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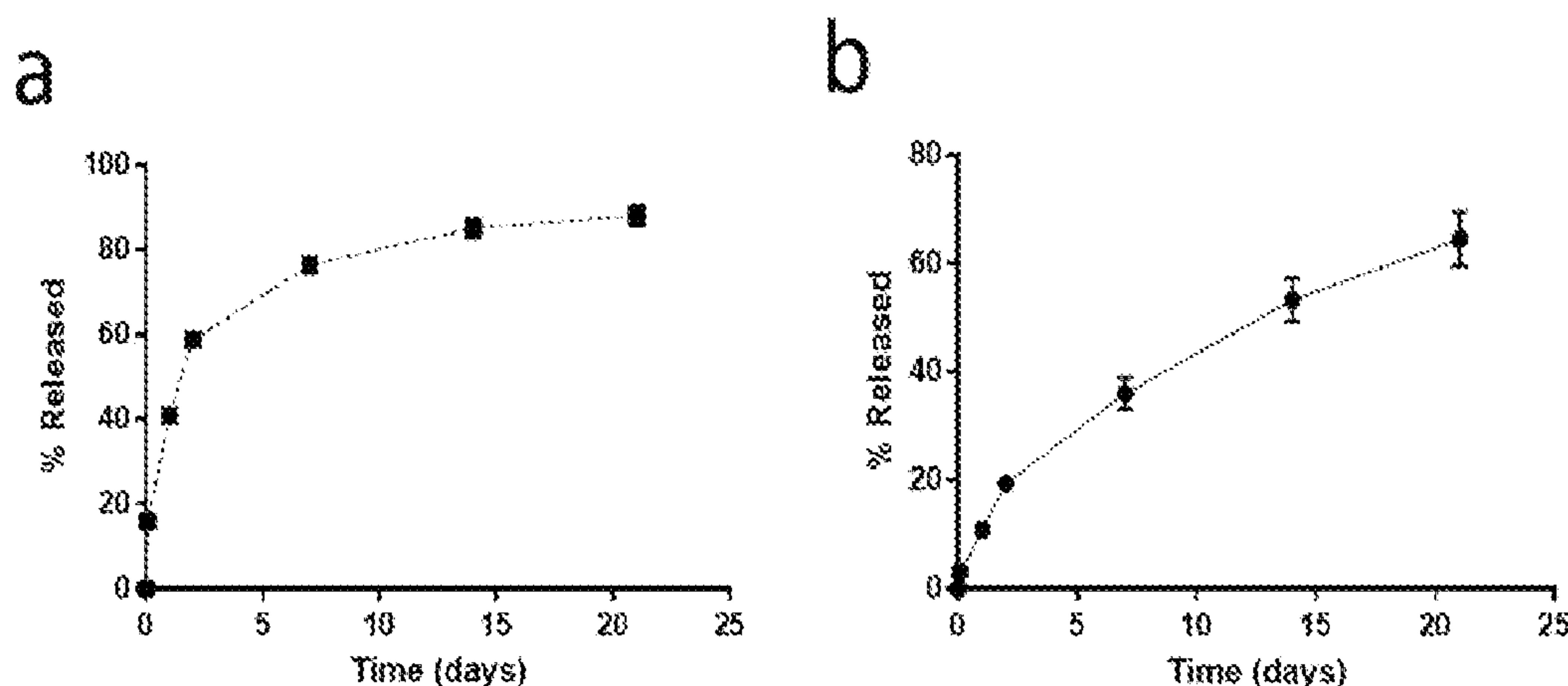
(71) Demandeur/Applicant:  
PIXARBIO CORPORATION, US

(72) Inventeurs/Inventors:  
CRISCIONE, JASON, M., US;  
WERTH, NICHOLAS, B., US;  
REYNOLDS, FRANCIS, M., US;  
DAI, HAINING, US;  
LANGER, ROBERT, S., US;  
ARMSTRONG, PATRICK, A., US;  
CHEN, XI, US

(74) Agent: SMART & BIGGAR

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ET LEURS PROCEDES D'UTILISATION  
(54) Title: COMPOSITIONS FOR TREATING ACUTE, POST-OPERATIVE, OR CHRONIC PAIN AND METHODS OF  
USING THE SAME

**FIG. 3**



(57) Abrégé/Abstract:

Provided herein are compositions for treating acute, chronic, or post-operative pain in a subject, said compositions comprising an anticonvulsant agent and a biodegradable carrier, wherein the agent is incorporated within the biodegradable carrier. Methods of treating pain in a subject and kits for producing compositions for treating acute, chronic or post-operative pain in a subject are also disclosed herein.

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(74) Agents: MURPHY, John, F. et al.; Baker & Hostetler LLP, 2929 Arch Street, Cira Center, 12th Floor, Philadelphia, PA 19104-2891 (US).

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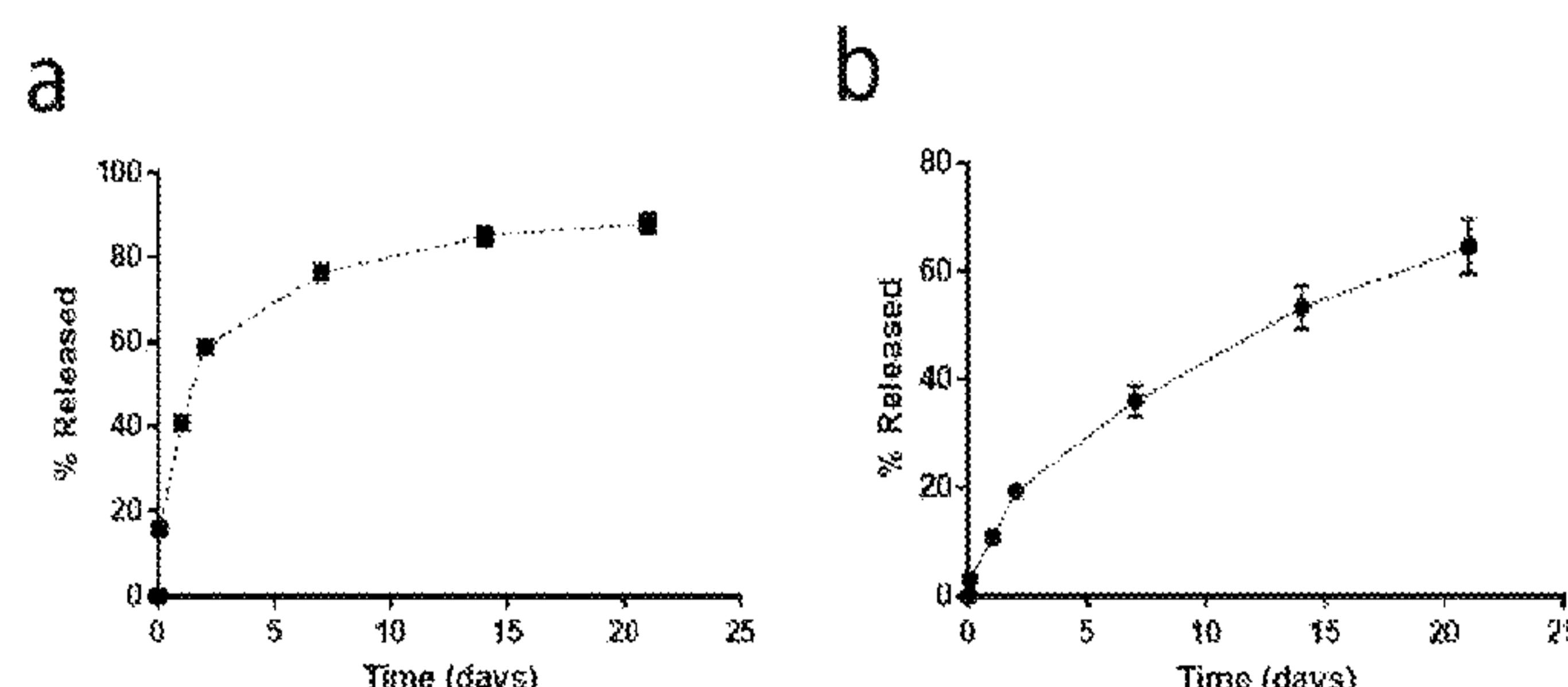
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(71) Applicant: PIXARBIO CORPORATION [US/US]; 200 Boston Ave., Suite 1875, Medford, MA 02155 (US).

(72) Inventors: CRISCIONE, Jason, M.; 29 Singlefoot Rd., Chelmsford, MA 01824 (US). WERTH, Nicholas, B.; 3 Highland St., Reading, MA 01867 (US). REYNOLDS, Francis, M.; 81 Lake Shore Rd., Salem, NH 03079 (US). DAI, Haining; 1087 Copperstone Ct., Rockville, MD 20852 (US). LANGER, Robert, S.; 98 Montvale Rd., Newton, MA 02459 (US). ARMSTRONG, Patrick, A.; 1125 Commonwealth Ave., Apt. #32, Boston, MA 02134 (US). CHEN, Xi; 43 Meyer Hill Dr., Acton, MA 01720 (US).

(54) Title: COMPOSITIONS FOR TREATING ACUTE, POST-OPERATIVE, OR CHRONIC PAIN AND METHODS OF USING THE SAME

FIG. 3



(57) Abstract: Provided herein are compositions for treating acute, chronic, or post-operative pain in a subject, said compositions comprising an anticonvulsant agent and a biodegradable carrier, wherein the agent is incorporated within the biodegradable carrier. Methods of treating pain in a subject and kits for producing compositions for treating acute, chronic or post-operative pain in a subject are also disclosed herein.

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## COMPOSITIONS FOR TREATING ACUTE, POST-OPERATIVE, OR CHRONIC PAIN AND METHODS OF USING THE SAME

### CROSS-REFERENCE TO RELATED APPLICATIONS

**[0001]** The present application claims priority to U.S. Provisional Application No. 62/081,162, filed November 18, 2014, the entire contents of which are incorporated herein by reference.

### TECHNICAL FIELD

**[0002]** Provided herein are compositions, methods, and kits for treating acute, post-operative, or chronic pain in a subject.

### BACKGROUND

**[0003]** Clinical management of acute, post-operative pain, or chronic pain predominantly comprises administration of opioids (e.g. morphine), local anesthetics (e.g. bupivacaine) and/or steroids (e.g. methylprednisolone). Traditional methods of acute pain management often necessitate longer hospitalization or clinical care. Long-term, systemic use of opioids has well-established side effects, including addiction, thus, alternatives to their use in the management of acute and/or post-operative pain is clinically desired. Extended, local delivery of anesthetics (e.g. bupivacaine) is effective, however the longevity of this approach is greatly restricted because of inherent toxicity concerns and associated motor deficits. Toxicity also limits therapeutic regimens of steroids for management of chronic pain indications.

**[0004]** Anticonvulsants have been shown to be useful in the treatment and management of many pain indications, as this class of drugs is known to exert important biochemical effects on nerve cells. Such effects reduce the tendency for nerves to transmit signals, and hence, drugs that have an antiepileptic effect are known to reduce the tendency for nerves to send pain signals to the brain. Most drugs belonging to these classes, however, have short circulation half-lives and considerable side effects including, but not limited to, sedation, vertigo, diplopia, skin rash, nausea, vomiting, chronic diarrhea, aplastic anemia, thrombocytopenia, jaundice, oliguria, hypertension, cardiac dysrhythmias, chronic suppression of white blood cell counts, and hyponatremia. These side effects limit the potential systemic therapeutic use of anticonvulsants for the management of pain. Consequently, physicians cannot always dose enough drug to have the desired anti-pain effect without causing problematic, pleiotropic systemic side effects. Local delivery of anticonvulsants would abrogate these pleiotropic, systemic side effects and enable

their therapeutic intervention for the management of pain. For example, a localized injection of a depot formulation of an anticonvulsant agent would permit the use of a lower initial dose than would be required for systemic or oral administration of the agent because the depot would establish therapeutically efficacious concentrations of the agent specifically at the desired site of action.

**[0005]** There remains an outstanding need for formulations comprising anticonvulsant agents that can provide desirable release profiles and that possess physical characteristics that are consistent with clinical translation as an injectable.

## SUMMARY

**[0006]** Provided herein are compositions for treating acute, post-operative, or chronic pain in a subject. In some embodiments, the compositions comprise an anticonvulsant agent and a biodegradable carrier.

**[0007]** Methods of treating acute, post-operative, or chronic pain comprising administering to a subject having the pain a composition comprising an anticonvulsant agent and a biodegradable carrier are also disclosed herein.

**[0008]** Further provided are kits for producing compositions for treating acute, post-operative, or chronic pain in a subject.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0009]** FIG. 1 illustrates an exemplary biodegradable, polymeric nanoparticle or microparticle releasing an anticonvulsant agent.

**[0010]** FIG. 2 shows a representative scanning electron micrograph of PLGA microparticles incorporating the anticonvulsant carbamazepine.

**[0011]** FIG. 3 shows examples of sustained, controlled release kinetic profiles of the anticonvulsant carbamazepine from PLGA microparticles comprising PLGA with inherent viscosities of (a) 0.15-0.25 dL/g and (b) 0.55-0.75 dL/g.

**[0012]** FIG. 4 shows an example of a sustained, controlled release kinetic profile of the anticonvulsant carbamazepine from poly(D,L-lactide) (PLA) microparticles.

## DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

**[0013]** The disclosed compositions, methods, and kits may be understood more readily by reference to the following detailed description taken in connection with the accompanying figures, which form a part of this disclosure. It is to be understood that the disclosed

compositions, methods, and kits are not limited to the specific compositions, methods, and kits described and/or shown herein, and that the terminology used herein is for the purpose of describing particular embodiments by way of example only and is not intended to be limiting of the claimed compositions, methods, and kits. Also, as used in the specification including the appended claims, the singular forms “a,” “an,” and “the” include the plural, and reference to a particular numerical value includes at least that particular value, unless the context clearly dictates otherwise. When a range of values is expressed, another embodiment includes from the one particular value and/or to the other particular value. Further, reference to values stated in ranges include each and every value within that range. All ranges are inclusive and combinable. Similarly, when values are expressed as approximations, by use of the antecedent “about,” it will be understood that the particular value forms another embodiment.

**[0014]** It is to be appreciated that certain features of the disclosed compositions, methods, and kits which are, for clarity, described herein in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the disclosed compositions, methods, and kits that are, for brevity, described in the context of a single embodiment, may also be provided separately or in any subcombination.

**[0015]** The term “about” when used in reference to numerical ranges, cutoffs, or specific values is used to indicate that the recited values may vary by up to as much as 25% from the listed value. As many of the numerical values used herein are experimentally determined, it should be understood by those skilled in the art that such determinations can, and often times will, vary among different experiments. The values used herein should not be considered unduly limiting by virtue of this inherent variation. The term “about” is used to encompass variations of  $\pm 25\%$  or less, variations of  $\pm 20\%$  or less, variations of  $10\%$  or less, variations of  $\pm 5\%$  or less, variations of  $\pm 1\%$  or less, variations of  $\pm 0.5\%$  or less, or variations of  $\pm 0.1\%$  or less from the specified value.

**[0016]** As used herein, “administering to said subject” and similar terms indicate a procedure by which the described anticonvulsant agents or compositions, together or separately, are introduced into, implanted in, injected into, or applied onto a subject such that target cells, tissues, or segments of the body of the subject are contacted with the agent.

**[0017]** The terms “near” and “around” when used in reference to the site of administration of the described anticonvulsant agents or compositions should be understood by those skilled in the art to mean administered to the anatomical area of interest within the limits of traditionally practiced surgical and image-guided surgical procedures. For example,

administration “near” the relevant anatomical site refers to a location that is not directly within or on the site, but sufficiently close to the site to provide a therapeutically relevant effect thereon. Those of ordinary skill in the art can readily determine the maximum distance from a given anatomical site that will be sufficient to provide a therapeutically relevant effect using a composition according to the present disclosure having a known concentration of active ingredient.

**[0018]** “Pharmaceutically acceptable” refers to those properties and substances which are acceptable to the patient from a pharmacological/toxicological point of view and to the manufacturing pharmaceutical chemist from a physical/chemical point of view regarding composition, formulation, stability, patient acceptance, and bioavailability.

**[0019]** “Pharmaceutically acceptable carrier” refers to a medium that does not interfere with the effectiveness of the biological activity of the active ingredient(s) and is not toxic to the host to which it is administered.

**[0020]** “Therapeutically effective dose” refers to an amount of a composition, as described herein, effective to achieve a particular biological or therapeutic result such as, but not limited to, biological or therapeutic results disclosed, described, or exemplified herein. The therapeutically effective dose may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the composition to cause a desired response in a subject. Such results may include, but are not limited to, the treatment of acute, post-operative or chronic pain, as determined by any means suitable in the art.

**[0021]** The terms “treating” or “treatment” refer to any success or indicia of success in the attenuation or amelioration of an injury, pathology or condition, including any objective or subjective parameter such as abatement, remission, diminishing of symptoms or making the injury, pathology, or condition more tolerable to the patient, slowing in the rate of inflammation, making the final point of inflammation less debilitating, improving a subject’s physical or mental well-being, or prolonging the length of survival. The treatment may be assessed by objective or subjective parameters; including the results of a physical examination, neurological examination, or psychiatric evaluations.

**[0022]** As used herein, “exposed on the surface” means that at least a portion of the anticonvulsant agent is not covered or encased by the biodegradable carrier and is accessible from the exterior of the biodegradable carrier. The anticonvulsant agent exposed on the surface can be fully exposed, such that the entire agent is on the surface of the biodegradable carrier, or can be partially exposed, such that only a portion of the agent is on the surface of the

biodegradable carrier. The anticonvulsant agent that is exposed on the surface of the biodegradable carrier can be bound to the surface of the biodegradable carrier through, for example, covalent or non-covalent bonds, or can be incorporated within the biodegradable carrier such that a portion of the agent is exposed on the surface.

**[0023]** As used herein, “incorporated within” means that the anticonvulsant agent is at least partially covered by, contained within, encased in, or entrapped by the biodegradable carrier. In such circumstances, the anticonvulsant agent may or may not be exposed on the surface of the biodegradable carrier. Depending on the type of biodegradable carrier present in the composition, the anticonvulsant agent may be located in a void space, such as a core, of the biodegradable carrier or dispersed within the biodegradable carrier with the potential for being exposed on the surface, or any combination thereof. In some embodiments, the anticonvulsant agent can be dispersed or distributed within the biodegradable carrier, and not partially exposed on the surface of the biodegradable carrier. In other embodiments, the anticonvulsant agent can be partially exposed on the surface of the biodegradable carrier. In other embodiments, the anticonvulsant agent can be both dispersed or distributed within the biodegradable carrier and partially exposed on the surface of the biodegradable carrier. In yet other embodiments, the anticonvulsant agent can be located in a void space of the biodegradable carrier. In yet other embodiments, the anticonvulsant agent can be both located in a void space of the biodegradable carrier and exposed on the surface of the biodegradable carrier.

**[0024]** Biodegradable, polymeric microparticles and nanoparticles represent an attractive means to achieve the desired local delivery of therapeutic agents, often by administration of a depot formulation. These particles can be fabricated by a variety of techniques to incorporate neurologically active therapeutic agents, including, anticonvulsants. The fabrication technique dictates the physical, chemical, and mechanical properties of the resulting particles. Thus, to achieve desired therapeutically efficacious concentrations and durations, the fabrication technique and polymer must be selected appropriately. For example, buoyant poly(D,L-lactide-co-glycolide) (PLGA) microspheres were created by oil-in-oil emulsification to encapsulate and deliver hydrophilic small-molecule agents (e.g. inosine) for intrathecal administration for the treatment of central nervous system disorders (WO2004/047768).

**[0025]** The formulation of anticonvulsants within different biodegradable implants or carriers has been examined for achieving sustained therapeutic efficacy in epilepsy [*see, e.g.*, Halliday *et al.*, *Adv Drug Deliv Rev.*, 2012, 64(10):953-64]. To these ends, the anticonvulsant,

carbamazepine, has been studied as a model drug for incorporation within these types of devices [Klose *et al.*, *Inter J Pharmaceutics.*, 2011, 404:75-82; Barakat *et al.*, *Drug Deliv.*, 2006, 13(1):9-18; Pepic *et al.*, *J Microencapsulation.*, 2013, 30(2):151-160]; however, in these reports, the fabrication technique, polymer, and size were not selected appropriately to yield a clinically relevant drug delivery system for the treatment of acute, post-operative, or chronic pain indications.. For example, different water-in-oil-in-water (w/o/w) double emulsification techniques have been utilized to fabricate either large, highly porous [Klose *et al.*, *Inter J Pharmaceutics.*, 2011, 404:75-82] or large, solid matrix [Barakat *et al.*, *Drug Deliv.*, 2006, 13(1):9-18] biodegradable poly(D,L-lactide-co-glycolide) (PLGA) microparticles incorporating carbamazepine. In both reports, the large particle size is necessary to extend the release duration, however, these forms are impractical for clinical translation as an injectable. Additionally, the intentional high, micro-scale porosity of the microparticles fabricated by Klose *et al.*, limits the ability for sustained, long-term release applications. Further, the carbamazepine within the solid matrix microparticles fabricated by Barakat *et al.*, is predominantly distributed on or within close proximity to the microparticle surface. This predominantly surface-associated carbamazepine gives rise to the observed high initial burst release and inability to sustain the release of therapeutically relevant concentrations. Furthermore, Pepic *et al.*, utilized an oil-in-water (o/w) single emulsification technique to fabricate large, porous poly( $\epsilon$ -caprolactone) (PCL) microspheres incorporating carbamazepine. In this report, the high hydrophobic character and crystallinity of the PCL causes extremely slow biodegradation that is too slow to be clinically relevant as a biodegradable carrier for therapeutic delivery in the treatment of acute, post-operative, or chronic pain indications. This slow biodegradation combined with the porosity inherent to the PCL polymer matrix causes the carbamazepine release mechanism to be solely diffusion-based, rather than biodegradation-based, necessitating large particle sizes to extend release. These large particle sizes reported are also impractical for clinical translation as an injectable. Further, the carbamazepine within the polymer matrix was observed to be predominantly distributed on or within close proximity to the microparticle surface. This predominantly surface-associated carbamazepine gives rise to the observed high initial burst release and inability to sustain the release of therapeutically relevant concentrations.

**[0026]** The present disclosure provides compositions that are formulated specifically to enable 1) control of anticonvulsant agent incorporation, including substantially even distribution throughout the polymer matrix, 2) control over anticonvulsant agent release rate, 3) clinically relevant biodegradation rates, and 4) control over the duration of anticonvulsant agent release at

therapeutically efficacious concentrations, including sustained release for an extended period of time, such as two weeks or more, from nanoparticles or microparticles that have sufficiently small mean and/or median hydrodynamic diameters up to 25 microns, inclusive, as measured by laser diffraction or dynamic light scattering in aqueous solution, to enable clinical administration as an injectable. Suitable instrumentation for aqueous solution phase laser diffraction includes the Malvern Instruments™ Mastersizer® 3000 equipped with the Hydro MV unit. Suitable instrumentation for aqueous solution phase dynamic light scattering includes the Malvern Instruments™ ZetaSizer® Nano ZS. Also described herein are methods for using these specifically designed compositions for the treatment of acute, post-operative, or chronic pain.

**[0027]** Disclosed herein are compositions for treating acute, post-operative, or chronic pain in a subject. In some embodiments, the compositions comprise an anticonvulsant agent and a biodegradable carrier. In other embodiments, the composition consists of an anticonvulsant agent and a biodegradable carrier.

**[0028]** Suitable anticonvulsant agents include, but are not limited to, carbamazepine, pregabalin, phenytoin, gabapentin, topiramate, oxcarbazepine, or any combination thereof. In some embodiments, the anticonvulsant is carbamazepine. In some embodiments, the anticonvulsant is gabapentin. In some embodiments, the anticonvulsant is pregabalin.

**[0029]** Suitable biodegradable carriers include, but are not limited to, a nanoparticle, a microparticle, or any combination thereof. In some embodiments, the biodegradable carrier is a nanoparticle. In some embodiments, the biodegradable carrier is a microparticle. In some embodiments, the biodegradable carrier is a nanoparticle. In some embodiments, the biodegradable carrier is a nanoparticle.

**[0030]** Suitable classes of nanoparticles or microparticles include, but are not limited to, polymeric. Further, said nanoparticles or microparticles may be solid, hollow, or a mixture thereof. Further, said nanoparticles or microparticles may be porous, wherein the porosity is defined solely by the density and packing arrangement of the polymer matrix and the incorporated anticonvulsant agent.

**[0031]** The disclosed compositions can comprise an anticonvulsant agent and a biodegradable carrier. In some embodiments, the composition comprises carbamazepine and a nanoparticle. In some embodiments, the composition comprises carbamazepine and a microparticle. In some embodiments, the composition comprises phenytoin and a nanoparticle. In some embodiments, the composition comprises phenytoin and a microparticle. In some embodiments, the composition comprises gabapentin and a nanoparticle. In some embodiments,

the composition comprises gabapentin and a microparticle. In some embodiments, the composition comprises pregablin and a nanoparticle. In some embodiments, the composition comprises pregablin and a microparticle. In some embodiments, the composition comprises topiramate and a nanoparticle. In some embodiments, the composition comprises topiramate and a microparticle. In some embodiments, the composition comprises oxcarbazepine and a nanoparticle. In some embodiments, the composition comprises oxcarbazepine and a microparticle.

**[0032]** Anticonvulsant agents also include mixtures of carbamazepine, pregablin, phenytoin, gabapentin, topiramate, and/or oxcarbazepine within the same biodegradable carrier. For example, and without intent to be limiting, in some aspects the composition can comprise carbamazepine and pregablin within a microparticle.

**[0033]** Throughout the present disclosure, the phrase “the anticonvulsant agent” can refer to more than one anticonvulsant agent if more than one such agent is present in the composition. For example, when only one anticonvulsant agent is contained within the biodegradable carrier, a reference to release of “60% of the anticonvulsant agent” means that there is release of 60% of the sole present anticonvulsant. When more than one anticonvulsant agent is contained within the biodegradable carrier, language referring to release of “60% of the anticonvulsant agent”, means that 60% of the total complement of anticonvulsant agents is released. Thus, if the composition includes 3 mg of a first anticonvulsant agent and 3 mg of a second anticonvulsant agent, then release of “60% of the anticonvulsant agent” can mean that 60% of the total complement of 6 mg of anticonvulsant agents is released.

**[0034]** Biodegradable carriers can comprise a number of materials suitable for delivering an anticonvulsant agent to a subject, including synthetically derived, biodegradable polymers. Exemplary polymers include, but are not limited to, poly(lactides) (PLA), poly(glycolides) (PGA), poly(lactide-co-glycolides) (PLGA), or copolymers of said polymers with poly(ethylene glycol)(PEG), or any combination thereof. In some embodiments, the biodegradable carrier comprises or consists of a synthetically derived biodegradable polymer. Additionally, in some embodiments, the synthetically derived biodegradable polymer can be poly(lactic-co-glycolic acid) (PLGA), having a lactic acid and glycolic acid content ranging from 0-100% for each monomer. For example, in some aspects, the biodegradable polymer can be a 50:50 PLGA, where 50:50 refers to the ratio of lactic to glycolic acid. In some embodiments, the biodegradable carrier comprises or consists of a copolymer. For example, in some embodiments, the biodegradable polymer can be a copolymer of poly(ethylene glycol) (PEG) and poly(lactic-

co-glycolic acid) (PLGA), having a lactic acid and glycolic acid content ranging from 0-100% for each monomer.

**[0035]** Biodegradable carriers can be configured to be injected into a subject. For example, in some aspects, the biodegradable carrier comprises a nanoparticle that is configured to be injected into a subject. In other aspects, the biodegradable carrier comprises a microparticle that is configured to be injected into a subject. For injection into a subject, the microparticle or nanoparticle must have a mean or median hydrodynamic diameter of not more than 25 microns, inclusive, as measured by the aforementioned aqueous solution phase laser diffraction or dynamic light scattering instrumentation.

**[0036]** Biodegradable carriers can be configured to be implanted into a subject. Implants can be any size and shape suitable for delivering an anticonvulsant to or near the site of pain.

**[0037]** Biodegradable carriers can further comprise one or more surface modifications. Examples of suitable surface modification include, but are not limited to, functional group modifications, PEGylation or affinity-based targeting moieties. In some embodiments, the biodegradable carrier can be PEGylated. Surface modifications can prevent the carrier from migrating from the site of administration, abrogate the foreign body response, and/or minimize clearance by immune system cells.

**[0038]** The anticonvulsant agent can be exposed on the surface of the biodegradable carrier, incorporated within the biodegradable carrier, or both. In some embodiments, the anticonvulsant agent is incorporated within the biodegradable carrier.

**[0039]** When the anticonvulsant agent is incorporated within the biodegradable carrier, the process of incorporation may be accomplished using solvent extraction/evaporation, oil-in-water (o/w) single emulsification in the presence of a stabilizing surfactant. Suitable surfactants for stabilizing this oil-in-water emulsion include, but are not limited to, poly(vinyl alcohol) (PVA), polysorbate 80, polysorbate 85, poly(ethylene glycol), or any combination thereof.

**[0040]** When the anticonvulsant agent is incorporated within the biodegradable carrier, exemplary polymers for forming the biodegradable carrier include, but are not limited to, PLGA, PLA, PLGA-PEG and PLA-PEG block copolymers, or any combination thereof.

**[0041]** The biodegradable carrier for use in an incorporated system can be chosen to begin to degrade within any suitable time frame following preparation for administration of the composition to a subject. In some embodiments, the biodegradable carrier can begin to degrade

upon resuspension in aqueous media. In some embodiments, the biodegradable carrier can begin to degrade upon administration of the composition to a subject.

**[0042]** Degradation, diffusion, or any combination thereof, can lead to the controlled release of the anticonvulsant agent from the biodegradable carrier. In some embodiments, the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 3 hours. In some embodiments, the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 6 hours. In some embodiments, the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 12 hours. In some embodiments, the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 1 day. In some embodiments, the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 2 days. In some embodiments, the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 3 days. In some embodiments, the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 4 days. In some embodiments, the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 5 days. In some embodiments, the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 6 days. In some embodiments, the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 7 days. In some embodiments, the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 8 days. In some embodiments, the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 9 days. In some embodiments, the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 10 days. In some embodiments, the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 12 days. In some embodiments, the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 14 days. In some embodiments, the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 18 days. In some embodiments, the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 21 days. In some embodiments, the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 28 days. In some embodiments, the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 35 days. In some embodiments, the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 42 days. In some embodiments, the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 56 days. In some embodiments, the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 3 months. In some embodiments, the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 4 months. In some embodiments,

the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 5 months. In some embodiments, the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 6 months. In some embodiments, the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 7 months. In some embodiments, the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 8 months. In some embodiments, the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 9 months. In some embodiments, the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 10 months. In some embodiments, the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 12 months.

**[0043]** Degradation of the biodegradable carrier can lead to the controlled release of and/or delivery of the anticonvulsant agent, thus providing a therapeutically effective dose of the agent to the subject. In some embodiments, the biodegradable carrier provides a therapeutically effective dose of the agent for up to 3 hours. In some embodiments, the biodegradable carrier provides a therapeutically effective dose of the agent for up to 6 hours. In some embodiments, the biodegradable carrier provides a therapeutically effective dose of the agent for up to 12 hours. In some embodiments, the biodegradable carrier provides a therapeutically effective dose of the agent for up to 1 day. In some embodiments, the biodegradable carrier provides a therapeutically effective dose of the agent for up to 2 days. In some embodiments, the biodegradable carrier provides a therapeutically effective dose of the agent for up to 3 days. In some embodiments, the biodegradable carrier provides a therapeutically effective dose of the agent for up to 4 days. In some embodiments, the biodegradable carrier provides a therapeutically effective dose of the agent for up to 5 days. In some embodiments, the biodegradable carrier provides a therapeutically effective dose of the agent for up to 6 days. In some embodiments, the biodegradable carrier provides a therapeutically effective dose of the agent for up to 7 days. In some embodiments, the biodegradable carrier provides a therapeutically effective dose of the agent for up to 8 days. In some embodiments, the biodegradable carrier provides a therapeutically effective dose of the agent for up to 9 days. In some embodiments, the biodegradable carrier provides a therapeutically effective dose of the agent for up to 10 days. In some embodiments, the biodegradable carrier provides a therapeutically effective dose of the agent for up to 12 days. In some embodiments, the biodegradable carrier provides a therapeutically effective dose of the agent for up to 14 days. In some embodiments, the biodegradable carrier provides a therapeutically effective dose of the agent for up to 18 days. In some embodiments, the biodegradable carrier provides a therapeutically

effective dose of the agent for up to 3 weeks. In some embodiments, the biodegradable carrier provides a therapeutically effective dose of the agent for up to 1 month. In some embodiments, the biodegradable carrier provides a therapeutically effective dose of the agent for up to 2 months. In some embodiments, the biodegradable carrier provides a therapeutically effective dose of the agent for up to 3 months. In some embodiments, the biodegradable carrier provides a therapeutically effective dose of the agent for up to 4 months. In some embodiments, the biodegradable carrier provides a therapeutically effective dose of the agent for up to 5 months. In some embodiments, the biodegradable carrier provides a therapeutically effective dose of the agent for up to 6 months. In some embodiments, the biodegradable carrier provides a therapeutically effective dose of the agent for up to 7 months. In some embodiments, the biodegradable carrier provides a therapeutically effective dose of the agent for up to 8 months. In some embodiments, the biodegradable carrier provides a therapeutically effective dose of the agent for up to 9 months. In some embodiments, the biodegradable carrier provides a therapeutically effective dose of the agent for up to 10 months. In some embodiments, the biodegradable carrier provides a therapeutically effective dose of the agent for up to 12 months.

**[0044]** Pharmaceutical agents may also be included in the compositions described herein. In some aspects, the pharmaceutical agents may stabilize the composition, allow it to be readily administered to a subject, increase its ability to treat acute, chronic, or post-operative pain, or otherwise make the composition suitable for therapeutic use in a subject. Accordingly, the described composition may further comprise a pharmaceutically acceptable carrier or excipient, as would be known to an individual skilled in the relevant art. In view of the inclusion of pharmaceutical agents in some of the described compositions, disclosed herein are also pharmaceutical compositions having an anticonvulsant and a biodegradable carrier, as provided herein. The described pharmaceutical compositions for delivery or injection of the described compositions may be administered to a subject in order to maintain the ability to treat chronic pain in the subject over a prolonged period of time. For example, composition viscosity and concentration of the agent may be altered to increase the half-life of composition's active ingredients.

**[0045]** The described pharmaceutical compositions may be formulated as any of various preparations that are known and suitable in the art, including those described and exemplified herein. In some embodiments, the pharmaceutical compositions are aqueous formulations. Aqueous solutions may be prepared by admixing the described compositions in water or suitable physiologic buffer, and optionally adding suitable colorants, preservatives,

stabilizing and thickening agents, ions such as calcium or magnesium, and the like as desired. Aqueous suspensions may also be made by dispersing the described compositions in water or physiologic buffer with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

**[0046]** When the present compositions are prepared as aqueous suspensions, the suspensions may be formulated by dispersing the present biodegradable carrier and active agent within injectable, in situ cross-linking hydrogel solution precursors, including, but not limited to, naturally derived polymers (e.g. polysaccharides) and/or synthetically derived polymers (e.g. PEG, PGA-PEG-PGA, PLA-PEG-PLA, PLGA-PEG-PLGA). The resulting compositions may then be administered to a subject, for example, by injection. Accordingly, a hydrogel may function as an excipient in which the biodegradable carrier and active agent are dispersed.

**[0047]** The present compositions may also be prepared as liquid formulations and solid form preparations which are intended to be converted, shortly before use, to liquid preparations. Such liquids include solutions, suspensions, syrups, slurries, and emulsions. Liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol syrup, cellulose derivatives or hydrogenated edible fats or oils); emulsifying agents (e.g., lecithin or acacia); non-aqueous vehicles (e.g., almond oil, oily esters, or fractionated vegetable oils); and preservatives (e.g., methyl or propyl-p-hydroxybenzoates or sorbic acid). These preparations may contain, in addition to the active agent, stabilizers, buffers, dispersants, thickeners, solubilizing agents, and the like. The compositions may be in powder or lyophilized form for constitution with a suitable vehicle such as sterile water, physiological buffer, saline solution, or alcohol, before use. The compositions may be formulated for injection into a subject. For injection, the compositions described may be formulated in aqueous solutions such as water or alcohol, or in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. The solution may contain one or more formulatory agents such as suspending, stabilizing or dispersing agents. Injection formulations may also be prepared as solid form preparations which are intended to be converted, shortly before use, to liquid form preparations suitable for injection, for example, by constitution with a suitable vehicle, such as sterile water, saline solution, or alcohol before use.

**[0048]** Also provided herein are methods of treating a subject having acute, post-operative, or chronic pain comprising administering to a subject having acute, post-operative, or chronic pain any one of the compositions disclosed herein. In some embodiments, the methods of treating a subject having acute, post-operative, or chronic pain can comprise administering to

a subject having the pain a composition comprising an anticonvulsant agent and a biodegradable carrier. In other embodiments, the methods of treating a subject having acute, post-operative, or chronic pain can comprise administering to a subject having the pain a composition consisting of an anticonvulsant agent and a biodegradable carrier.

**[0049]** The disclosed compositions can be administered by injection or implantation. For example, the composition can be injected or surgically placed on or near the nerve of interest. Local delivery allows a therapeutic concentration of the composition to be delivered to the nerve in question, without the systemic levels rising as high as when oral or systemic delivery is used for the same effect. Consequently, the systemic side effects can be greatly reduced or entirely eliminated.

**[0050]** The compositions can be injected by a number of routes, including, but not limited to, epidurally, intravenously, intra-arterially, transdermally, subcutaneously, intra-articularly, intramuscularly, perineurally, or any combination thereof. Alternatively, the compositions can be implanted at or near a site of acute, post-operative, or chronic pain.

**[0051]** In some embodiments, the composition can be administered to a sensory neuron. For example, in some aspects, the composition can be injected near a sensory neuron. In other aspects, the composition can be surgically implanted near a sensory neuron. In other embodiments, the composition can be administered to a synapse. In some aspects, the composition can be injected near a synapse. In other aspects, the composition can be surgically implanted near a synapse. In yet other embodiments, the composition can be administered near or to a dorsal root ganglion. In some aspects, the composition can be injected near a dorsal root ganglion. In other aspects, the composition can be surgically implanted near a dorsal root ganglion. In yet other embodiments, the composition can be administered near or to sensory nerve. In some aspects, the composition can be injected near a sensory nerve. In other aspects, the composition can be surgically implanted near a sensory nerve. In yet other embodiments, the composition can be administered near or to a peripheral nerve. In some aspects, the composition can be injected near a peripheral nerve. In other aspects, the composition can be surgically implanted near a peripheral nerve. In yet other embodiments, the composition can be administered near or to a medial nerve branch. In some aspects, the composition can be injected near a medial nerve branch. In other aspects, the composition can be surgically implanted near a medial nerve branch. In yet other embodiments, the composition can be administered into or around intramuscular tissue. In some aspects, the composition can be injected into or around intramuscular tissue. In other aspects, the composition can be surgically implanted into

intramuscular tissue. In yet other embodiments, the composition can be administered into or around an intra-articular joint. In some aspects, the composition can be injected into or around an intra-articular joint. In other aspects, the composition can be surgically implanted into an intra-articular joint. In yet other embodiments, the composition can be administered into or around a facet joint. In some aspects, the composition can be injected into or around a facet joint. In other aspects, the composition can be surgically implanted into a facet joint. In yet other embodiments, the composition can be administered near or to the femoral nerve. In some aspects, the composition can be injected near the femoral nerve. In other aspects, the composition can be surgically implanted near the femoral nerve. In yet other embodiments, the composition can be administered near or to the sciatic nerve. In some aspects, the composition can be injected near the sciatic nerve. In other aspects, the composition can be surgically implanted near the sciatic nerve. In yet other embodiments, the composition can be administered near or to the brachial plexus. In some aspects, the composition can be injected near the brachial plexus. In other aspects, the composition can be surgically implanted near the brachial plexus. In yet other embodiments, the composition can be administered into and around the epidural space. In some aspects, the composition can be injected into and around the epidural space. In other aspects, the composition can be surgically implanted into and around the epidural space. In yet other embodiments, the composition can be administered near or to the inferior alveolar nerve. In some aspects, the composition can be injected near the inferior alveolar nerve. In other aspects, the composition can be surgically implanted near the inferior alveolar nerve. In yet other embodiments, the composition can be administered near or to the trigeminal nerve. In some aspects, the composition can be injected near the trigeminal nerve. In other aspects, the composition can be surgically implanted near the trigeminal nerve.

**[0052]** The disclosed methods can be used to treat acute, post-operative, or chronic pain caused by a number of ailments, diseases, and/or injuries including, but not limited to pain caused by trauma, post-operative pain, dental pain, degenerative disk disease, spinal stenosis, spinal disc herniation, radiculopathy, radiculitis, arachnoiditis, trigeminal neuralgia, postherpetic neuralgia, shingles, occipital neuralgia, cervicogenic headache, migraine headaches, cluster headaches, back pain, facet joint pain, intra-articular joint pain, intramuscular pain, complex regional pain syndrome, cancer associated pain, neuropathy, diabetic neuropathic pain, tabetic neuralgia, sciatic neuralgia, sciatica, or any combination thereof.

**[0053]** The disclosed compositions can be used to treat acute or chronic pain associated with back pain or facet joint pain by, for example, administering the composition on or near the nerve root or the medial branch nerves near the source of the pain.

**[0054]** The disclosed compositions can be used to treat chronic pain associated with cervicogenic headache, migraine headaches, and cluster headaches by, for example, administering the composition onto or near the greater occipital nerve.

**[0055]** The disclosed compositions can be used to treat chronic pain associated with trigeminal neuralgia and the trigeminal nerve by, for example, administering the composition onto or near the Gasserian ganglion or into Meckel's Cave.

**[0056]** The disclosed compositions can be used to treat chronic pain associated with postherpetic neuralgia by, for example, administering the composition onto or near the nerve root, the dorsal nerve root ganglion, or distal to the dorsal nerve root ganglion.

**[0057]** The disclosed compositions can be used to treat acute or chronic pain associated with sciatic neuralgia and the sciatic nerve by, for example, administering the composition onto or near the sciatic nerve.

**[0058]** The disclosed compositions can be used to treat acute or post-operative pain associated with knee surgery or knee-replacement surgery by, for example, administering the composition onto or near the femoral nerve.

**[0059]** The disclosed compositions can be used to treat acute or post-operative pain associated with hip surgery or hip-replacement surgery by, for example, administering the composition onto or near the femoral or sciatic nerve.

**[0060]** The disclosed compositions can be used to treat acute or post-operative pain associated with shoulder surgery by, for example, administering the composition onto or near the brachial plexus.

**[0061]** The disclosed compositions can be used to treat acute or post-operative pain associated with dental procedures or surgery by, for example, administering the composition onto or near the inferior alveolar nerve or trigeminal nerve.

**[0062]** Any chronic, acute, or post-operative pain that can be temporarily relieved by a local anesthetic nerve block or corticosteroid injection can potentially be treated long term by delivering the disclosed compositions to the same location that the local anesthetic is applied.

**[0063]** The disclosed compositions can be used to treat acute, post-operative, or chronic pain that can be relieved by a sensory and/or peripheral nerve block.

**[0064]** Also provided herein are kits for producing a composition to treat acute, post-operative, or chronic pain in a subject; the kit comprising an anticonvulsant agent, a biodegradable carrier, and instructions for producing the composition. The instructions may describe the steps and reagents for producing the composition by solvent extraction/evaporation, oil-in-water single emulsification, by spray drying, or by precipitation using a solvent/non-solvent system. Such steps and reagents may be in accordance with those that the present application discloses for solvent extraction/evaporation, oil-in-water single emulsification, spray drying, and precipitation using a solvent/non-solvent system.

## EXAMPLES

**[0065]** *Microencapsulated anticonvulsant agent by solvent extraction/evaporation, single oil-in-water emulsification.* Biodegradable, polymeric microparticles were fabricated using a solvent extraction/evaporation, single oil-in-water (o/w) emulsification method. PLGA (0-20 wt%) and carbamazepine (0-20 wt%) were dissolved in a suitable, volatile organic solvent (e.g. dichloromethane, ethyl acetate). The resulting polymer solution dispersant phase was added to an aqueous continuous phase containing 1-5% (w/v) of surfactant (PVA) under constant shear rate mixing to create a single o/w microemulsion. The resulting stable microemulsion was subsequently added to an evaporation bath containing 100 mL of deionized water containing a trace concentration (0-0.5% (w/v)) of surfactant (PVA) under stirring at 350 rpm for 3 hours to effectively extract and evaporate the organic solvent. The hardened microparticles were then collected, purified with deionized water, and lyophilized.

**[0066]** Those skilled in the art will appreciate that numerous changes and modifications can be made to the preferred embodiments of the invention and that such changes and modifications can be made without departing from the spirit of the invention. It is, therefore, intended that the appended claims cover all such equivalent variations as fall within the true spirit and scope of the invention.

**What is Claimed:**

1. A composition for treating acute, post-operative, or chronic pain in a subject comprising:  
an anticonvulsant agent; and  
a biodegradable carrier comprising poly(lactide-co-glycolides), poly(lactides), or  
copolymers of these said polymers with poly(ethylene glycol),  
wherein the anticonvulsant agent is incorporated within the biodegradable carrier by  
solvent extraction/evaporation, oil-in-water single emulsification.
2. A composition for treating acute, post-operative, or chronic pain in a subject comprising:  
an anticonvulsant agent; and  
a biodegradable carrier comprising a poly(lactide-co-glycolides), a poly(lactides), or  
copolymers of these said polymers with poly(ethylene glycol),  
wherein the anticonvulsant agent is incorporated within the biodegradable carrier by  
spray drying.
3. A composition for treating acute, post-operative, or chronic pain in a subject comprising:  
an anticonvulsant agent; and  
a biodegradable carrier comprising poly(lactide-co-glycolides), poly(lactides), or  
copolymers of these said polymers with poly(ethylene glycol),  
wherein the anticonvulsant agent is incorporated within the biodegradable carrier by  
precipitation using a solvent/non-solvent system.
4. The composition of any one of the preceding claims, wherein the anticonvulsant agent  
comprises carbamazepine, pregabalin, phenytoin, gabapentin, topiramate, or oxcarbazepine, or  
any combination thereof.
5. The composition of claim 4, wherein the anticonvulsant is carbamazepine.
6. The composition of claim 4, wherein the anticonvulsant is gabapentin.
7. The composition of claim 4, wherein the anticonvulsant is pregabalin.

8. The composition of any of claims 1 to 7, wherein the anticonvulsant agent is exposed on the surface of the biodegradable carrier, incorporated within the biodegradable carrier, or both.
9. The composition of any one of claims 1 to 3, wherein the biodegradable carrier comprises a microparticle, a nanoparticle, or any combination thereof.
10. The composition of claim 9, wherein the biodegradable carrier has a mean hydrodynamic diameter of up to 25 microns, inclusive, as measured by aqueous solution phase laser diffraction or dynamic light scattering instrumentation.
11. The composition of claim 9, wherein the biodegradable carrier has a median hydrodynamic diameter of up to 25 microns, inclusive, as measured by aqueous solution phase laser diffraction or dynamic light scattering instrumentation.
12. The composition of any one of the preceding claims, wherein the biodegradable carrier degrades following administration to said subject, resulting in the release of the anticonvulsant agent.
13. The composition of any one of the preceding claims, wherein the anticonvulsant agent comprises up to 25% percent by weight, inclusive, of the biodegradable carrier.
14. The composition of any one of the preceding claims, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 3 hours.
15. The composition of any one of the preceding claims, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 6 hours.
16. The composition of any one of the preceding claims, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 12 hours.
17. The composition of any one of the preceding claims, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 1 day.

18. The composition of any one of the preceding claims, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 2 days.
19. The composition of any one of the preceding claims, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 3 days.
20. The composition of any one of the preceding claims, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 4 days.
21. The composition of any one of the preceding claims, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 5 days.
22. The composition of any one of the preceding claims, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 6 days.
23. The composition of any one of the preceding claims, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 7 days.
24. The composition of any one of the preceding claims, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 8 days.
25. The composition of any one of the preceding claims, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 9 days.
26. The composition of any one of the preceding claims, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 10 days.
27. The composition of any one of the preceding claims, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 12 days.
28. The composition of any one of the preceding claims, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 14 days.

29. The composition of any one of the preceding claims, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 16 days.
30. The composition of any one of the preceding claims, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 18 days.
31. The composition of any one of the preceding claims, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 21 days.
32. The composition of any one of the preceding claims, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 28 days.
33. The composition of any one of the preceding claims, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 35 days.
34. The composition of any one of the preceding claims, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 42 days.
35. The composition of any one of the preceding claims, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 49 days.
36. The composition of any one of the preceding claims, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 56 days.
37. The composition of any one of the preceding claims, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 3 months.
38. The composition of any one of the preceding claims, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 4 months.
39. The composition of any one of the preceding claims, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 5 months.

40. The composition of any one of the preceding claims, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 6 months.
41. The composition of any one of the preceding claims, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 7 months.
42. The composition of any one of the preceding claims, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 8 months.
43. The composition of any one of the preceding claims, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 9 months.
44. The composition of any one of the preceding claims, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 10 months.
45. The composition of any one of the preceding claims, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 12 months.
46. The composition of any one of the preceding claims, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 3 hours, inclusive.
47. The composition of any one of the preceding claims, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 6 hours, inclusive.
48. The composition of any one of the preceding claims, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 12 hours, inclusive.
49. The composition of any one of the preceding claims, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 1 day, inclusive.
50. The composition of any one of the preceding claims, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 2 days, inclusive.
51. The composition of any one of the preceding claims, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 3 days, inclusive.

52. The composition of any one of the preceding claims, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 4 days, inclusive.

53. The composition of any one of the preceding claims, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 5 days, inclusive.

54. The composition of any one of the preceding claims, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 6 days, inclusive.

55. The composition of any one of the preceding claims, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 7 days, inclusive.

56. The composition of any one of the preceding claims, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 8 days, inclusive.

57. The composition of any one of the preceding claims, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 9 days, inclusive.

58. The composition of any one of the preceding claims, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 10 days, inclusive.

59. The composition of any one of the preceding claims, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 12 days, inclusive.

60. The composition of any one of the preceding claims, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 14 days, inclusive.

61. The composition of any one of the preceding claims, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 18 days, inclusive.

62. The composition of any one of the preceding claims, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 3 weeks, inclusive.

63. The composition of any one of the preceding claims, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 1 month, inclusive.

64. The composition of any one of the preceding claims, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 2 months, inclusive.

65. The composition of any one of the preceding claims, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 3 months, inclusive.

66. The composition of any one of the preceding claims, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 4 months, inclusive.

67. The composition of any one of the preceding claims, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 5 months, inclusive.

68. The composition of any one of the preceding claims, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 6 months, inclusive.

69. The composition of any one of the preceding claims, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 7 months, inclusive.

70. The composition of any one of the preceding claims, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 8 months, inclusive.

71. The composition of any one of the preceding claims, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 9 months, inclusive.

72. The composition of any one of the preceding claims, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 10 months, inclusive.

73. The composition of any one of the preceding claims, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 12 months, inclusive.

74. The composition of any one of the preceding claims, further comprising a pharmaceutically acceptable carrier or excipient.

75. A method of treating a subject having acute, post-operative, or chronic pain comprising administering to said subject the composition of any one of claims 1 to 74.

76. A method of treating a subject having acute, post-operative, or chronic pain comprising administering to said subject a composition comprising:

an anticonvulsant agent; and  
a biodegradable carrier.

77. The method of claim 75 or 76, wherein the composition is administered into and/or around the epidural space in said subject.

78. The method of claim 75 or 76, wherein the composition is administered into and/or around an intra-articular joint of said subject.

79. The method of claim 75 or 76, wherein the composition is administered into and/or around a facet joint of said subject.

80. The method of claim 75 or 76, wherein the compositions is administered into and/or around intramuscular tissue in said subject.

81. The method of claim 75 or 76, wherein the composition is administered on or near a sensory nerve of said subject.

82. The method of claim 81, wherein the sensory nerve is the femoral nerve.

83. The method of claim 81, wherein the sensory nerve is the sciatic nerve.
84. The method of claim 81, wherein the sensory nerve is the brachial plexus.
85. The method of claim 81, wherein the sensory nerve is the inferior alveolar nerve.
86. The method of claim 81, wherein the sensory nerve is the trigeminal nerve.
87. The method of claim 75 or 76, wherein the composition is administered on or near a peripheral nerve of said subject.
88. The method of claim 87, wherein the peripheral nerve is the femoral nerve.
89. The method of claim 87, wherein the peripheral nerve is the sciatic nerve.
90. The method of claim 87, wherein the peripheral nerve is the brachial plexus.
91. The method of claim 87, wherein the peripheral nerve is the inferior alveolar nerve.
92. The method of claim 87, wherein the peripheral nerve is the trigeminal nerve.
93. The method of claim 75 or 76, wherein the composition is administered near a dorsal root ganglion of said subject.
94. The method of claim 75 or 76, wherein the composition is administered on or near a medial nerve branch of said subject.
95. The method of claim 75 or 76, wherein the composition is injected or surgically implanted in said subject.
96. The method of any one of claims 75 to 95, wherein the acute, post-operative, or chronic pain is caused by trauma, post-operative pain, dental pain, degenerative disk disease, spinal stenosis, spinal disc herniation, radiculopathy, radiculitis, arachnoiditis, trigeminal neuralgia, postherpetic neuralgia, shingles, occipital neuralgia, cervicogenic headache, migraine headaches, cluster headaches, back pain, facet pain, intra-articular joint pain, intramuscular pain, complex

regional pain syndrome, cancer associated pain, neuropathy, diabetic neuropathic pain, tabetic neuralgia, sciatic neuralgia, sciatica, or any combination thereof.

97. The method according to claim 76, wherein the anticonvulsant agent comprises carbamazepine, pregablin, phenytoin, gabapentin, topiramate, or oxcarbazepine, or any combination thereof.

98. The method according to claim 97, wherein the anticonvulsant is carbamazepine.

99. The method according to claim 97, wherein the anticonvulsant is gabapentin.

100. The method according to claim 97, wherein the anticonvulsant is pregabalin.

101. The method according to any one of claims 76 and 97-100, wherein the anticonvulsant agent is exposed on the surface of the biodegradable carrier, incorporated within the biodegradable carrier, or both.

102. The method according to claim 76, wherein the biodegradable carrier comprises a microparticle, a nanoparticle, or any combination thereof.

103. The method according to claim 102, wherein the biodegradable carrier comprises poly(lactide), poly(lactide-co-glycolide), a copolymer of poly(lactide) and poly(ethylene glycol), or a copolymer of poly(lactide-co-glycolide) and poly(ethylene glycol), or any combination thereof.

104. The method according to any one of claims 76 and 97-103, wherein the biodegradable carrier has a mean hydrodynamic diameter of up to 25 microns, inclusive, as measured by aqueous solution phase laser diffraction or dynamic light scattering instrumentation.

105. The method according to any one of claims 76 and 97-103, wherein the biodegradable carrier has a median hydrodynamic diameter of up to 25 microns, inclusive, as measured by aqueous solution phase laser diffraction or dynamic light scattering instrumentation.

106. The method according to any one of claims 76 and 97-105, wherein the biodegradable carrier degrades following being administered to the subject, resulting in the release of the anticonvulsant agent.

107. The method according to any one of claims 76 and 97-105, wherein the anticonvulsant agent comprises up to 25% percent by weight, inclusive, of the biodegradable carrier.

108. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 3 hours.

109. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 6 hours.

110. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 12 hours.

111. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 1 day.

112. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 2 days.

113. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 3 days.

114. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 4 days.

115. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 5 days.

116. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 6 days.

117. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 7 days.

118. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 8 days.

119. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 9 days.

120. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 10 days.

121. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 12 days.

122. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 14 days.

123. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 16 days.

124. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 18 days.

125. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 21 days.

126. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 28 days.

127. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 35 days.

128. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 42 days.

129. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 49 days.

130. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 56 days.

131. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 3 months.

132. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 4 months.

133. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 5 months.

134. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 6 months.

135. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 7 months.

136. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 8 months.

137. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 9 months.

138. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 10 months.

139. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier releases less than 60% of the anticonvulsant agent over about 12 months.

140. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 3 hours, inclusive.

141. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 6 hours, inclusive.

142. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 12 hours, inclusive.

143. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 1 day, inclusive.

144. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 2 days, inclusive.

145. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 3 days, inclusive.

146. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 4 days, inclusive.

147. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 5 days, inclusive.

148. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 6 days, inclusive.

149. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 7 days, inclusive.

150. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 10 days, inclusive.

151. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 12 days, inclusive.

152. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 14 days, inclusive.

153. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 18 days, inclusive.

154. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 3 weeks, inclusive.

155. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 1 month, inclusive.

156. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 2 months, inclusive.

157. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 3 months, inclusive.

158. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 4 months, inclusive.

159. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 5 months, inclusive.

160. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 6 months, inclusive.

161. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 7 months, inclusive.

162. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 8 months, inclusive.

163. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 9 months, inclusive.

164. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 10 months, inclusive.

165. The method according to any one of claims 76 and 97-107, wherein the biodegradable carrier provides a therapeutically effective dose of the anticonvulsant agent for up to 12 months, inclusive.

166. The method according to any one of claims 76 and 97-107, further comprising a pharmaceutically acceptable carrier or excipient.

167. A kit for producing the composition of any one of claims 1 to 75, the kit comprising:  
an anticonvulsant agent;  
a biodegradable carrier comprising poly(lactide-co-glycolides), poly(lactides), or copolymers of these said polymers with poly(ethylene glycol); and  
instructions for producing said composition.

168. The kit according to claim 167 wherein said instructions are for incorporating the anticonvulsant agent within the biodegradable carrier by solvent extraction/evaporation, oil-in-water single emulsification.

169. The kit according to claim 167 wherein said instructions are for incorporating the anticonvulsant agent within the biodegradable carrier by spray drying.

170. The kit according to claim 167 wherein said instructions are for incorporating the anticonvulsant agent within the biodegradable carrier by precipitation using a solvent/non-solvent system.

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FIG. 1

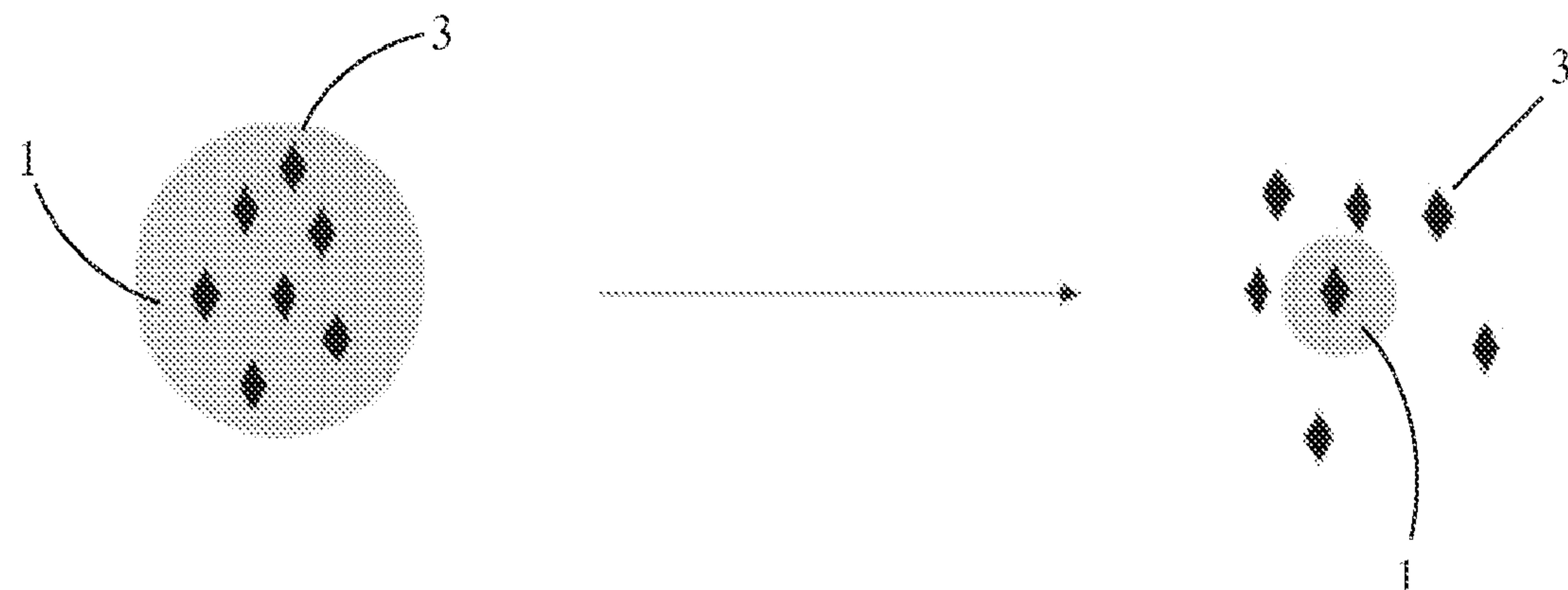


FIG. 2

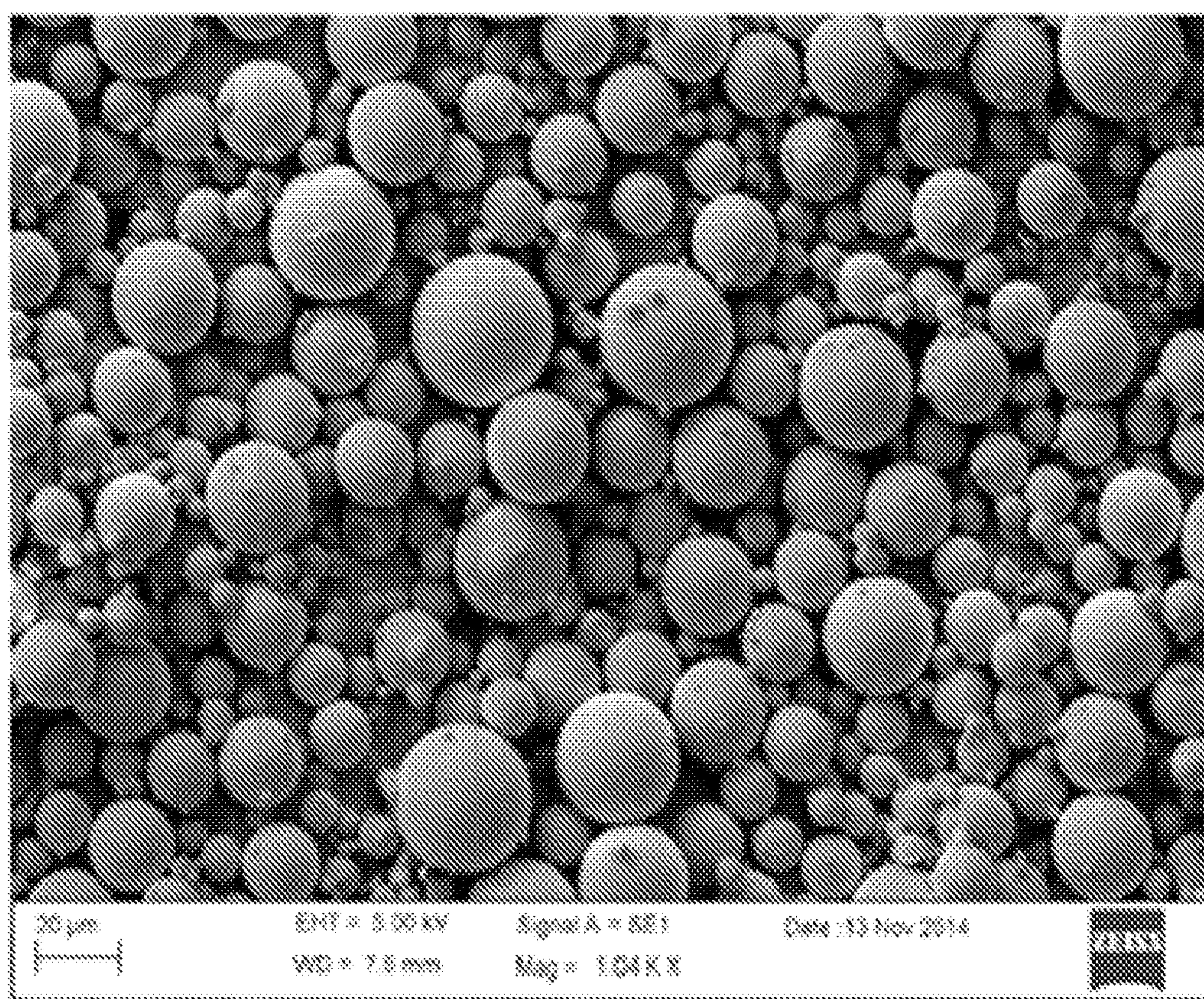


FIG. 3

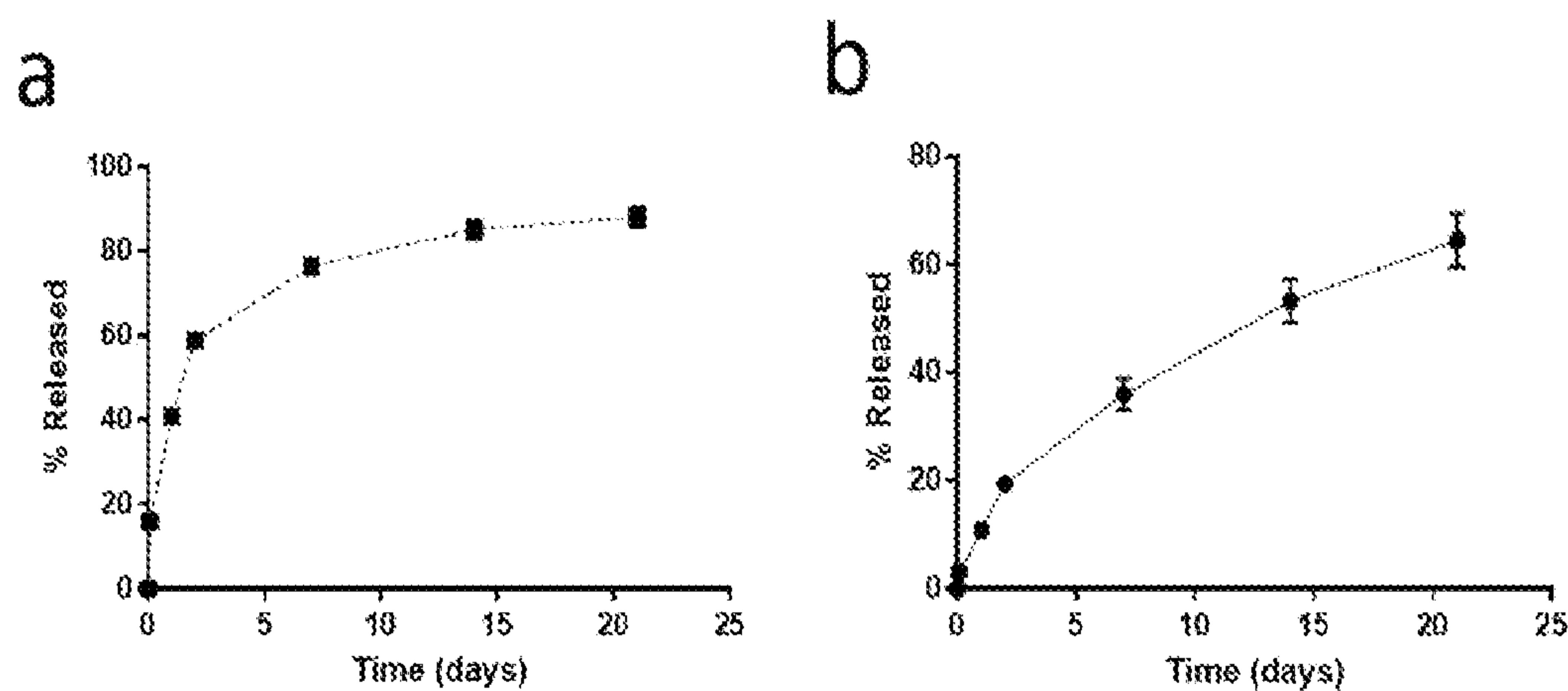


FIG. 4

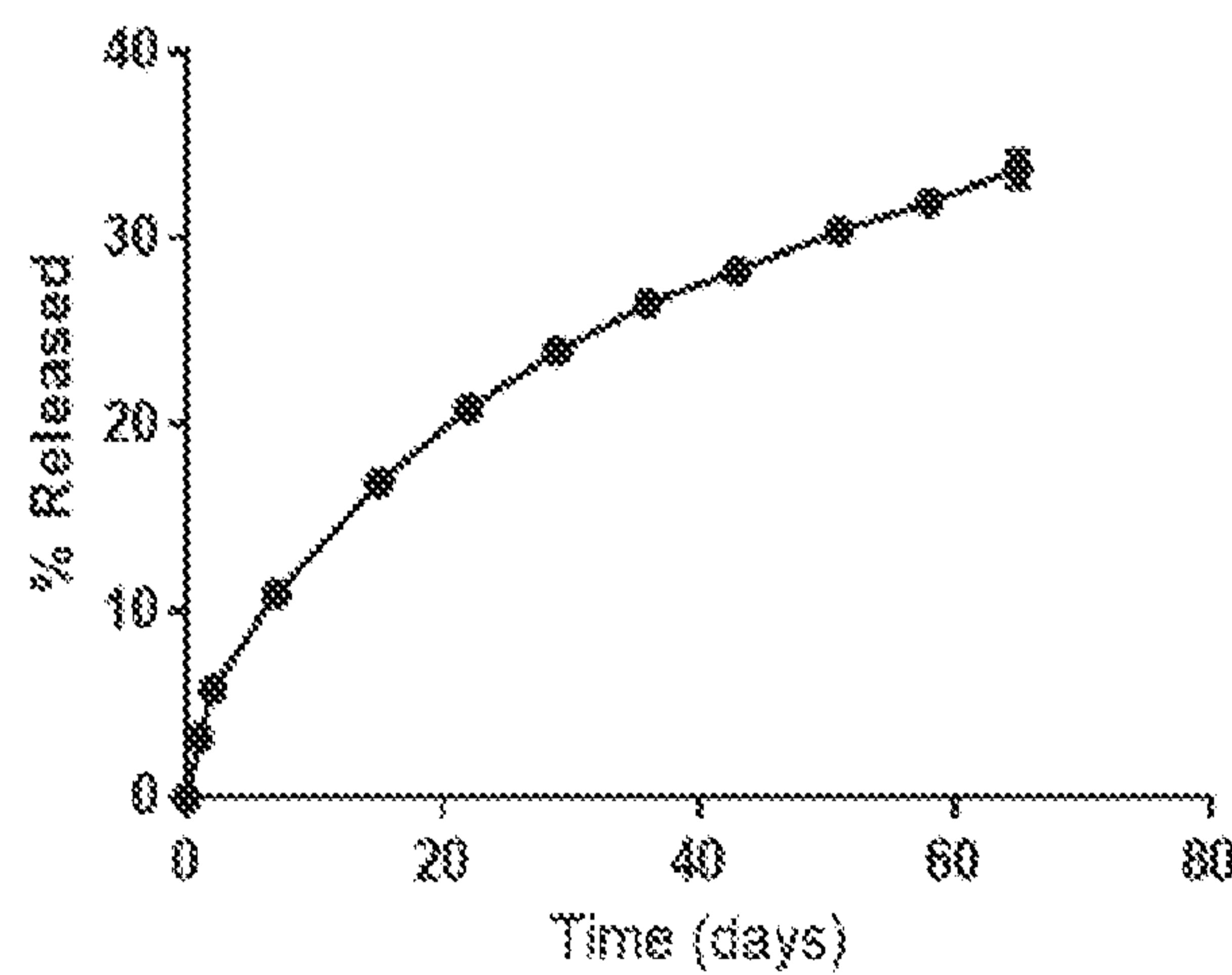
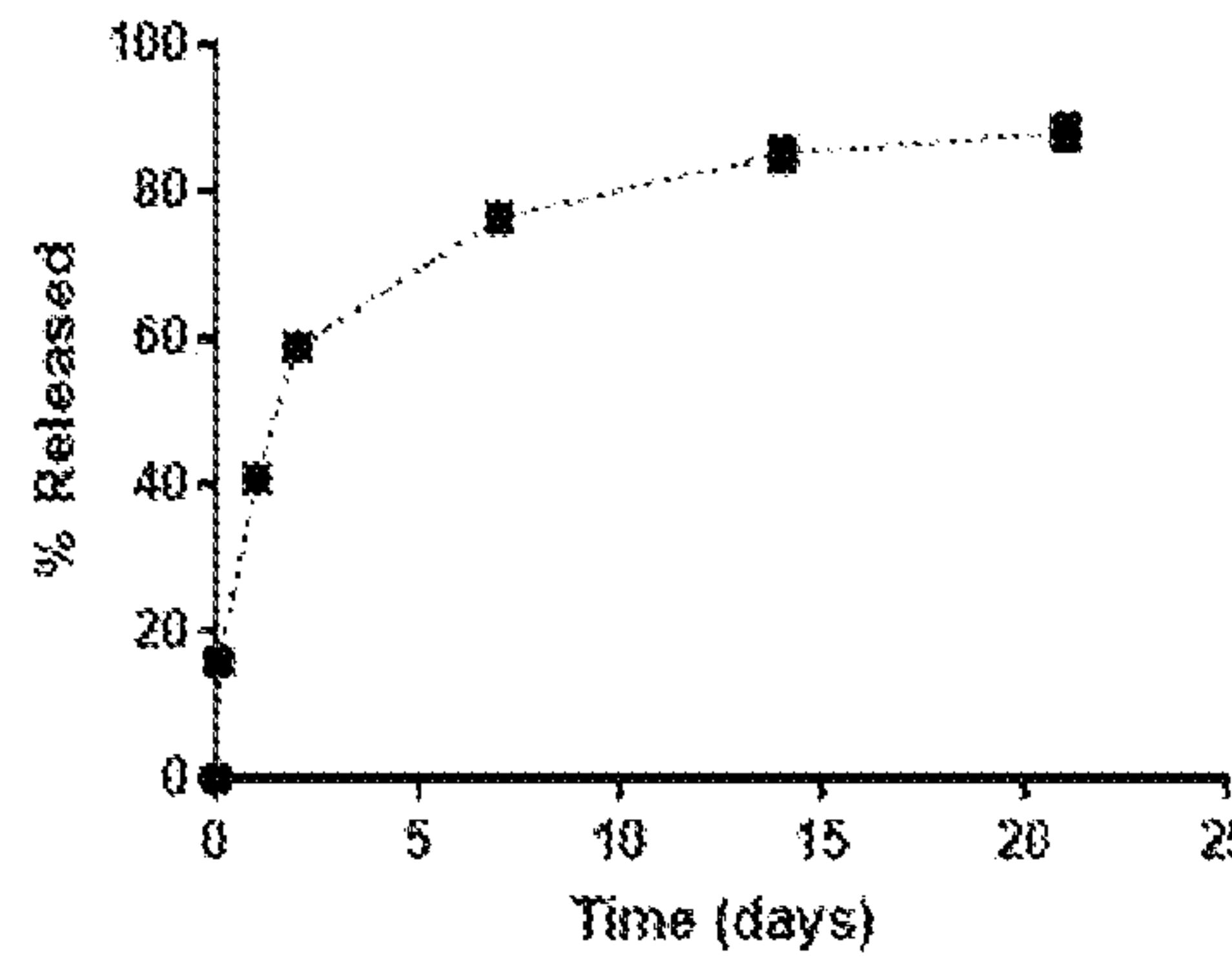


FIG. 3

a)



b

