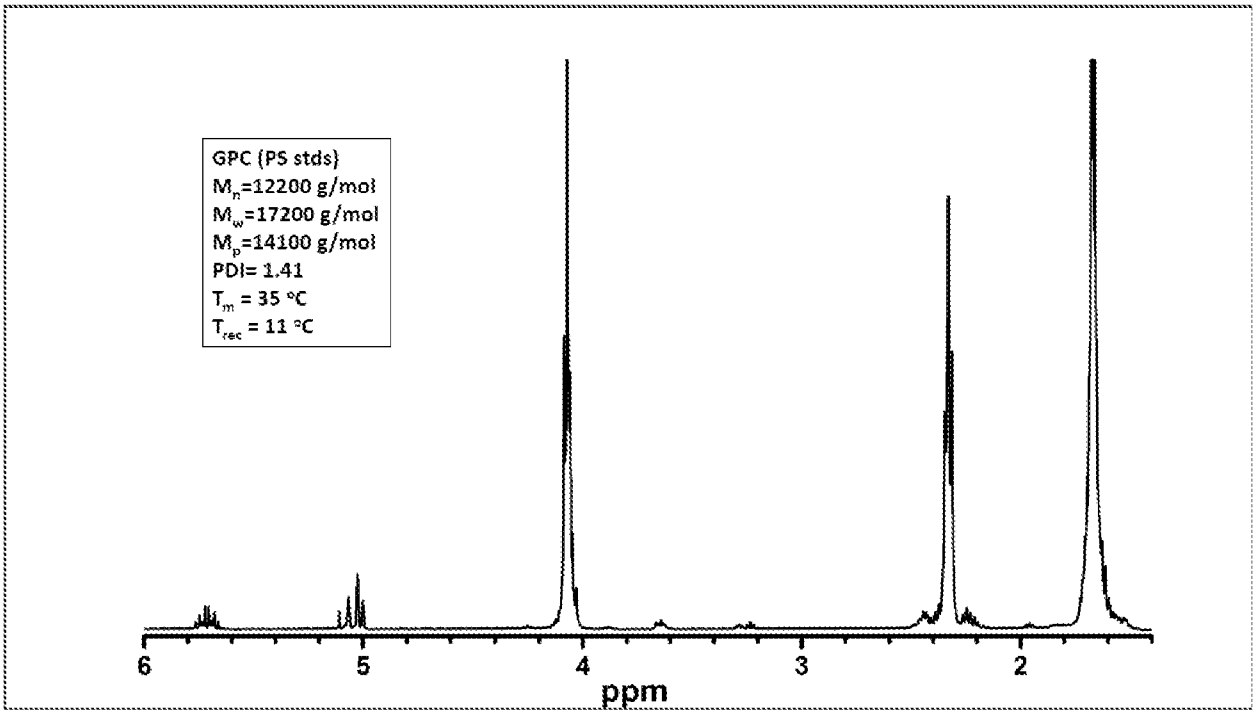

GPC (PS stds)
M_n=12200 g/mol
M_w=17200 g/mol
M_p=14100 g/mol
PDI= 1.41
T_m = 35 °C
T_{rec} = 11 °C
6
5
4
3
2
ppm

FIG. 10B

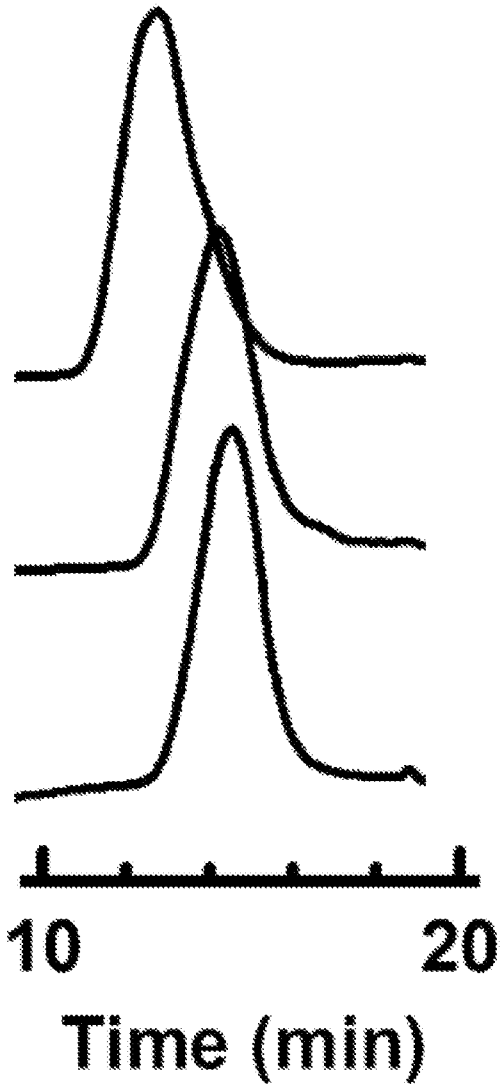


FIG. 11A

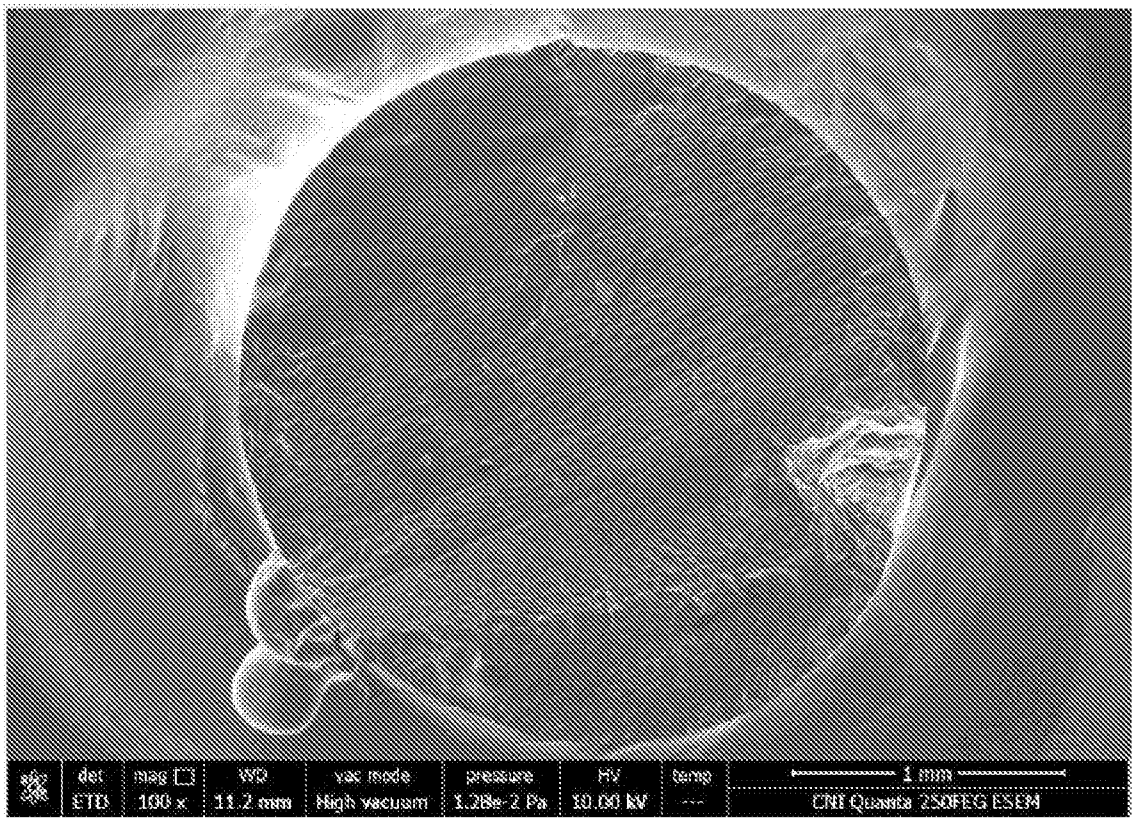

det
ETD
mag
100 x
WD
11.2 mm
vac mode
High vacuum
pressure
1.28e-2 Pa
HV
10.00 kV
temp
---
1 mm
CNF Quanta 250FEG ESEM

FIG. 11B

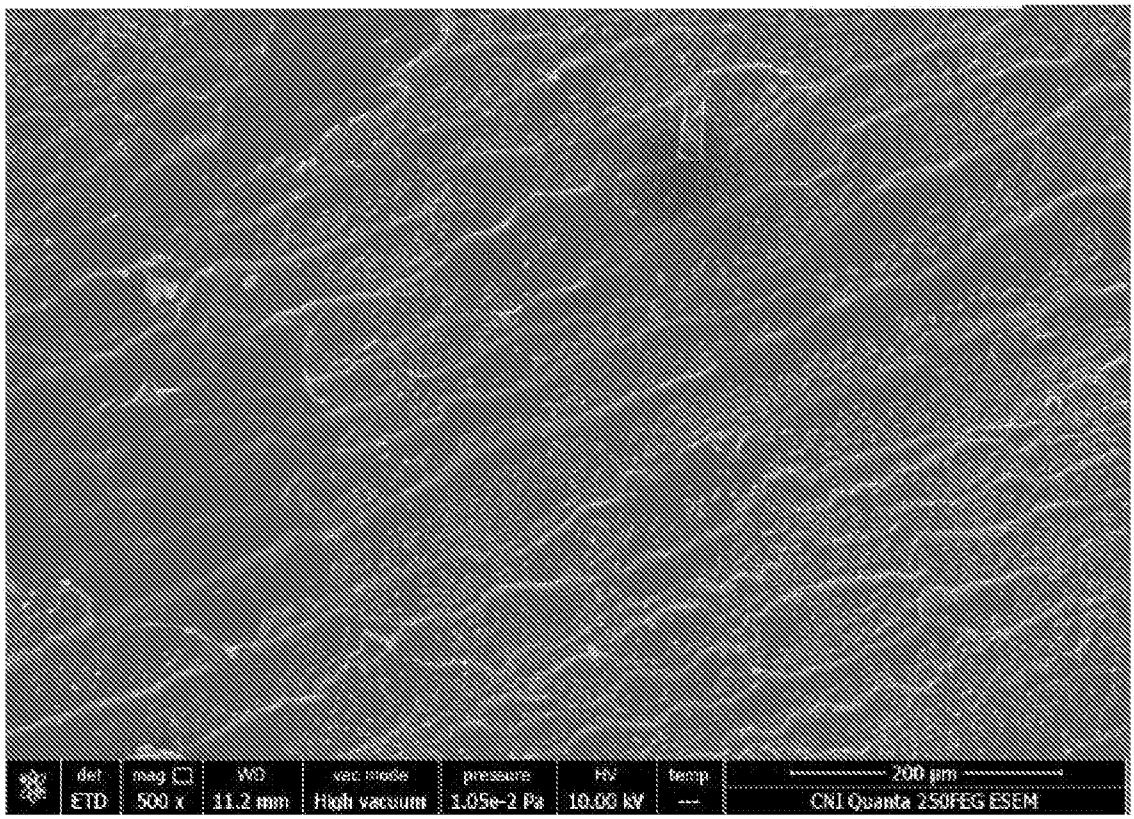

det
ETD
mag
500 x
WD
11.2 mm
vac mode
High vacuum
pressure
1.05e-2 Pa
HV
10.00 kV
temp
---
200 µm
CNI Quanta 250FEG ESEM

FIG. 11C

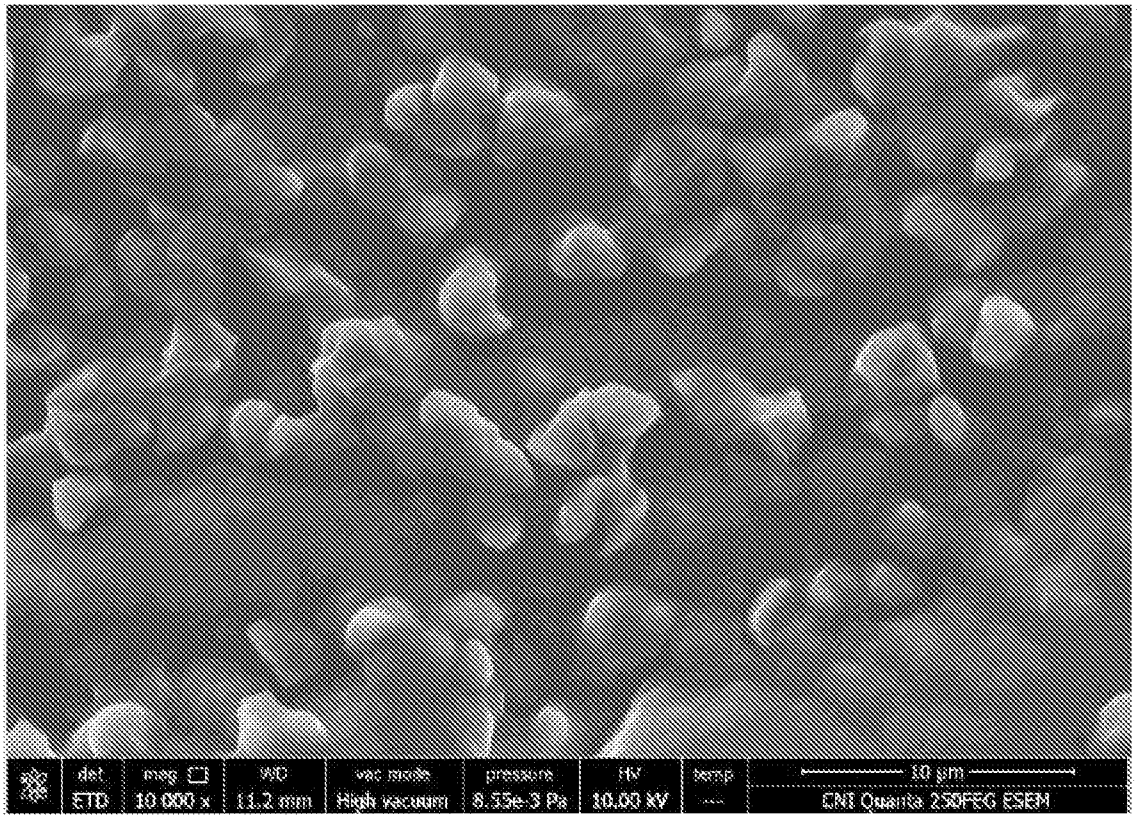

det
ETD
mag
10 000 x
WD
11.2 mm
vac mode
High vacuum
pressure
8.55e-3 Pa
HV
10.00 kV
temp
---
10 µm
CNI Quanta 250FEG ESEM

FIG. 11D

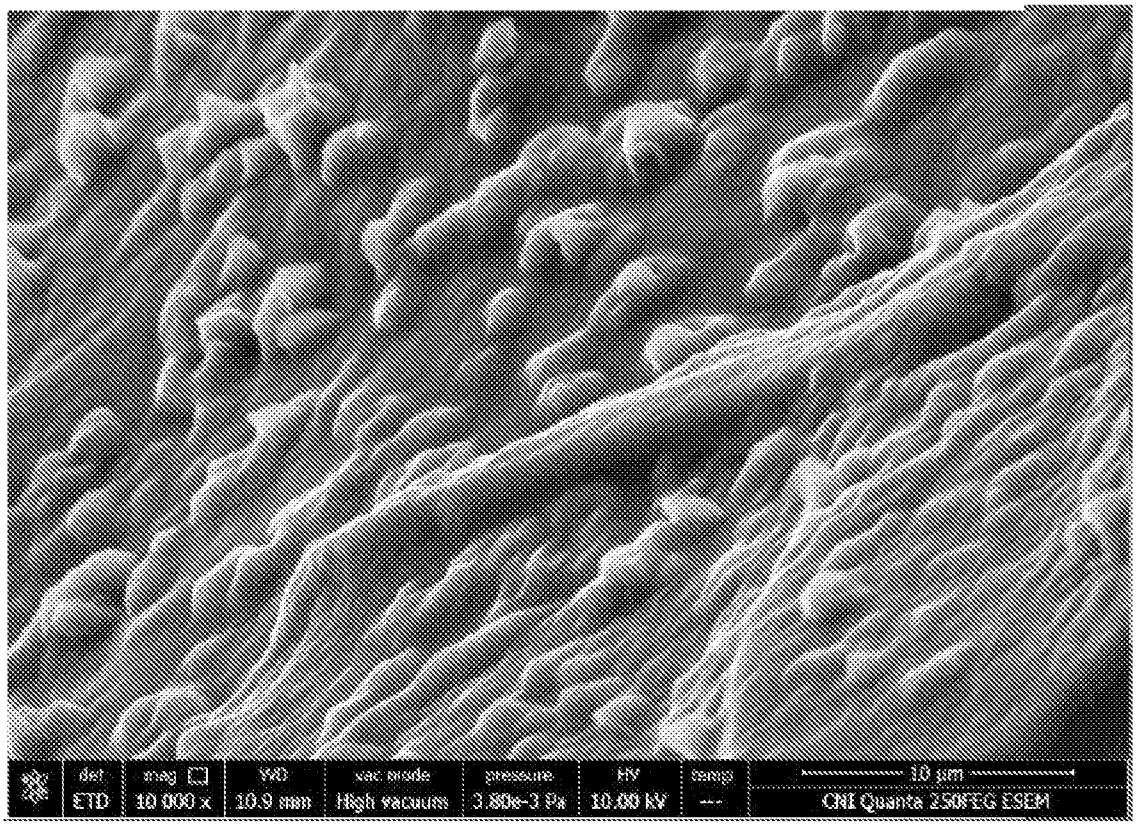

det
ETD
mag
10 000 x
WD
10.9 mm
vac mode
High vacuum
pressure
3.80e-3 Pa
HV
10.00 kV
temp
---
10 µm
CNI Quanta 250FEG ESEM

FIG. 12

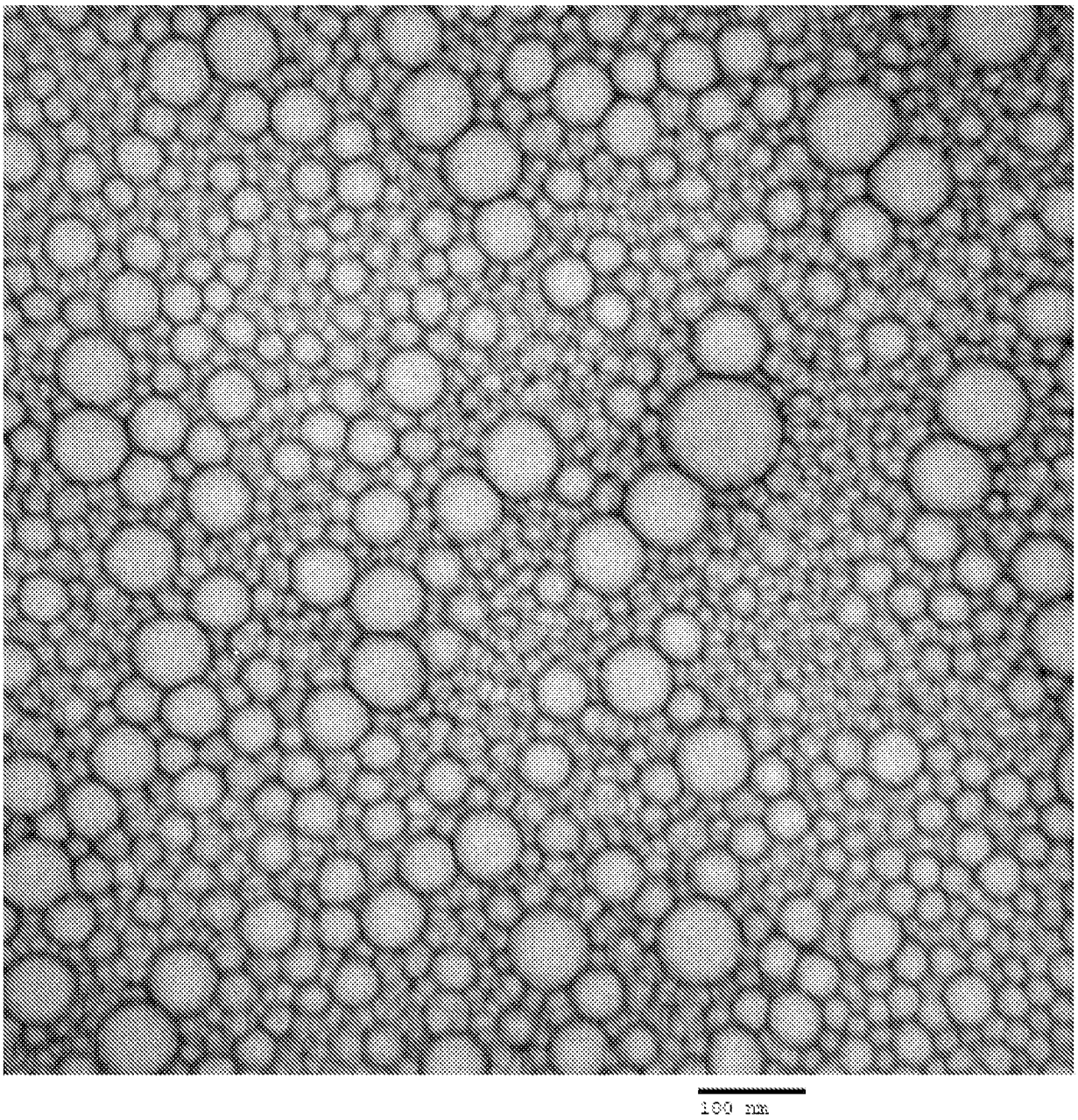


FIG. 13

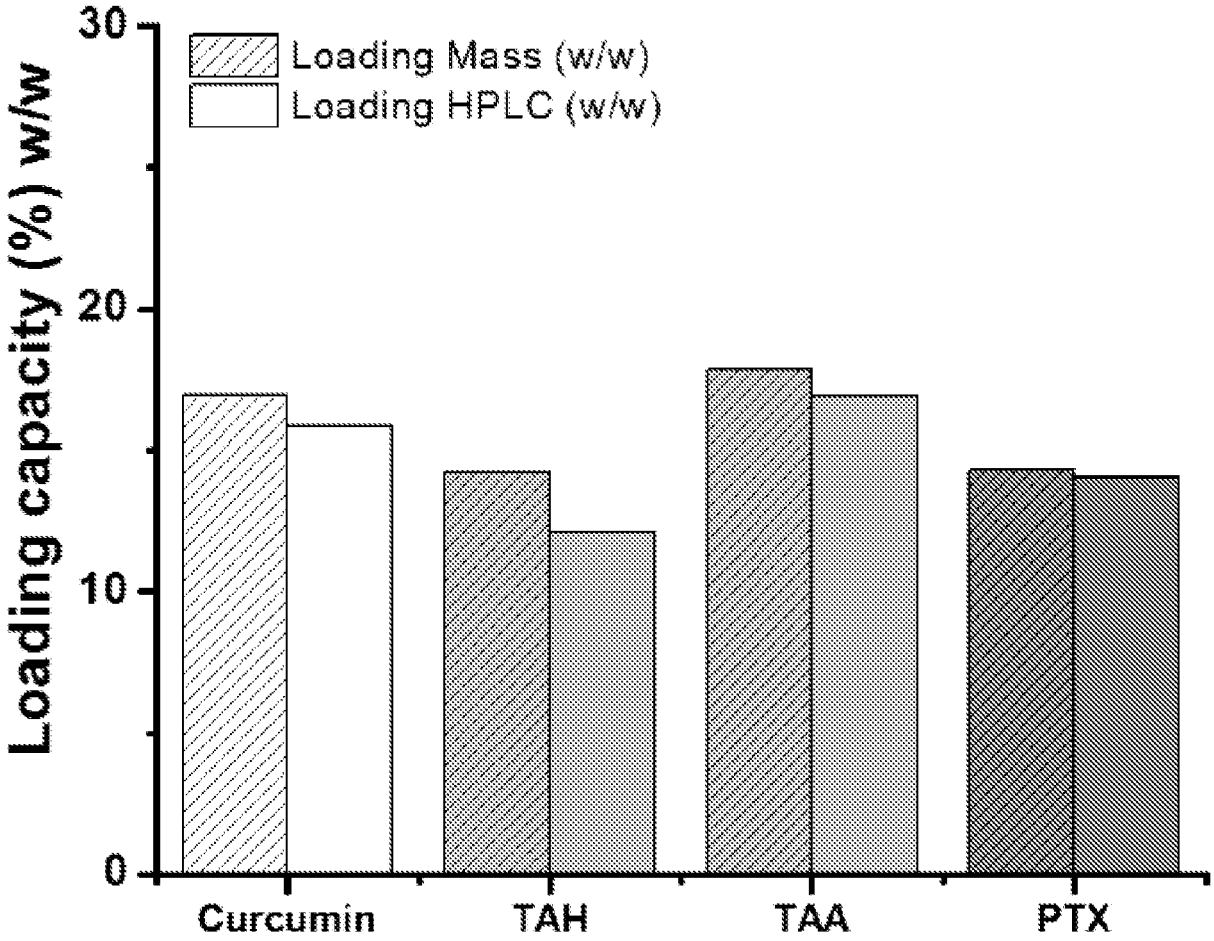

Loading capacity (%) w/w
30
20
10
0
Loading Mass (w/w)
Loading HPLC (w/w)
Curcumin
TAH
TAA
PTX

FIG. 14

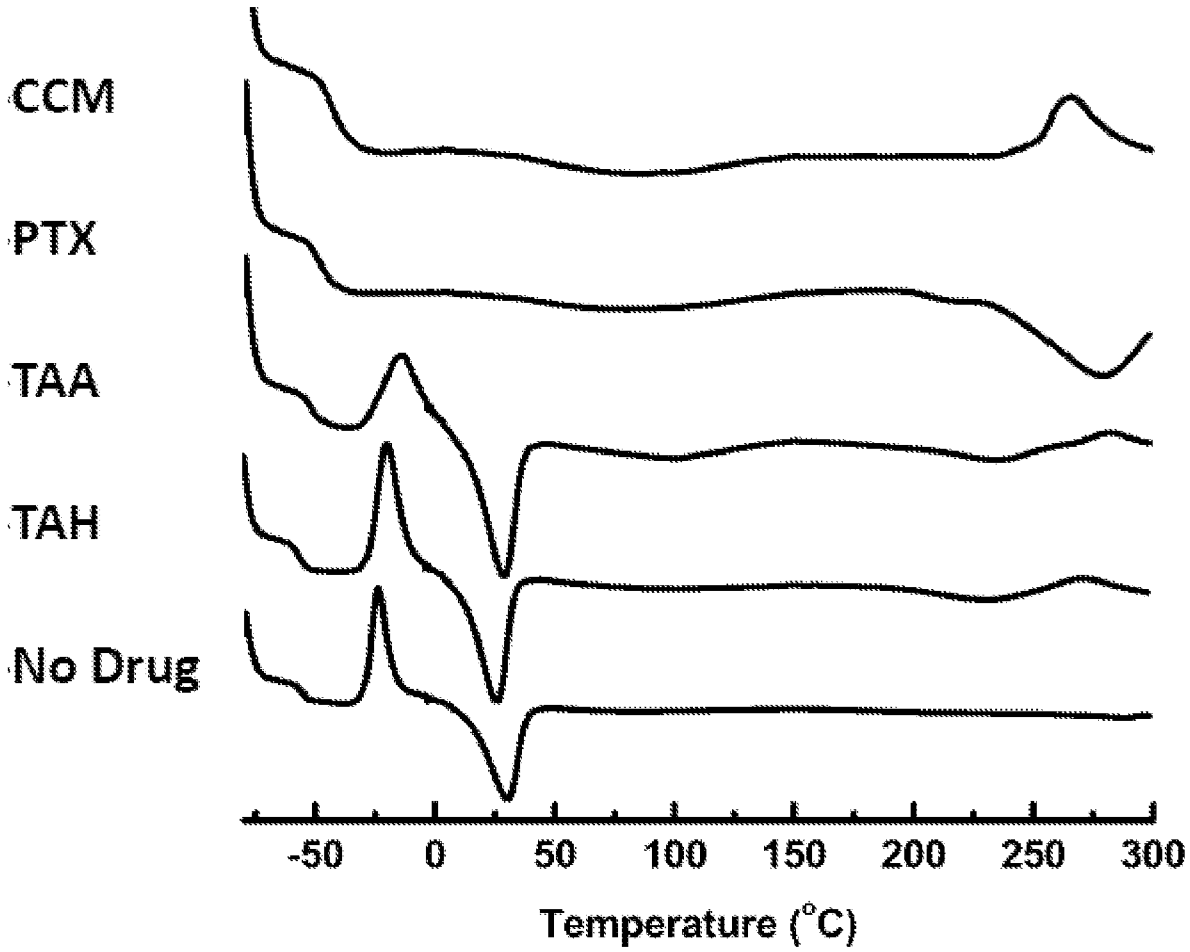

CCM
PTX
TAA
TAH
No Drug
-50
0
50
100
150
200
250
300
Temperature (°C)

FIG. 15

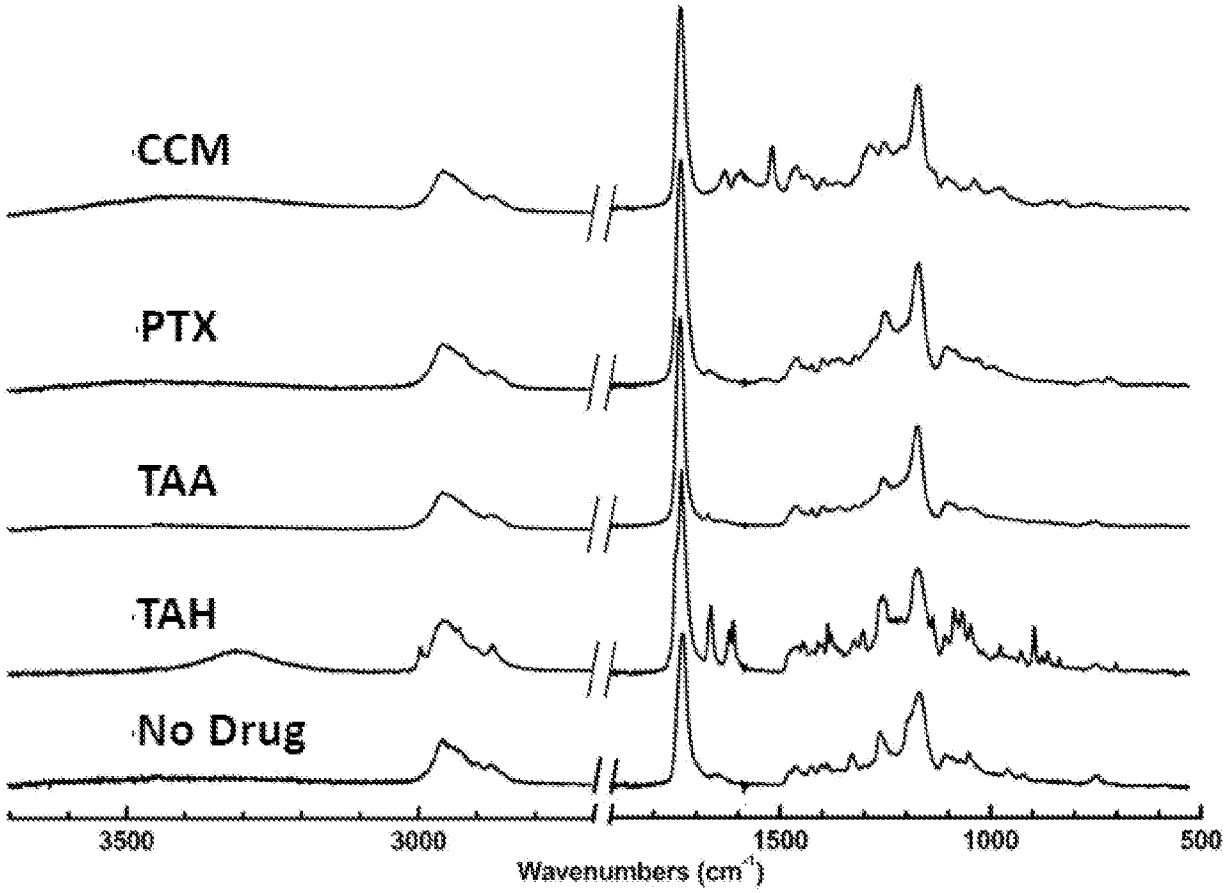

CCM
PTX
TAA
TAH
No Drug
3500
3000
1500
1000
500
Wavenumbers (cm-1)

FIG. 16

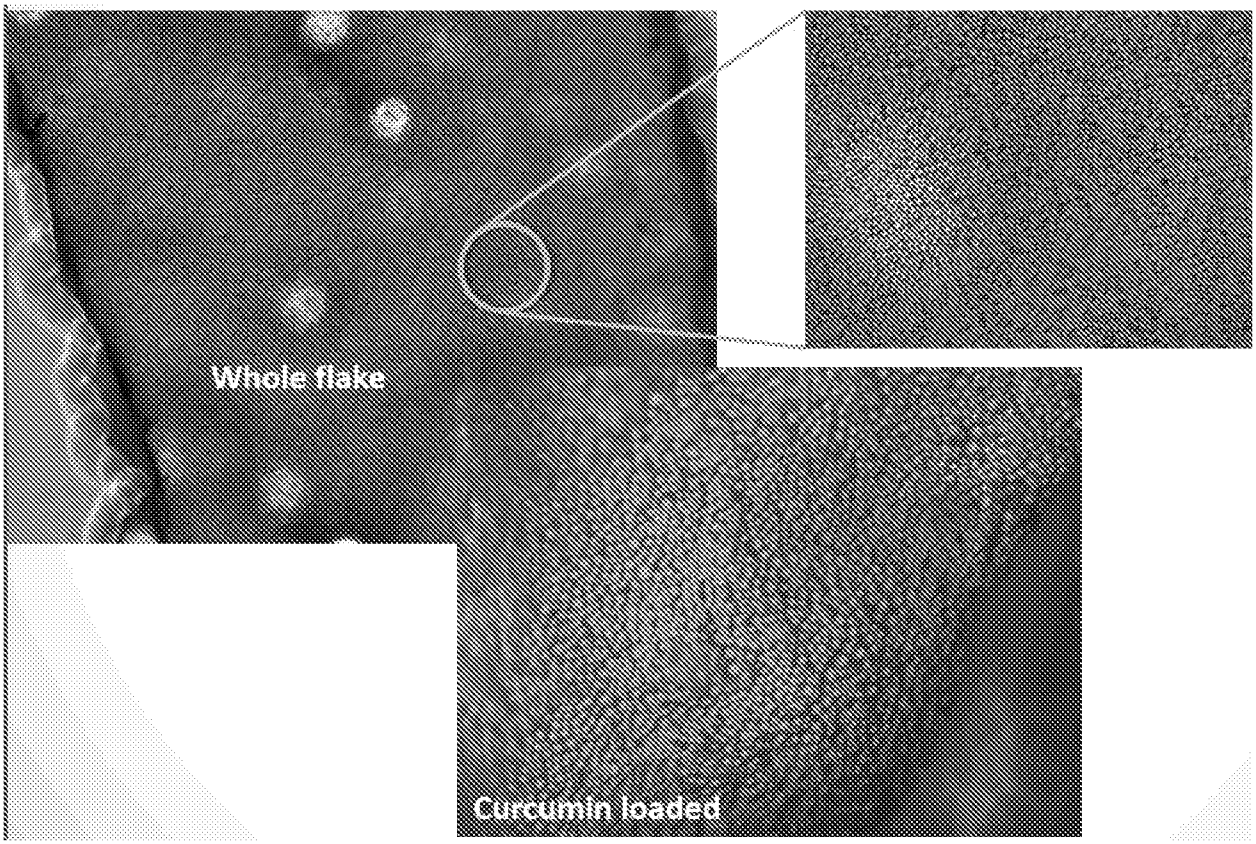


FIG. 17

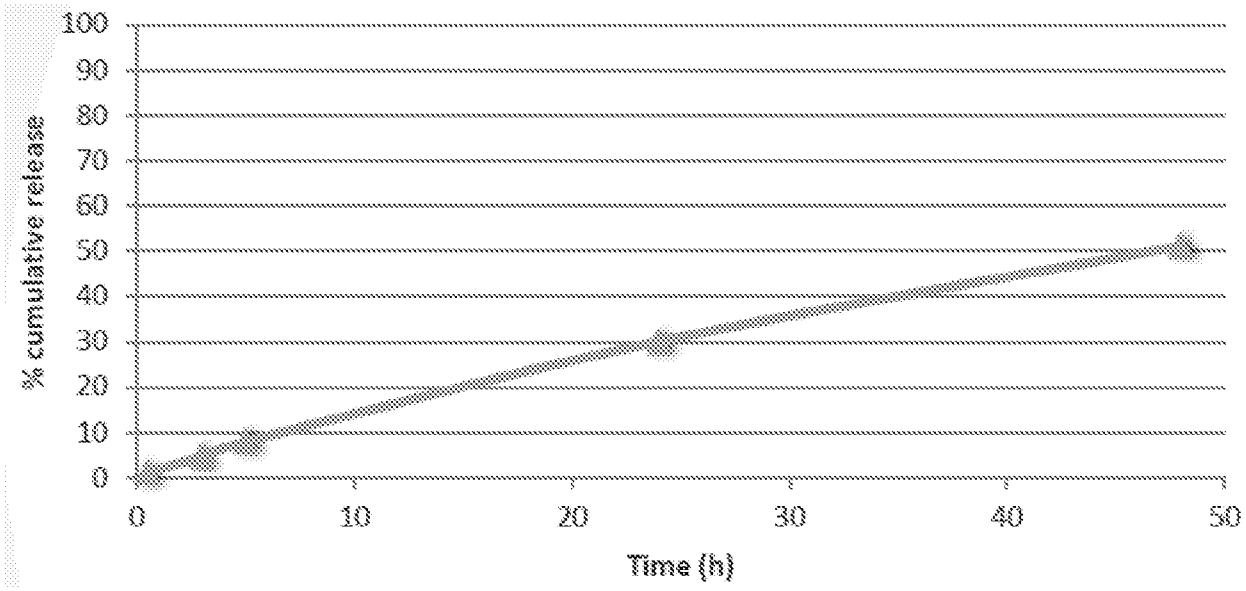

% cumulative release
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
Time (h)

FIG. 18A

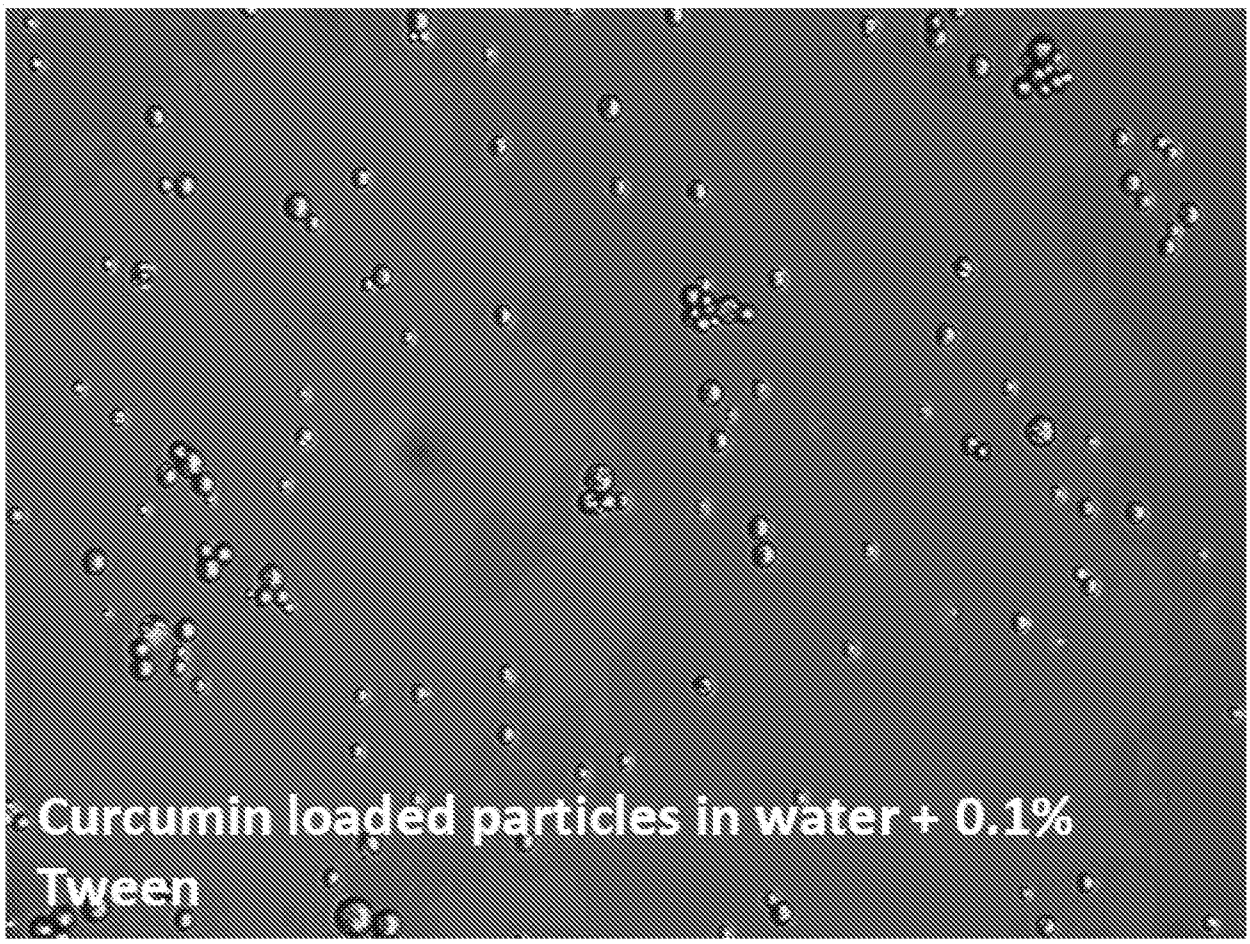


FIG. 18B

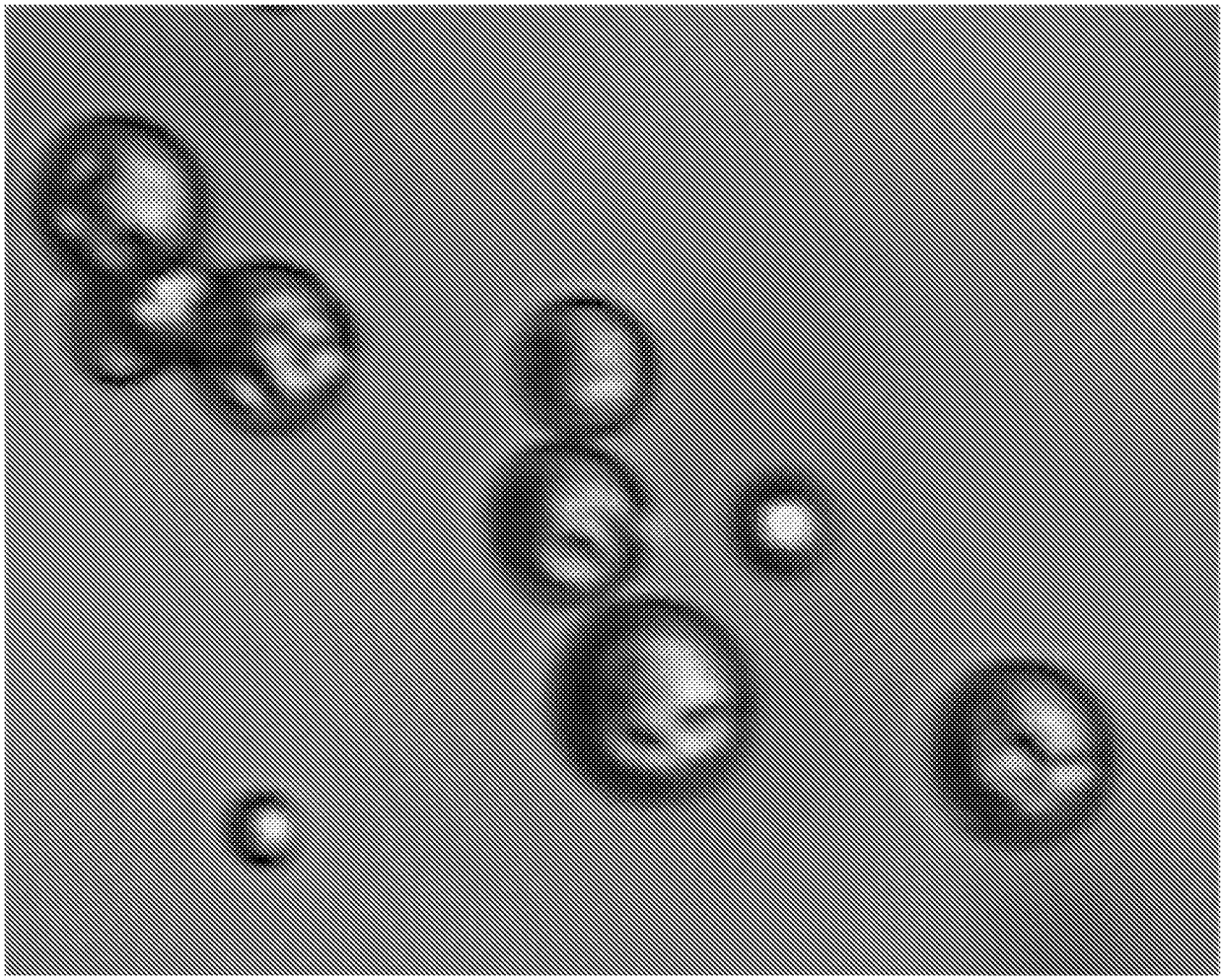


FIG. 19A

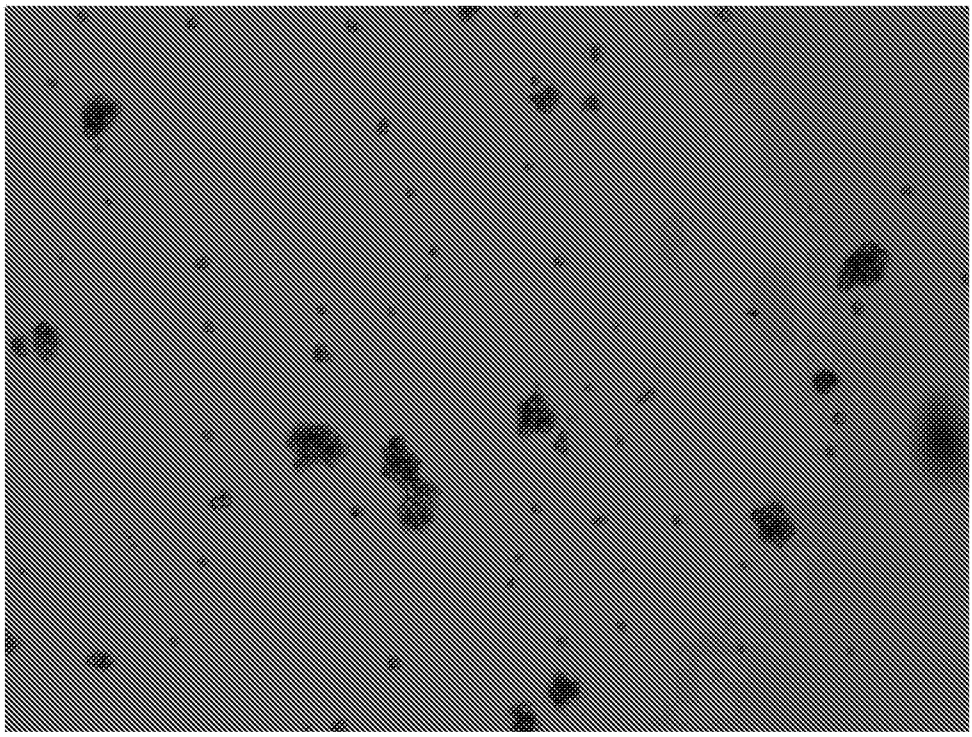


FIG. 19B

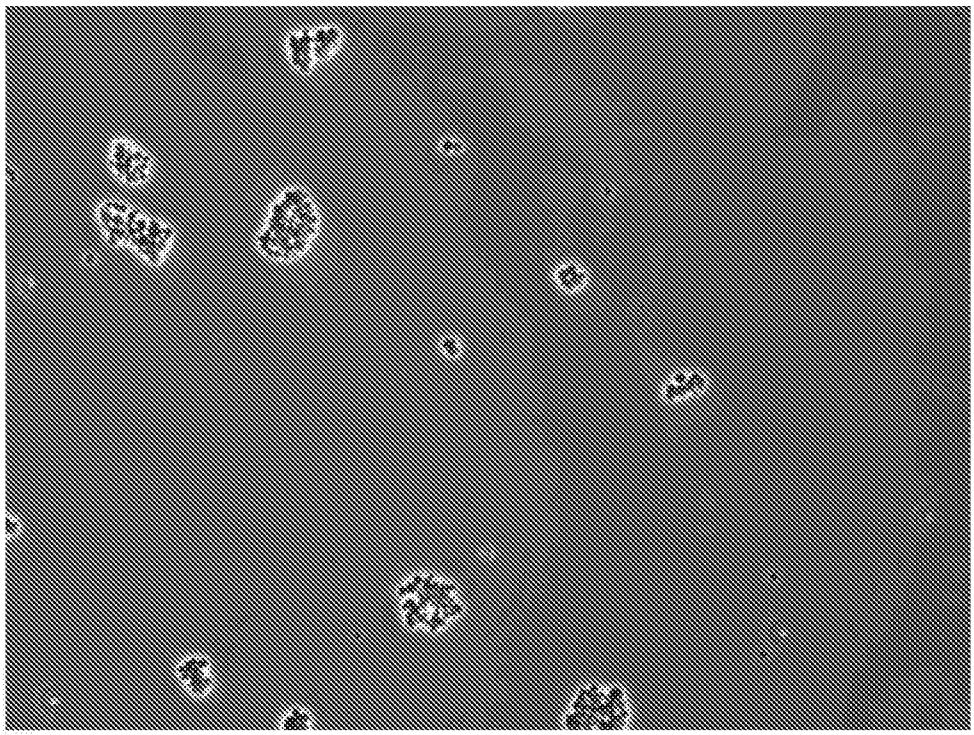


FIG. 19C

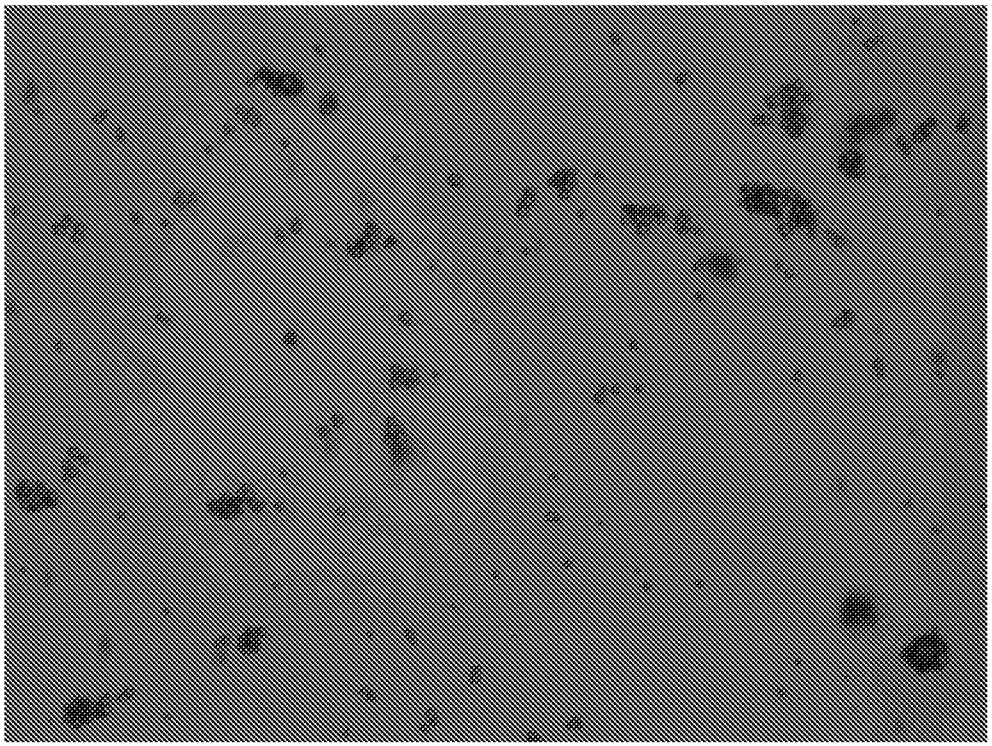


FIG. 19D

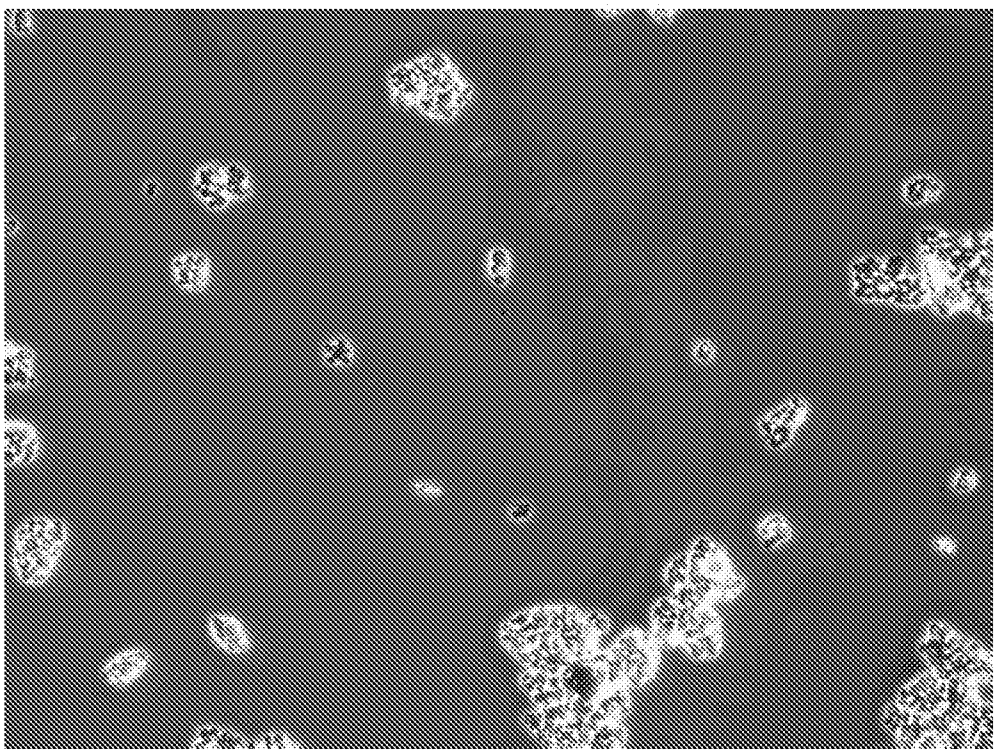


FIG. 20A

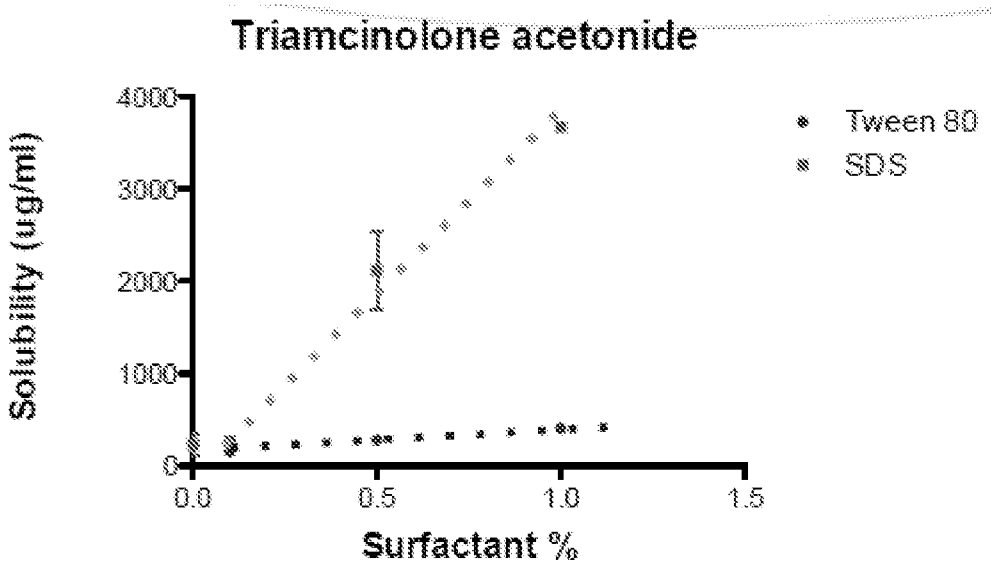

Triamcinolone acetonide
Solubility (ug/ml)
4000
3000
2000
1000
0
0.0
0.5
1.0
1.5
Surfactant %
Tween 80
SDS

FIG. 20B

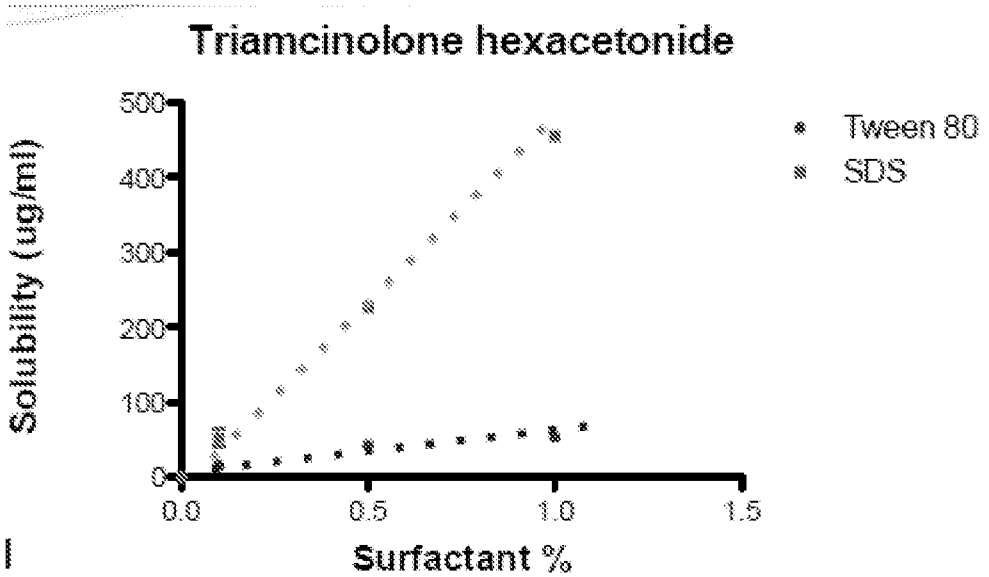

Triamcinolone hexacetonide
Solubility (ug/ml)
500
400
300
200
100
0
0.0
0.5
1.0
1.5
Surfactant %
Tween 80
SDS

FIG. 20C

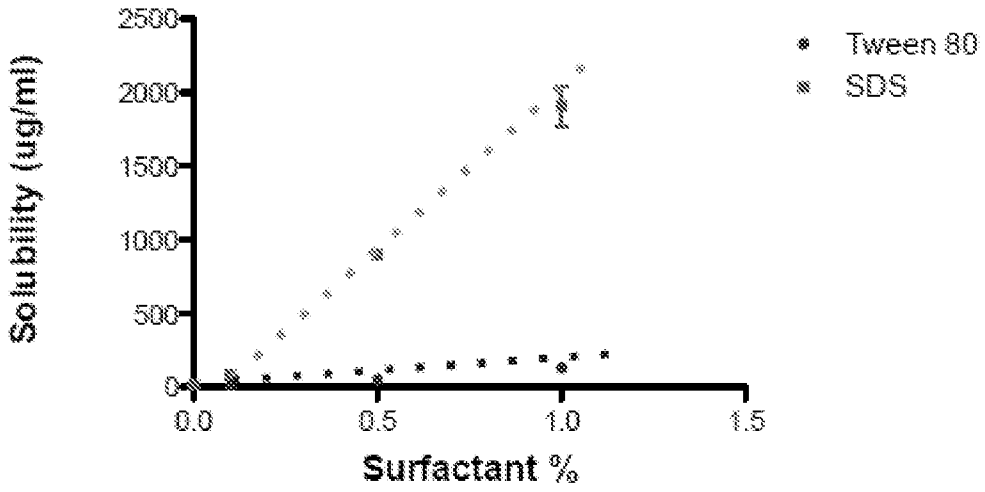

Solubility (ug/ml)
2500
2000
1500
1000
500
0
0.0
0.5
1.0
1.5
Surfactant %
Tween 80
SDS

FIG. 21

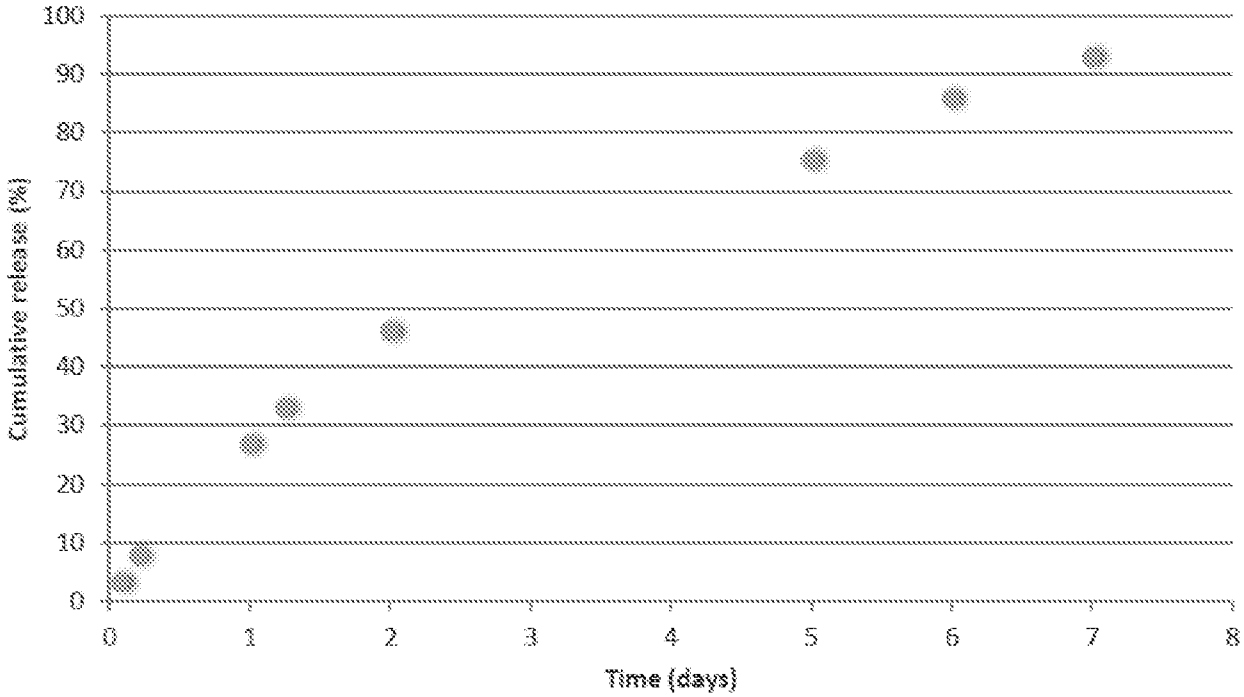

Cumulative release (%)
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
8
Time (days)

FIG. 22

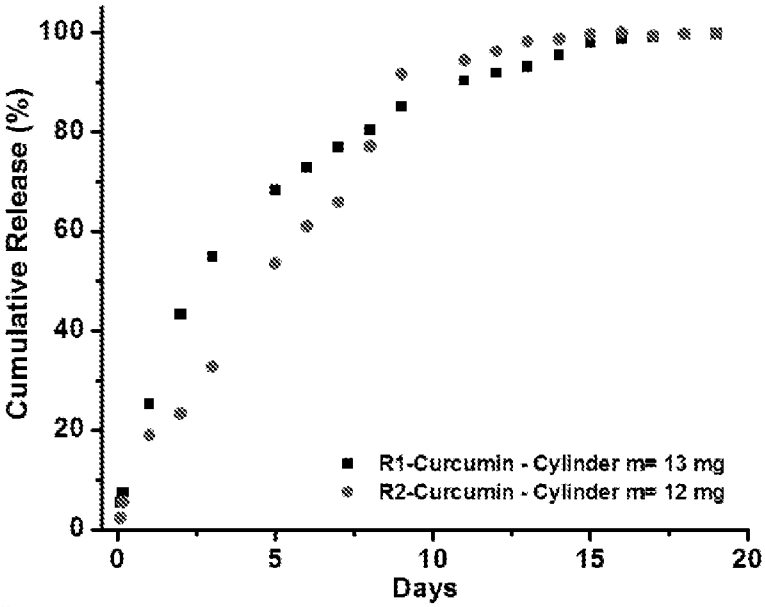

Cumulative Release (%)
100
80
60
40
20
0
0
5
10
15
20
Days
R1-Curcumin - Cylinder m= 13 mg
R2-Curcumin - Cylinder m= 12 mg

FIG. 23

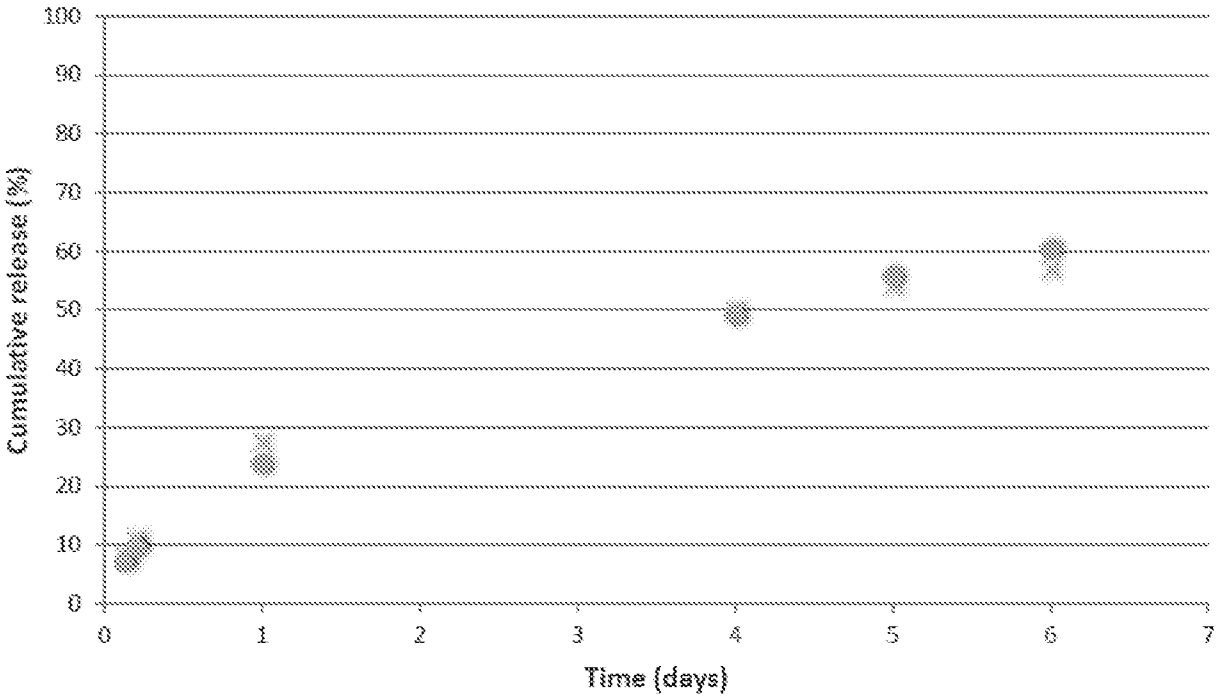

100
90
80
70
60
50
40
30
20
10
0
Cumulative release (%)
0
1
2
3
4
5
6
7
Time (days)

FIG. 24

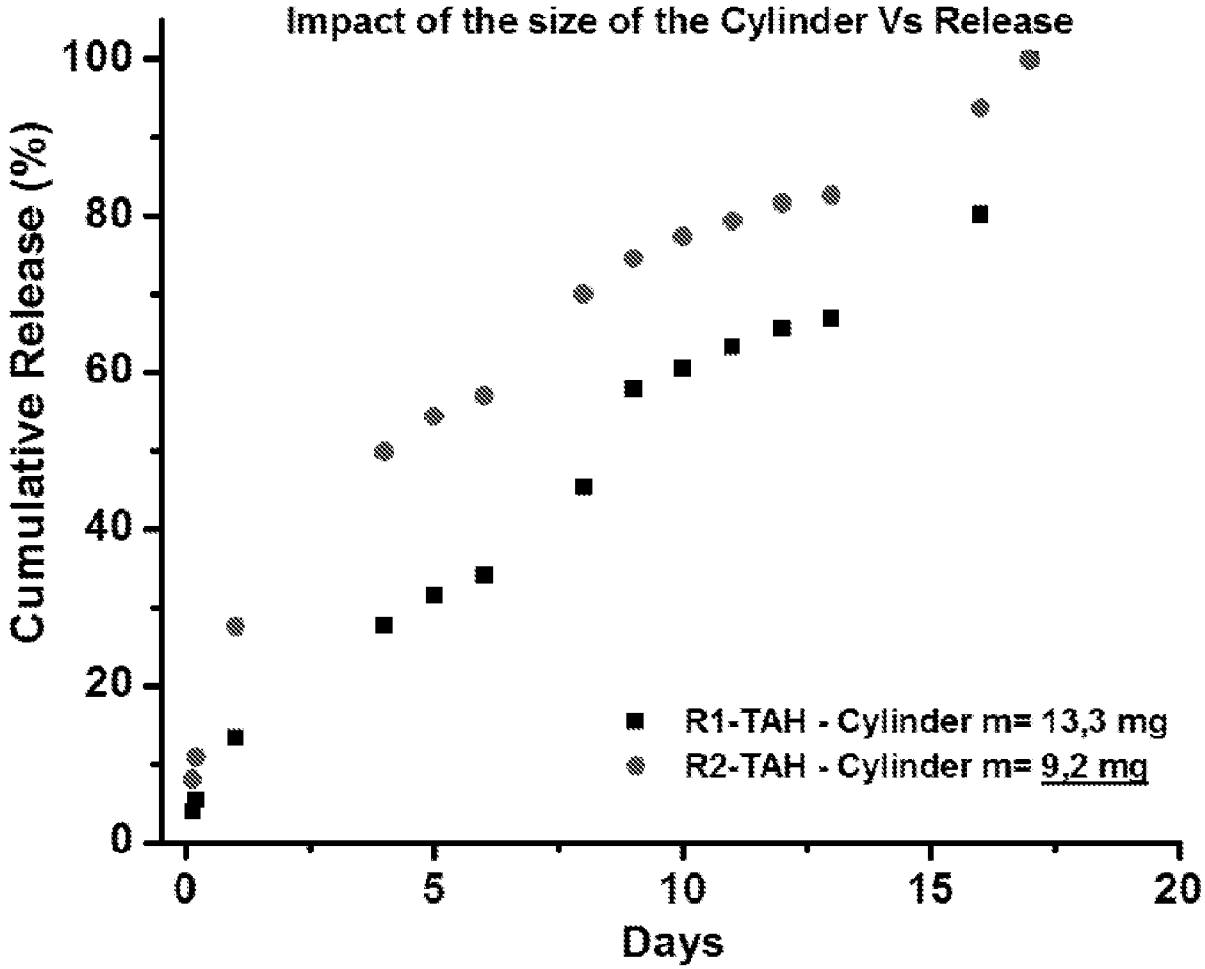

Impact of the size of the Cylinder Vs Release
Cumulative Release (%)
100
80
60
40
20
0
0
5
10
15
20
Days
R1-TAH - Cylinder m= 13,3 mg
R2-TAH - Cylinder m= 9,2 mg

FIG. 25

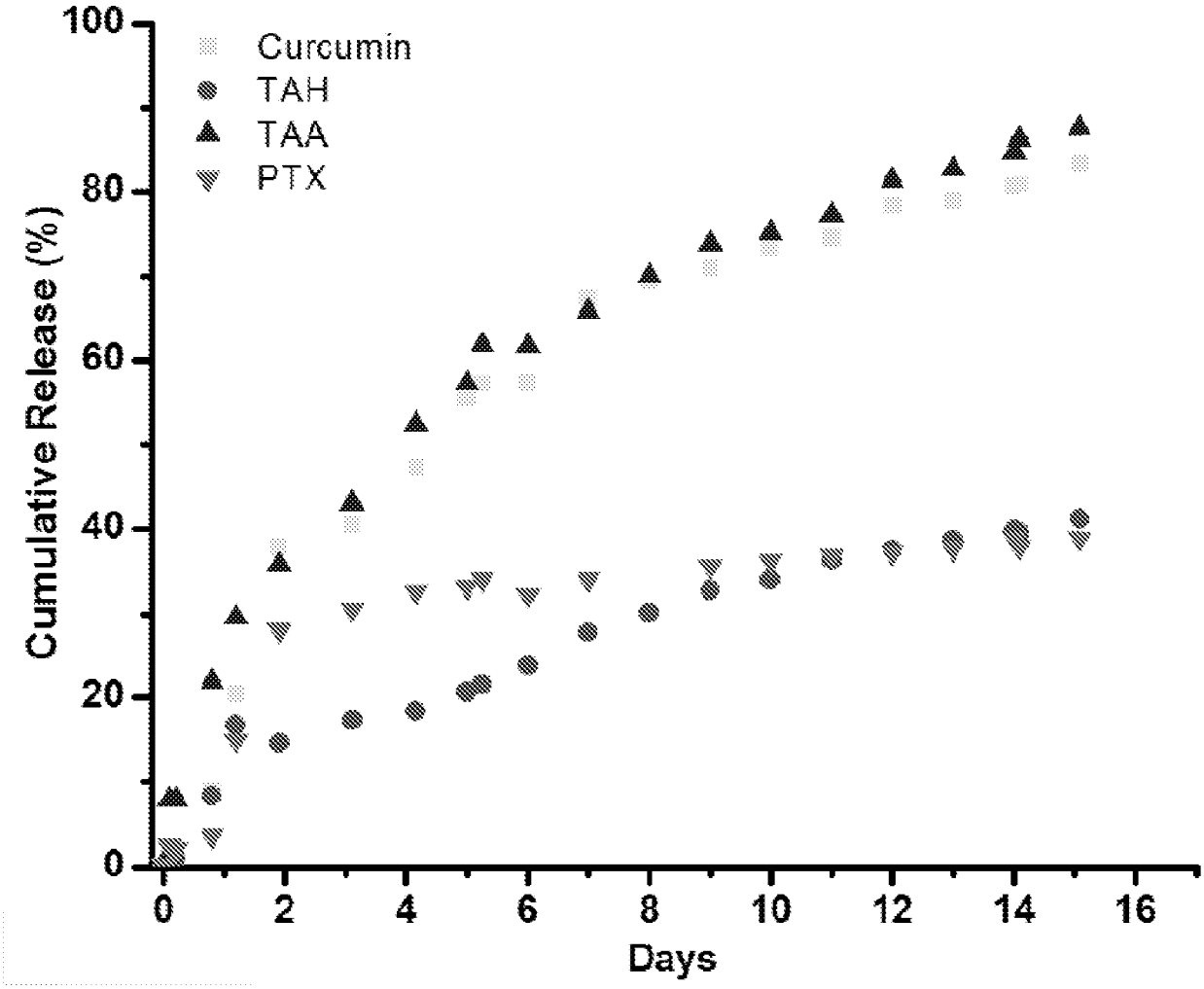

Curcumin
TAH
TAA
PTX
Cumulative Release (%)
0
20
40
60
80
100
0
2
4
6
8
10
12
14
16
Days

FIG. 26

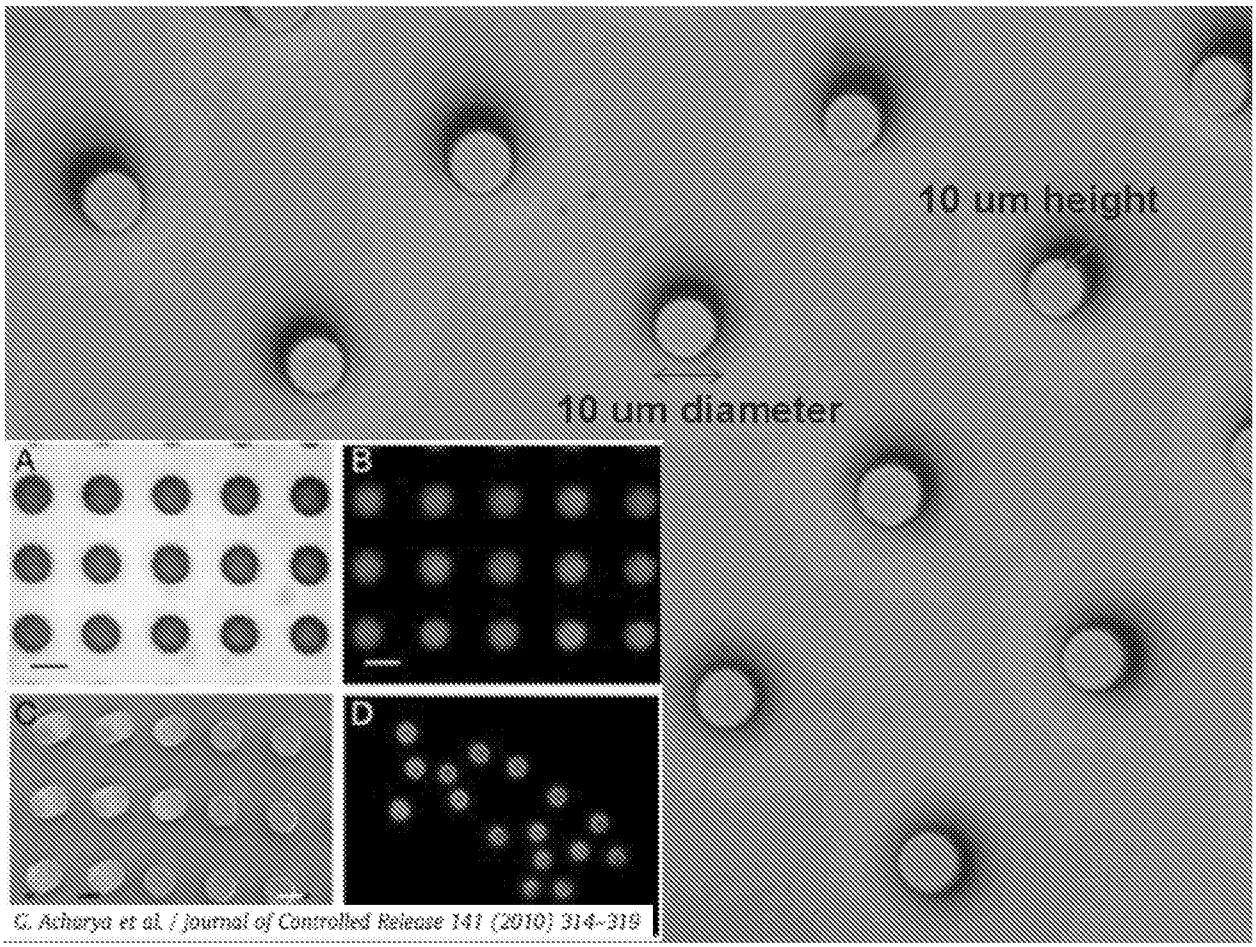

10 um height
10 um diameter
A
B
C
D
C. Acharya et al. / Journal of Controlled Release 141 (2010) 314–319

FIG. 27A

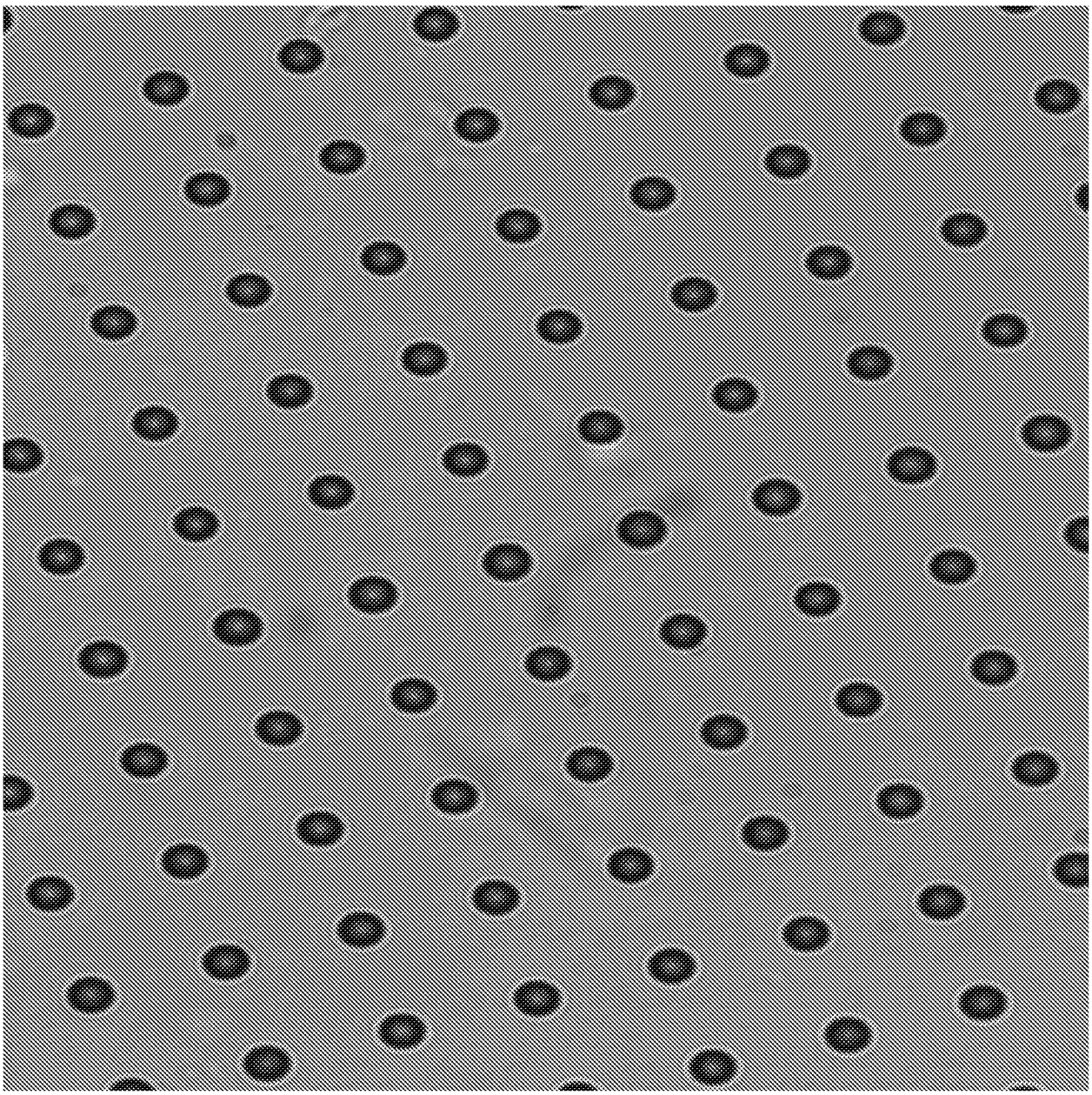


FIG. 27B

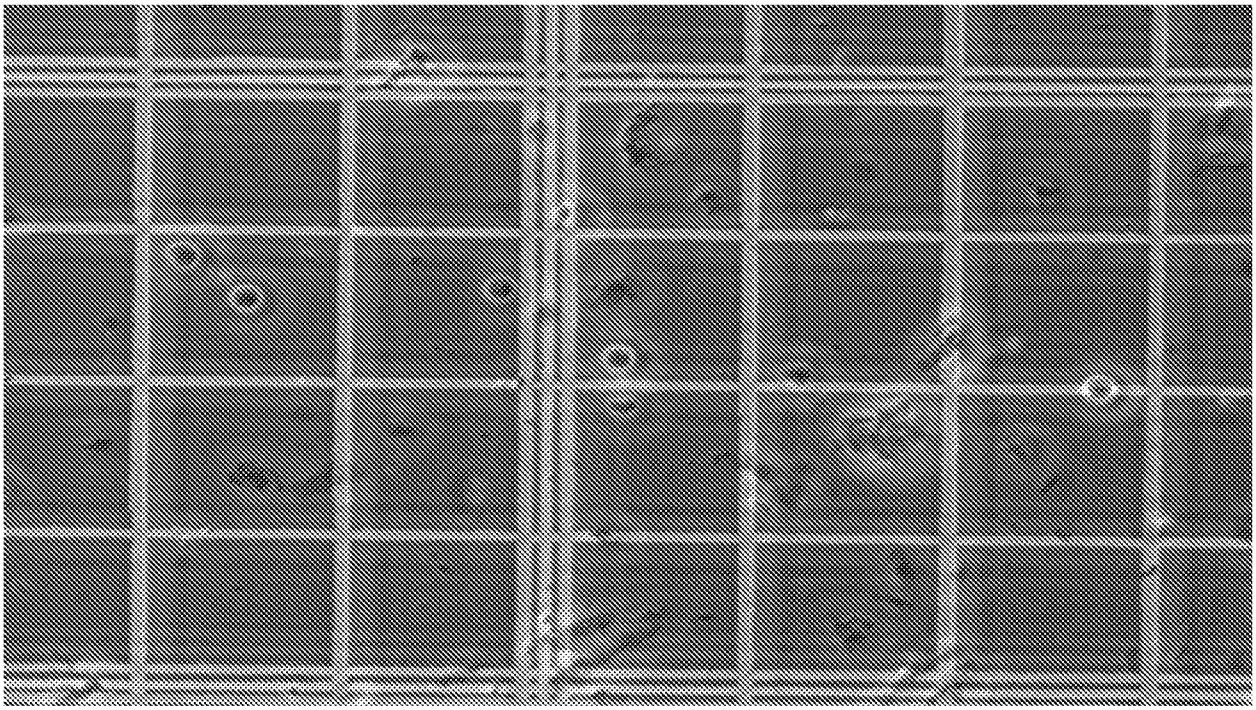


FIG. 27C

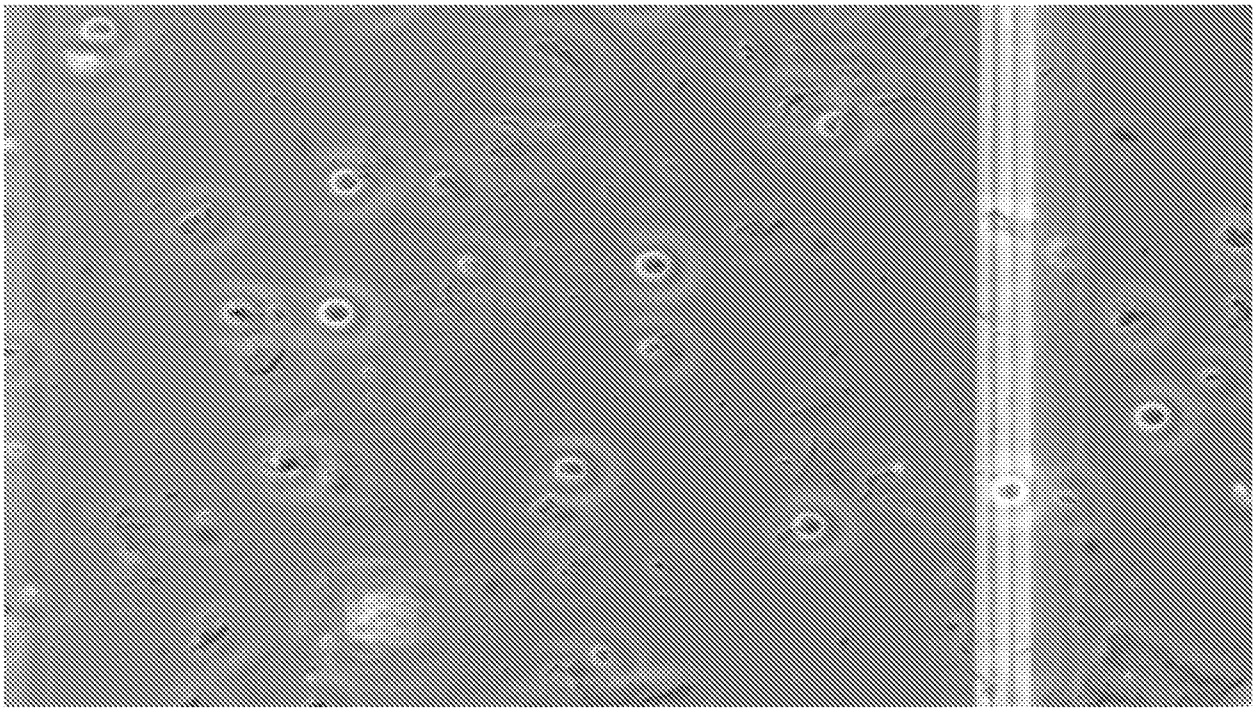


FIG. 28A

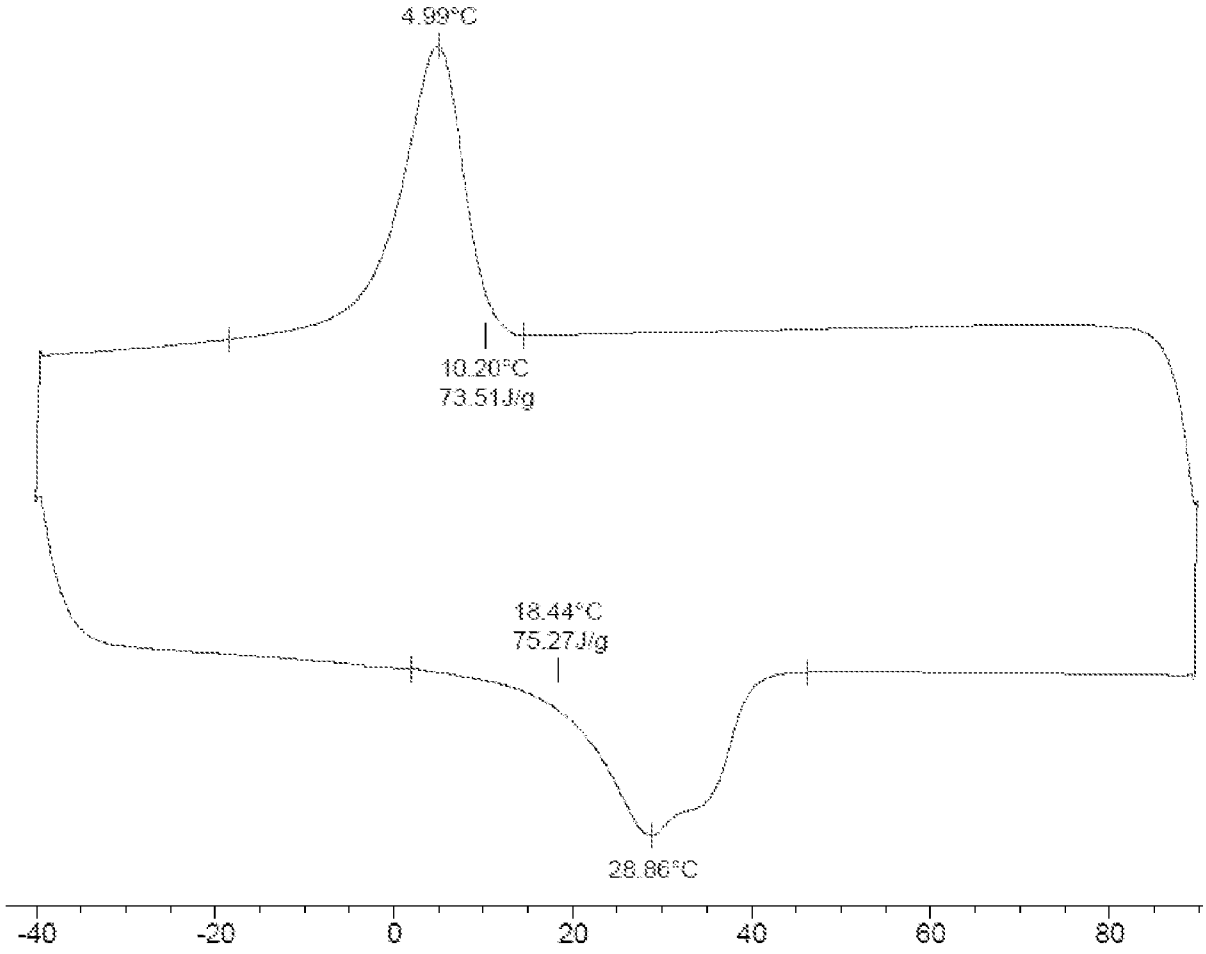


FIG. 28B

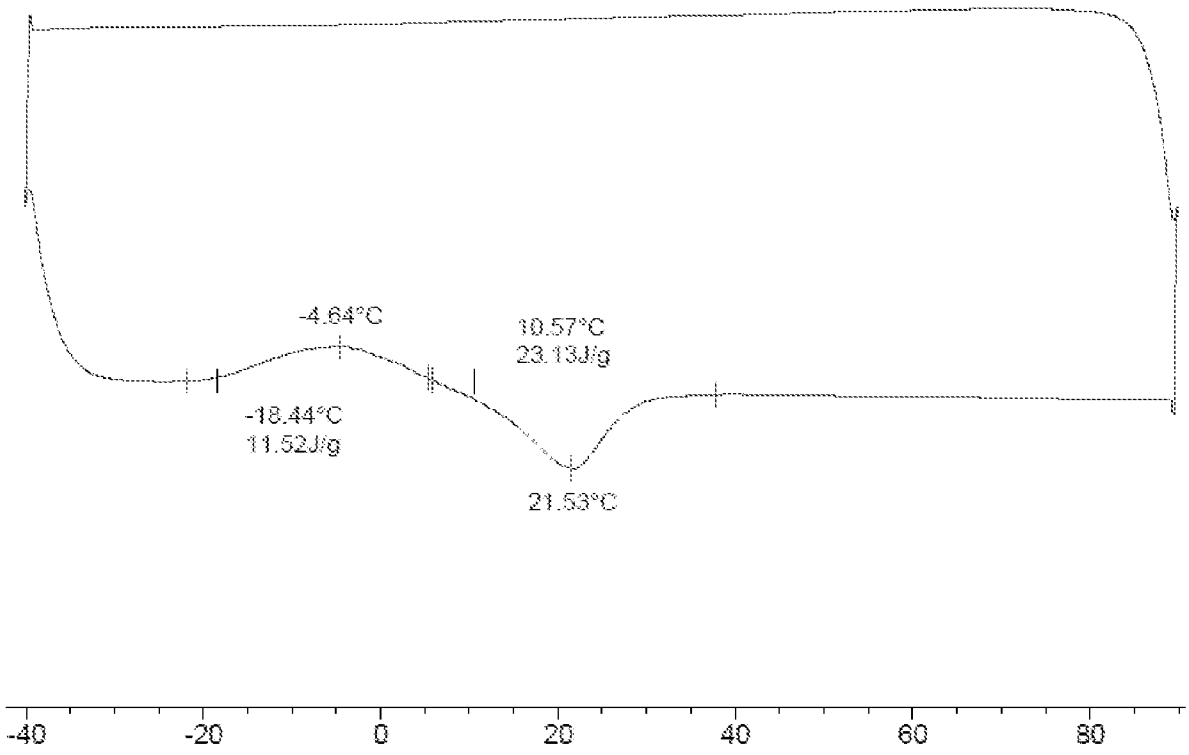


FIG. 28C

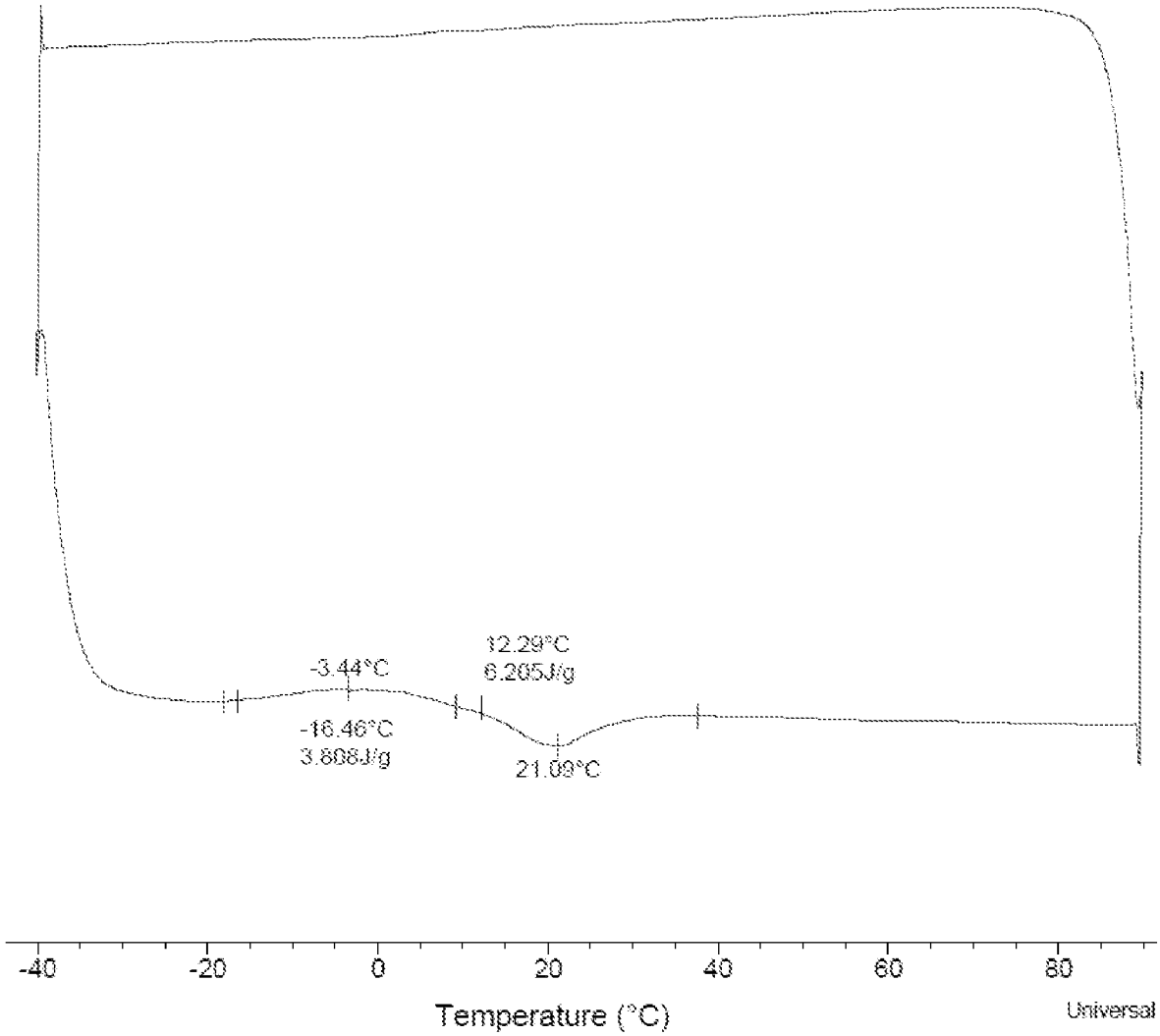

12.29°C
6.205J/g
-3.44°C
-16.46°C
3.808J/g
21.09°C
-40
-20
0
20
40
60
80
Temperature (°C)
Universal

FIG. 29A

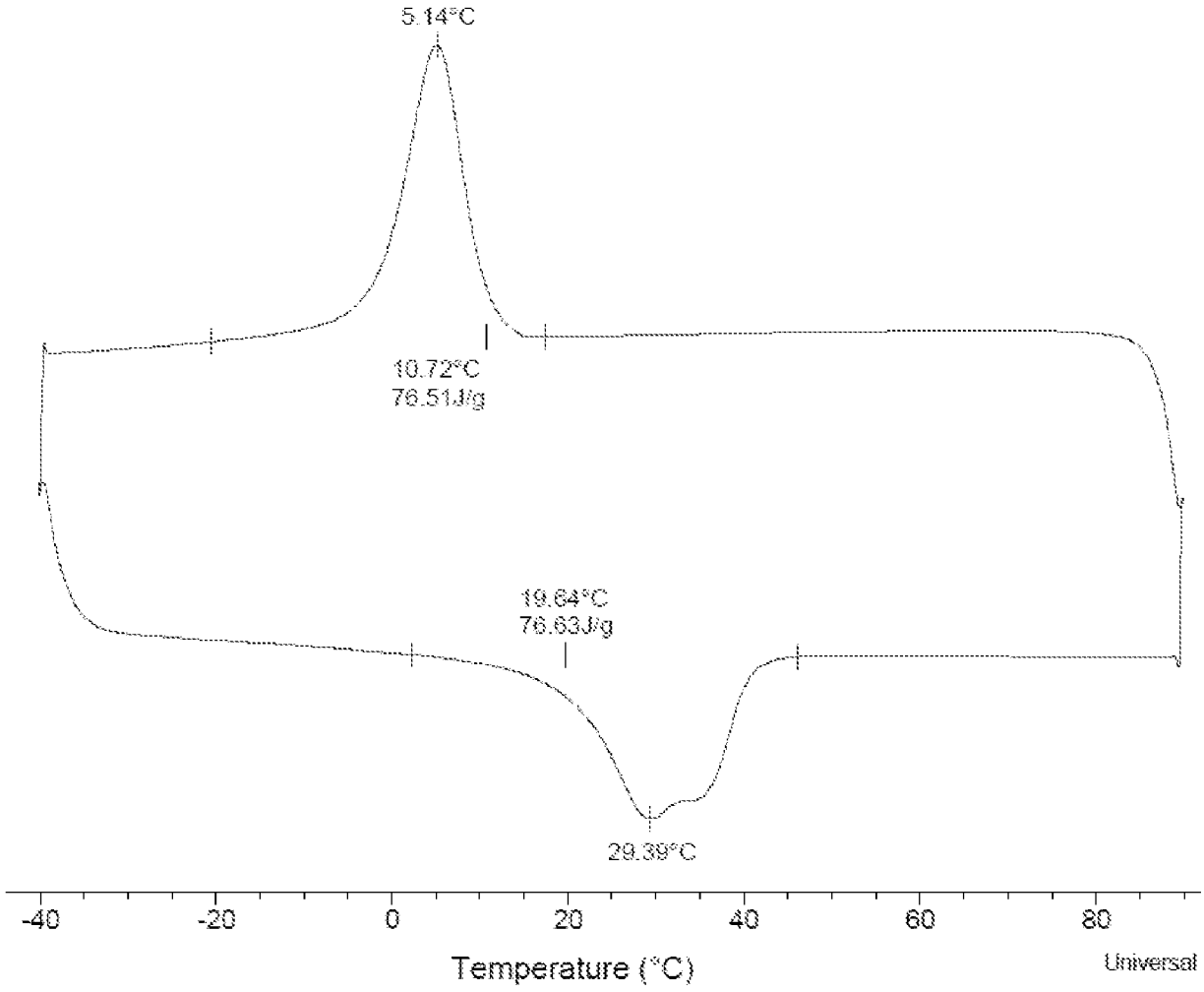

5.14°C
10.72°C
76.51J/g
19.64°C
76.63J/g
29.39°C
-40
-20
0
20
40
60
80
Temperature (°C)
Universal

FIG. 29B

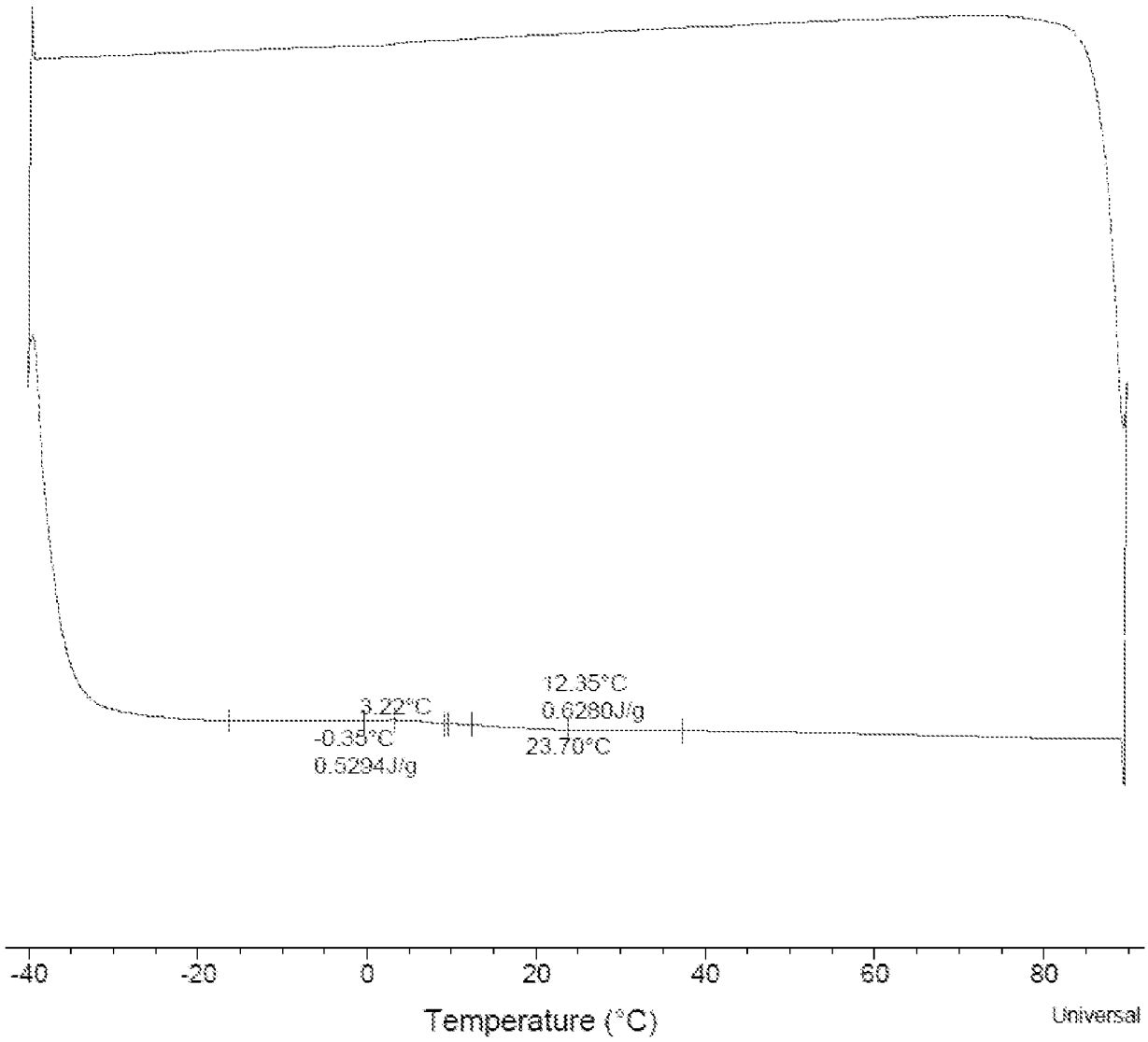
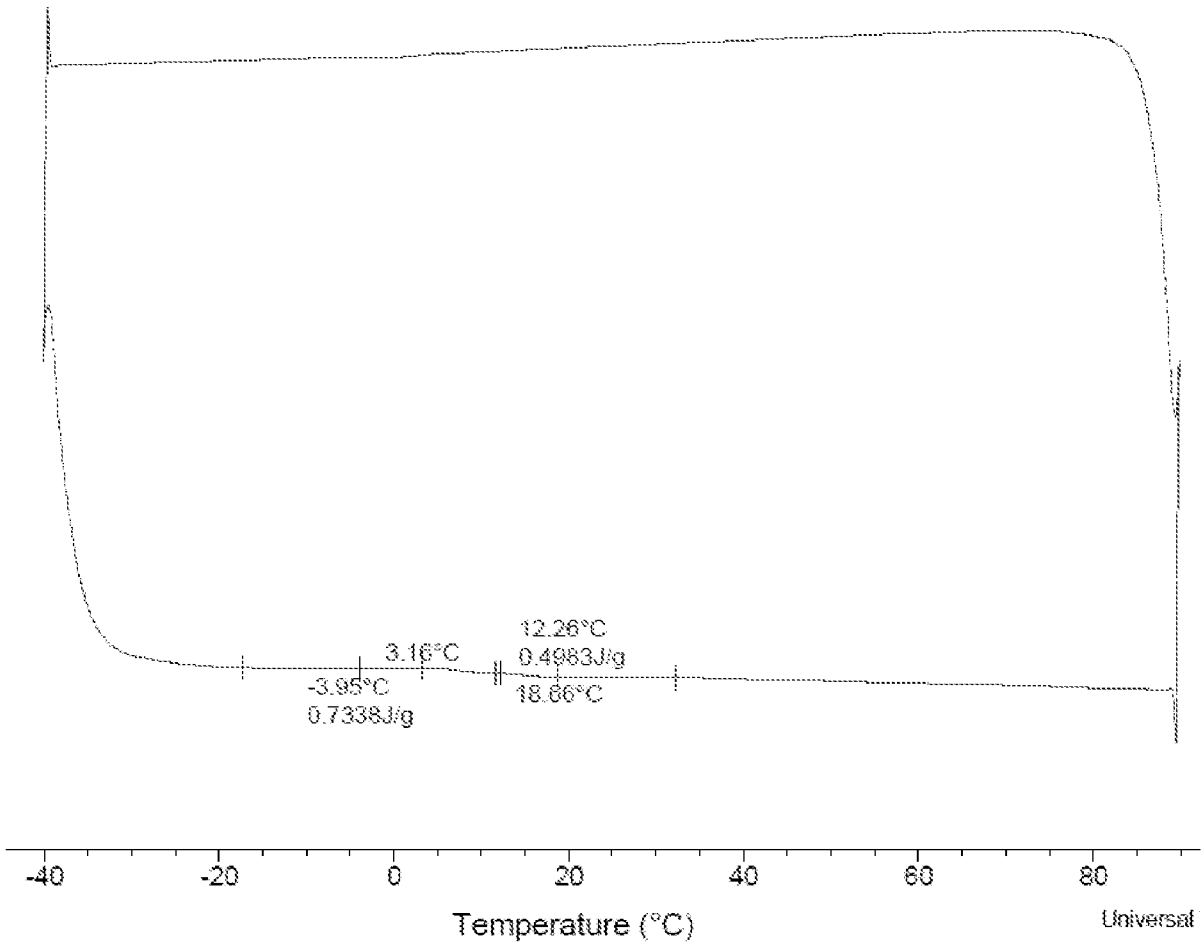

12.35°C
0.6280J/g
3.22°C
-0.35°C
0.5294J/g
23.70°C
-40
-20
0
20
40
60
80
Temperature (°C)
Universal

FIG. 29C


12.26°C
0.4983J/g
3.16°C
-3.95°C
0.7338J/g
18.66°C
-40
-20
0
20
40
60
80
Temperature (°C)
Universal

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 16/56135

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C08J 9/16, C08J 9/22 (2017.01)
CPC - C08J 2367/02, C08J 9/16
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)
IPC(8)- C08J 9/16, C08J 9/22 (2017.01)
CPC- C08J 2367/02, C08J 9/16

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Google Patents, Google Scholar (without Patents)
Keywords:crosslinked degradable particle polyester backbones polyester backbones thioethers , triazoles amides drug dispersed

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2013/0142733 A1 (Harth et al.) 06 June 2013 (06.06.2013) Abstract, para [0006], para [0014], para [0012], para [00648], para [00350], para [00287], para [00286], para [0063], para [0067], para [0024], para [0098], para [00212], para [00174], para [0027], para [00352], para [00401], para [00308], para [00402], para [00413], para [00414], para [00398] and full document	1-83,220
A	US 2011/0257343 A1 (Harth et al.) 20 October 2011 (20.10.2011) Abstract, para [0006]-[0035]	1-83,220
A	US 2006/0239924 A1 (Bolotin) 26 October 2006 (26.10.2006) Abstract, para [0007]-[0023]	1-83,220
A	US 2008/0145338 A1 (Anderson et al.) 19 June 2008 (19.06.2008) Abstract, para [0008]-[0049]	1-83,220
A	US 2005/0020734 A1 (Asgarzadeh et al.) 27 January 2005 (27.01.2005) Abstract, par[028]-[041]	1-83,220
X,E	WO 2016/174116 A1 (Eggplant SRL) 03 November 2016 (03.11.2016) Abstract, pages 5-6	1-83,220

☐ 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	Date of mailing of the international search report
07 February 2017	27 FEB 2017
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

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 16/56135

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:

----------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.:
1-83,220

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

International application No.
PCT/US 16/56135

----------continued from Box III----------

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.

Group I: Claims 1-83 and 220 directed to a crosslinked degradable particle and method of treating disease, comprising: a plurality of polyester backbones, wherein the plurality of polyester backbones are crosslinked via thioethers , triazoles, or amides; and a drug dispersed within the crosslinked degradable particle

Group II: Claims 84-91 and 221-253 directed to a method of preparing a crosslinked degradable particle by evaporating at least a portion of the solvent from the emulsion.

Group III: Claims 92-110 directed to a method of reducing aggregation of a plurality of crosslinked degradable particles, comprising attaching a plurality of polyethylene glycol chains to an exterior of the plurality of crosslinked degradable particles.

Group IV: Claims 111-129, directed to a method of dispersing a drug within a crosslinked degradable particle, comprising: swelling the crosslinked degradable particle with a solvent to form a swollen crosslinked degradable particle, wherein the solvent further comprises a drug dispersed therein; and removing the crosslinked degradable particles from the solvent.

Group V: Claims 130-159, directed to a method of preparing a crosslinked degradable implant, comprising: dissolving a polyester containing a plurality of functional groups and a crosslinker in at least one solvent to form a solution; treating the solution to react the crosslinker with two of the functional groups to form a crosslink; wherein the crosslinked degradable implant has a diameter of at least about 1 millimeter

Group VI: Claims 160-219, directed to a method of controlling an average size of a distribution of crosslinked degradable particles, comprising: preparing a plurality of molds of uniform size and shape; combining a polyester containing a plurality of functional groups and a crosslinker to form a mixture; dispersing the mixture within the molds; and treating the mixture to react the crosslinker with two of the functional groups to form a crosslink

Group VII: Claims 254, directed to a crosslinked degradable particle, comprising: a polyester backbone of the Formula I,

Group VIII: Claims 255, directed to a crosslinked degradable particle, comprising: a polyester backbone of the Formula II

Group IX: Claims 256, directed to a crosslinked degradable particle, comprising: a polyester backbone of the Formula III

Group X: Claims 257, directed to a crosslinked degradable particle, comprising: a polyester backbone of the Formula IV

The group of inventions listed above 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 II includes a method of preparing a crosslinked degradable particle by evaporating at least a portion of the solvent from the emulsion, which is not required by Groups I and III-X

Group III includes a method of reducing aggregation of a plurality of crosslinked degradable particles, comprising attaching a plurality of polyethylene glycol chains to an exterior of the plurality of crosslinked degradable particles, which is not required by Groups I-II and IV-X

Group IV includes a method of dispersing a drug within a crosslinked degradable particle, comprising: swelling the crosslinked degradable particle with a solvent to form a swollen crosslinked degradable particle, wherein the solvent further comprises a drug dispersed therein; and removing the crosslinked degradable particles from the solvent, which is not required by Groups I-III and V-X

Group V includes method of preparing a crosslinked degradable implant, comprising: dissolving a polyester containing a plurality of functional groups and a crosslinker in at least one solvent to form a solution; treating the solution to react the crosslinker with two of the functional groups to form a crosslink; wherein the crosslinked degradable implant has a diameter of at least about 1 millimeter, which is not required by Groups I-IV and VI-VIII

Group VI includes a method of controlling an average size of a distribution of crosslinked degradable particles, comprising: preparing a plurality of molds of uniform size and shape; combining a polyester containing a plurality of functional groups and a crosslinker to form a mixture; dispersing the mixture within the molds; and treating the mixture to react the crosslinker with two of the functional groups to form a crosslink, which is not required by Groups I-V and VII-X

Group VII includes a polyester backbone of the Formula I, which is not required by Groups I-VI and VIII-X

Group VIII includes a polyester backbone of the Formula II, which is not required by Groups I-VII and IX-X

Group IX includes a polyester backbone of the Formula III, which is not required by Groups I-VIII and X

Group X includes a polyester backbone of the Formula IV, which is not required by Groups I-IX

----------continued in supplemental box ----------

----------continued from Box III----------

Common technical features:

Groups I-X share the technical feature of a crosslinked degradable particle

Groups I and III share the technical feature of plurality of crosslinked degradable particles

Groups I and IV share the technical feature of dispersing a drug within a crosslinked degradable particle.

Groups VII-X share the technical feature of polyester polyol fraction of formula I-IV.

These shared technical feature, however, do not provide a contribution over the prior art, as being as being anticipated by US 2011/0257343 A1 to Harth et al. (hereinafter 'Harth') Harth teaches plurality of crosslinked degradable particles (see abstract; crosslinked polymers, functionalized polymers, nanoparticles, and functionalized nanoparticles and methods of making and using same?. degradable polymer and degradable nanoparticles..) and dispersing a drug within a crosslinked degradable particle (para [0109], ..njectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide..). Harth further teaches polyester polyol fraction of formula I-IV (see scheme 6-7, page 77, 79; page 76, formula)

As said method was known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the inventions of Groups I-X. The inventions of Groups I-X, thus, lack unity under PCT Rule 13.

Note:

claim 86 is improperly depending from claim 82. For the purpose of completing this ISR, claim 86 is assumed as it is depending from claim 85.

claim 87 is improperly depending from claim 83. For the purpose of completing this ISR, claim 87 is assumed as it is depending from claim 86

claim 91 is improperly depending from claim 87. For the purpose of completing this ISR, claim 91 is assumed as it is depending from claim 86

claim 93 is improperly depending from claim 89. For the purpose of completing this ISR, claim 93 is assumed as it is depending from claim 92

claims 94-97 are improperly depending from claim 90. For the purpose of completing this ISR, claim 94 is assumed as it is depending from claim 93

claims 98-99 are improperly depending from claim 89. For the purpose of completing this ISR, claims 98-99 are assumed as they are depending from claim 92

claims 103 and 108-110 are improperly depending from claim 89. For the purpose of completing this ISR, claims 103 and 108-110 are assumed as they are depending from claim 92

Claims 112-114, 124-126 depend on the method of claim 111. claim 111 lack antecedent basis for ?the polymer backbones?.

claim 142 is improperly depending from claim 127. For the purpose of completing this ISR, claim 142 is assumed as it is depending from claim 130

claim 143 is improperly depending from claim 136. For the purpose of completing this ISR, claim 143 is assumed as it is depending from claim 142

claims 153-155 are improperly depending from claim 130. For the purpose of completing this ISR, claims 153-155 are assumed as they are depending from claim 152

claim 163 is improperly depending from claim 152. For the purpose of completing this ISR, claim 163 is assumed as it is depending from claim 162

claim 196 is improperly depending from claim 188. For the purpose of completing this ISR, claim 196 is assumed as it is depending from claim 195

claim 205 is improperly depending from claim 203. For the purpose of completing this ISR, claim 205 is assumed as it is depending from claim 204