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(71) Applicants (for all designated States except US): **WARSAW ORTHOPEDIC, INC.** [US/US]; 2500 Silveus Crossing, Warsaw, IN 46581 (US). **MEDTRONIC, INC.** [US/US]; 710 Medtronic Parkway Ms LC340, Minneapolis, MN 55432 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **KING, Vanja, Margareta** [US/US]; 1400 Carr Avenue, Memphis, TN 38104 (US). **HOBOT, Christopher, M.** [US/US]; 40 Pleasant Lane W., Tonka Bay, MN 55331 (US). **BIGGS, Dr. Danielle** [US/US]; 915 North Madison Row Court, Apt 303, Colliverville, TN 38017 (US). **SHAW, Katara** [US/US]; 712 Mohican Circle, Birmingham, AL 35214 (US). **WOHABREBBI, Amira** [US/US]; 56 S. Arcadian Circle #101, Memphis, TN 38103 (US). **MCKAY, William, F.** [US/US]; 3870 McElrie Cove, Memphis, TN 38133 (US). **MCDONALD, Phillip, Edward** [US/US]; 300 Zinnia Lane N., Plymouth, MN 55441 (US).

(74) Agents: **PATEL, Samir, R.** et al.; 710 Medtronic Parkway Ms LC340, Minneapolis, MN 55432 (US).

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(54) Title: METHODS AND COMPOSITIONS FOR TREATING POST-OPERATIVE PAIN COMPRISING A LOCAL ANESTHETIC

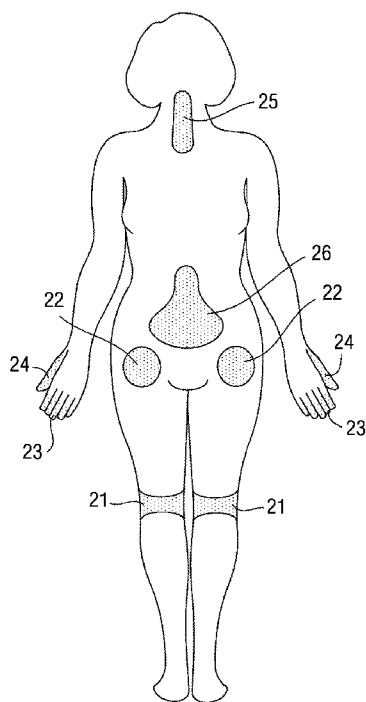


FIG. 1

(57) Abstract: The present invention is directed to an implantable drug depot useful for reducing, preventing or treating post-operative pain in a patient in need of such treatment, the implantable drug depot comprising a polymer and a therapeutically effective amount of a local anesthetic or pharmaceutically acceptable salt thereof, wherein the drug depot is implantable at a site beneath the skin to reduce, prevent or treat post-operative pain, and the drug depot is capable of releasing (i) a bolus dose of the local anesthetic or pharmaceutically acceptable salt thereof at a site beneath the skin and (ii) a sustained release dose of an effective amount of the local anesthetic or pharmaceutically acceptable salt thereof over a period of at least 4 days.

WO 2009/129509 A2



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METHODS AND COMPOSITIONS FOR TREATING POST-OPERATIVE PAIN COMPRISING A LOCAL ANESTHETIC

5 [0001] This application claims the benefit of the filing date of: U.S. Patent
Application No. 12/420,177 filed April 8, 2009 and entitled "Methods and Compositions
for Treating Post-Operative Pain Comprising a Local Anesthetic," and U.S. Provisional
Application No. 61/046,343 filed April 18, 2008 and entitled "Methods and Compositions
10 for Treating Post-Operative Pain Comprising a Local Anesthetic," which are hereby
incorporated by reference thereto.

BACKGROUND OF THE INVENTION

[0002] Pain relief is of prime importance to anyone treating patients undergoing
surgery. Proper pain relief imparts significant physiological and psychological benefits to
15 the patient. Not only does effective pain relief mean a smoother more pleasant post-
operative course (*e.g.*, mood, sleep, quality of life, *etc.*) with earlier discharge from
medical/surgical/outpatient facilities, but it may also reduce the onset of chronic pain
syndromes (*e.g.*, fibromyalgia, myalgia, *etc.*).

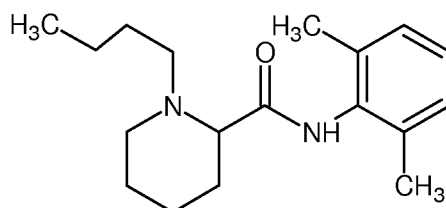
[0003] Pain serves a biological function. It often signals the presence of damage or
20 disease within the body and is often accompanied by inflammation (redness, swelling,
and/or burning). In the case of post-operative pain, it may be a result of the surgery, or
other treatments such as, for example, management of acute pain following burns or non-
surgical trauma. The goal for post-operative pain management is to reduce or eliminate
pain and discomfort with medication that cause minimum or no side effects.

25 [0004] The site of the surgery has a profound effect upon the degree of post-
operative pain a patient may suffer. In general, operations on the thorax and upper
abdomen are more painful than operations on the lower abdomen, which in turn are more
painful than peripheral operations on the limbs. However, any operation involving a body
cavity, large joint surfaces, the spine or deep tissues should be regarded as painful. In
30 particular, operations on the thorax or upper abdomen may produce widespread changes in
pulmonary function, an increase in abdominal muscle tone and an associated decrease in
diaphragmatic function. The result will be an inability to cough and clear secretions,

which may lead to lung collapse and pneumonia. Prolonged pain can reduce physical activity and lead to venous stasis and an increased risk of deep vein thrombosis and consequently pulmonary embolism. In addition, there can be widespread effects on gut and urinary tract motility, which may lead in turn to post-operative ileus, nausea, vomiting and urinary retention. These problems are unpleasant for the patient and may prolong hospital stay. Most patients who experience moderate to severe post-operative pain, post-traumatic pain and burn pain, often require pain control at least in the first 3 days after trauma or surgery.

[0005] One known class of pharmaceuticals to treat post-operative pain is opioids. This class of compounds is well-recognized as being among the most effective type of drugs for controlling post-operative pain. Unfortunately, because opioids are administered systemically, the associated side effects raise significant concerns, including disabling the patient, depressing the respiratory system, constipation, and psychoactive effects such as sedation and euphoria, thereby instituting a hurdle to recovery and regained mobility. Further, because of these side-effects, physicians typically limit the administration of opioids to within the first 24 hours post-surgery. Thus, it would be preferable to use non-narcotic drugs that deliver direct, localized pain control at a surgical site.

[0006] One pharmaceutical that is known to the medical profession is bupivacaine, which is widely recognized as a local anesthetic for infiltration, nerve block, epidural and intrathecal administration. In general, bupivacaine, also referred to as 1-butyl-N-(2,6-dimethylphenyl) piperidine-2-carboxamide ($C_{18}H_{28}N_2O$) may be represented by the following structure:



[0007] Because of the unique manifestation and relatively predictable risks for post-operative pain, there is a need for effective treatments for post-operative pain and/or inflammation, including methods and compositions to alleviate and/or to treat post-operative pain and/or inflammation.

SUMMARY OF THE INVENTION

[0008] New compositions and methods are provided that effectively prevent, treat or reduce post-operative pain and/or inflammation. In various embodiments, compositions and methods are provided that have long acting analgesic and anti-inflammatory effects over periods of at least 4 days in a single drug depot or multiple drug depots. New compositions and methods are provided, which can easily allow accurate and precise implantation of a drug depot including an analgesic with minimal physical and psychological trauma to a patient. The drug depot can now be easily delivered to the target tissue site (*e.g.*, abdomen, synovial joint, at or near the spinal column, *etc.*) and alleviate and/or treat pain for at least 4 to 10 days. In this way, accurate and precise implantation of the drug depot in a minimally invasive procedure can be accomplished.

[0009] In one exemplary embodiment, an implantable drug depot useful for reducing, preventing or treating post-operative pain or inflammation in a patient in need of such treatment is provided. The implantable drug depot comprises a therapeutically effective amount of an analgesic or pharmaceutically acceptable salt thereof and the depot is implantable at a site beneath the skin to reduce, prevent or treat post-operative pain. The drug depot is capable of releasing an effective amount of the analgesic or pharmaceutically acceptable salt thereof over a period of at least 4 days. The drug depot in the above embodiments may be capable of releasing (i) a bolus dose of the analgesic or local anesthetic or pharmaceutically acceptable salt thereof at a site beneath the skin and (ii) a sustained release dose of an effective amount of the analgesic or local anesthetic or pharmaceutically acceptable salt thereof over a period of at least 4 days. The drug depot may comprise a polymer comprising one or more of poly(lactide-co-glycolide), polylactide, polyglycolide, polyorthoester, D-lactide, D,L-lactide, poly(D,L-lactide), L-lactide, poly(D,L-lactide-co-caprolactone), poly(D,L-lactide-co-glycolide-co-caprolactone), polycaprolactone or a combination thereof. The polymer may be biodegradable. The drug depot can be a ribbon-like strip or fiber that releases the local anesthetic over the period of at least 4 days. The drug depot can also be a gel formulation that releases the local anesthetic over the period of at least 4 days.

[0010] In another exemplary embodiment, a method of making an implantable drug depot is provided. The method comprises combining a biocompatible polymer and a

therapeutically effective amount of local anesthetic or pharmaceutically acceptable salt thereof and forming the implantable drug depot from the combination.

[0011] In yet another exemplary embodiment, a method of treating or preventing post-operative pain or inflammation in a patient in need of such treatment is provided. The method comprises administering one or more biodegradable drug depots comprising a therapeutically effective amount of an analgesic or pharmaceutically acceptable salt thereof to a target tissue site beneath the skin, wherein the drug depot releases an effective amount of the analgesic or pharmaceutically acceptable salt thereof over a period of at least 4 days. The drug depot may be capable of releasing (i) a bolus dose of the analgesic or local anesthetic or pharmaceutically acceptable salt thereof at a site beneath the skin and (ii) a sustained release dose of an effective amount of the analgesic or local anesthetic or pharmaceutically acceptable salt thereof over a period of at least 4 days. The drug depot may comprise a polymer comprising one or more of poly(lactide-co-glycolide), polylactide, polyglycolide, polyorthoester, D-lactide, D,L-lactide, poly(D,L-lactide), L-lactide, poly(D,L-lactide-co-caprolactone), poly(D,L-lactide-co-glycolide-co-caprolactone), polycaprolactone or a combination thereof. The polymer may be biodegradable. The drug depot can be a ribbon-like strip that releases the local anesthetic over the period of at least 4 days. The drug depot can also be a gel formulation that releases the local anesthetic over the period of at least 4 days.

[0012] In still yet another exemplary embodiment, a method of reducing post-operative pain in a patient in need of such treatment is provided. The method comprises delivering one or more biodegradable drug depots comprising a therapeutically effective amount of bupivacaine or pharmaceutically acceptable salt thereof to a target tissue site beneath the skin before, during or after surgery, wherein the drug depot is capable of releasing an initial bolus dose of an effective amount of bupivacaine or pharmaceutically acceptable salt thereof at a site beneath the skin followed by a sustained release dose of an effective amount of bupivacaine or pharmaceutically acceptable salt thereof over a period of 4 to 30 days, 4 to 10 days, or 5 to 7 days. The drug depot may comprise a polymer and the polymer may comprise one or more of poly(lactide-co-glycolide), polylactide, polyglycolide, polyorthoester, D-lactide, D,L-lactide, poly(D,L-lactide), L-lactide, poly(D,L-lactide-co-caprolactone), poly(D,L-lactide-co-glycolide-co-caprolactone), polycaprolactone or a combination thereof. Bupivacaine may be in the form of a salt

and/or in the form of a base. The polymer may be biodegradable. The drug depot may be a ribbon-like strip. The drug depot is capable of releasing about 40 to 90% of the bupivacaine or pharmaceutically acceptable salt thereof relative to a total amount of bupivacaine or pharmaceutically acceptable salt thereof loaded in the drug depot over the period of 4 to 10 days after the drug depot is administered to the target tissue site.

[0013] In yet another exemplary embodiment, an implantable drug depot useful for reducing, preventing or treating post-operative pain in a patient in need of such treatment is provided. The implantable drug depot comprises a therapeutically effective amount of bupivacaine or pharmaceutically acceptable salt thereof and a polymer. The depot is implantable at a site beneath the skin to reduce, prevent or treat post-operative pain. The depot is capable of releasing (i) about 2% to about 50% of the bupivacaine or pharmaceutically acceptable salt thereof relative to a total amount of the bupivacaine or pharmaceutically acceptable salt thereof loaded in the drug depot over a first period of up to 48 hours, a first period of up to 24 hours, or a first period of about 24 to 48 hours and (ii) about 50% to about 98% of the bupivacaine or pharmaceutically acceptable salt thereof relative to a total amount of the bupivacaine or pharmaceutically acceptable salt thereof loaded in the drug depot over a subsequent period of up to 3 to 30 days, 2 to 10 days or 3 to 10 days. The polymer comprises one or more of poly(lactide-co-glycolide), polylactide, polyglycolide, polyorthoester, D-lactide, D,L-lactide, poly(D,L-lactide), L-lactide, poly(D,L-lactide-co-caprolactone), poly(D,L-lactide-co-glycolide-co-caprolactone), polycaprolactone or a combination thereof. The polymer may be biodegradable. In various embodiments, when the first period is up to 24 hours or about 24 to 48 hours, the depot is capable of releasing about 2% to about 40% of the bupivacaine or pharmaceutically acceptable salt thereof.

[0014] In another exemplary embodiment, an implantable drug depot is provided. The implantable drug depot comprises: (i) a therapeutically effective amount of bupivacaine or pharmaceutically acceptable salt thereof; and (ii) a polymer. The depot is capable of releasing an initial bolus dose of bupivacaine or pharmaceutically acceptable salt thereof at a site beneath the skin, and the depot is capable of releasing a sustained release dose of an effective amount of bupivacaine or pharmaceutically acceptable salt thereof over a subsequent period of 4 to 30 days or 4 to 10 days. The drug depot is capable of releasing about 40% to about 70% of the bupivacaine or pharmaceutically

acceptable salt thereof relative to a total amount of bupivacaine loaded in the drug depot over the sustained release period of 4 to 30 days or 4 to 10 days after the drug depot is administered. The polymer comprises one or more of poly(lactide-co-glycolide), polylactide, polyglycolide, polyorthoester, D-lactide, D,L-lactide, poly(D,L-lactide), L-lactide, poly(D,L-lactide-co-caprolactone), poly(D,L-lactide-co-glycolide-co-caprolactone), polycaprolactone or a combination thereof.

[0015] In various embodiments, the analgesic may be a local anesthetic or a pharmaceutically acceptable salt thereof and the local anesthetic may be at least one of bupivacaine, ropivacaine, mepivacaine, etidocaine, levobupivacaine, trimecaine, carticaine or articaine. Bupivacaine may be in the form of a salt and/or in the form of a base. The local anesthetic or pharmaceutically acceptable salt thereof may be encapsulated in a plurality of depots comprising microparticles, microspheres, microcapsules, and/or microfibers suspended in a gel.

[0016] In various embodiments, the drug depot may comprise a polymer and further an excipient. In particular, the drug depot may comprise a local anesthetic in an amount of about 30 to about 90 weight percent (wt.%), about 10 to about 80 wt.% of a polymer and about 0.5 to about 20 wt.% of an excipient. For example, the drug depot can include a local anesthetic at an amount of about 30 to about 90 wt.% of the implantable drug depot, about 10 to about 80 wt.% PLGA and about 0.5 to about 20 wt.% mPEG.

[0017] The drug depot in various embodiments is capable of releasing an effective amount of the analgesic or pharmaceutically acceptable salt thereof over a period of at least 4 days. For example, the drug depot may release about 40% to about 70% of the analgesic or local anesthetic or pharmaceutically acceptable salt thereof relative to a total amount of the analgesic or local anesthetic loaded in the drug depot over a period of 4 to 10 days after the drug depot is administered to a target tissue site. The analgesic or local anesthetic is released in an amount between 50 and 800 mg per day during this period of 4 to 10 days. The drug depot, though, is capable of releasing an effective amount of the analgesic or local anesthetic or pharmaceutically acceptable salt thereof over a much greater period, e.g., at least 7 days and in the range of 7 to 30 days, after the drug depot is administered to the site.

[0018] The polymer(s) in various embodiments may comprise about 10% to about 70% of the total wt.% of the drug depot or about 15% to about 55% of the total wt.% of

the drug depot. The polymer(s) is capable of degrading or degrades in 30 days or less after the drug depot is implanted at the site.

[0019] The drug depot in various embodiments may comprise a radiographic marker adapted to assist in radiographic imaging. The radiographic marker may comprise barium, calcium phosphate, and/or metal beads.

[0020] The drug depot in various embodiments may comprise at least one additional anti-inflammatory or analgesic agent, at least one anabolic or an anti-catabolic growth factor or a combination thereof.

[0021] The drug depot is capable of releasing or releases between 0.5 and 1,000 mg/day of the analgesic or local anesthetic including bupivacaine or a pharmaceutically acceptable salt thereof to reduce post-operative pain.

[0022] In various embodiments, bupivacaine may be in the form of a salt or base. Further, bupivacaine or a pharmaceutically acceptable salt thereof may be encapsulated in a plurality of depots comprising microparticles, microspheres, microcapsules, and/or microfibers suspended in a gel. The drug depot may be a ribbon-like strip or a gel formulation.

[0023] The target tissue site comprises at least one muscle, ligament, tendon, cartilage, spinal disc, spinal foraminal space near the spinal nerve root, facet or synovial joint, or spinal canal.

[0024] The pain may be associated with hernia repair, orthopedic or spine surgery or a combination thereof. The surgery may be arthroscopic surgery, an excision of a mass, hernia repair, spinal fusion, thoracic, cervical, or lumbar surgery, pelvic surgery or a combination thereof.

[0025] One or more drug depots of the present invention may be used to treat conditions of pain and/or inflammation in chronic conditions including rheumatoid arthritis, osteoarthritis, sciatica, carpal tunnel syndrome, lower back pain, lower extremity pain, upper extremity pain, cancer, tissue pain and pain associated with injury or repair of cervical, thoracic, and/or lumbar vertebrae or intervertebral discs, rotator cuff, articular joint, TMJ, tendons, ligaments, muscles, or the like.

[0026] Additional features and advantages of various embodiments will be set forth in part in the description that follows, and in part will be apparent from the description, or may be learned by practice of various embodiments. The objectives and other advantages

of various embodiments will be realized and attained by means of the elements and combinations particularly pointed out in the description and appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

5 [0027] In part, other aspects, features, benefits and advantages of the embodiments will be apparent with regard to the following description, appended claims and accompanying drawings where:

10 [0028] Figure 1 illustrates a number of common locations within a patient that may be sites where surgery is conducted and locations where the drug depot containing an analgesic or local anesthetic can be administered thereto.

[0029] Figure 2 illustrates a schematic dorsal view of the spine and sites where a drug depot containing an analgesic or local anesthetic can be administered thereto.

[0030] Figure 3 is a graphic representation of the average percentage cumulative release of bupivacaine formulations from Example 1.

15 [0031] Figure 4 is a graphic representation of the average cumulative daily release in milligrams for the bupivacaine formulations from Example 1.

[0032] Figure 5 is a graphic representation of the efficacy data from *in vivo* testing of bupivacaine formulations from Example 1.

20 [0033] Figure 6 is a graphic representation of the efficacy data from *in vivo* testing of bupivacaine formulations from Example 1.

[0034] Figure 7 is a graphic representation of a study of the average cumulative release in μg of bupivacaine sterilized POP implants described in Example 2. (POP refers to post-operative pain).

25 [0035] Figure 8 is a graphic representation of a study of the average percentage cumulative release of sterilized bupivacaine POP implants described in Example 2.

[0036] Figure 9 is a graphic representation of the thermal paw withdrawal threshold in grams per days post-surgery for bupivacaine implants from Example 2.

[0037] Figure 10 is a graphic representation of the average cumulative *in vitro* release profile for bupivacaine formulations from a study described in Example 4.

30 [0038] Figure 11 is a graphic representation of the average cumulative *in vitro* release profile for bupivacaine formulations from a study described in Example 4.

[0039] Figure 12 is a graphic representation of the average cumulative *in vitro* release profile for another bupivacaine formulation from a study described in Example 4.

[0040] Figure 13 is a graphic representation of the average cumulative *in vitro* release profile for bupivacaine implants from a study described in Example 5.

5 [0041] Figure 14 is a graphic representation of the average cumulative *in vitro* release profile for bupivacaine implants from a study described in Example 5.

[0042] Figure 15A is a graphic representation of the percentage cumulative release for three bupivacaine strips from a study described in Example 6.

10 [0043] Figure 15B is a graphic representation of the average percentage cumulative release for the bupivacaine strips shown in Figure 15A.

[0044] Figure 16A is a graphic representation of the cumulative *in vitro* release in *ug* for the three bupivacaine strips described in Example 6.

[0045] Figure 16B is a graphic representation of the average cumulative *in vitro* release in *ug* for the bupivacaine strips shown in Figure 16B.

15 [0046] Figure 17 is a graphic representation of pain scores of bupivacaine depots implanted post-operatively at the surgical incision.

[0047] It is to be understood that the figures are not drawn to scale. Further, the relation between objects in a figure may not be to scale, and may in fact have a reverse relationship as to size. The figures are intended to bring understanding and clarity to the structure of each object shown, and thus, some features may be exaggerated in order to illustrate a specific feature of a structure.

DETAILED DESCRIPTION

25 [0048] For the purposes of this specification and appended claims, unless otherwise indicated, all numbers expressing quantities of ingredients, percentages or proportions of materials, reaction conditions, and other numerical values used in the specification and claims, are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in the following specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained by the present invention. At the very
30 least, and not as an attempt to limit the application of the doctrine of equivalents to the

scope of the claims, each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques.

5 [0049] Notwithstanding that the numerical ranges and parameters setting forth the broad scope of the invention are approximations, the numerical values set forth in the specific examples are reported as precisely as possible. Any numerical value, however, inherently contains certain errors necessarily resulting from the standard deviation found in their respective testing measurements. Moreover, all ranges disclosed herein are to be understood to encompass any and all subranges subsumed therein. For example, a range of “1 to 10” includes any and all subranges between (and including) the minimum value of 1 and the maximum value of 10, that is, any and all subranges having a minimum value of equal to or greater than 1 and a maximum value of equal to or less than 10, *e.g.*, 5.5 to 10.

10 [0050] It is noted that, as used in this specification and the appended claims, the singular forms “a,” “an,” and “the,” include plural referents unless expressly and unequivocally limited to one referent. Thus, for example, reference to “a drug depot” includes one, two, three or more drug depots.

15 [0051] Reference will now be made in detail to certain embodiments of the invention, examples of which are illustrated in the accompanying drawings. While the invention will be described in conjunction with the illustrated embodiments, it will be understood that they are not intended to limit the invention to those embodiments. On the contrary, the invention is intended to cover all alternatives, modifications, and equivalents, which may be included within the invention as defined by the appended claims.

20 [0052] The headings below are not meant to limit the disclosure in any way; embodiments under any one heading may be used in conjunction with embodiments under any other heading.

25 [0053] New compositions and methods are provided that effectively prevent, treat or reduce post-operative pain or inflammation. In various embodiments, compositions and methods are provided that have long acting analgesic and anti-inflammatory effects over periods of at least 4 days in a single drug depot or multiple drug depots. New analgesic compositions and methods are provided, which can easily allow accurate and precise implantation of a drug depot including an analgesic such as bupivacaine with minimal physical and psychological trauma to a patient. The drug depot can now be easily delivered to the target tissue site (*e.g.*, abdomen, synovial joint, at or near the spinal

30

column, *etc.*) and alleviate and/or treat pain for at least 4 to 10 days. In this way, accurate and precise implantation of the drug depot in a minimally invasive procedure as well as an open procedure can be accomplished.

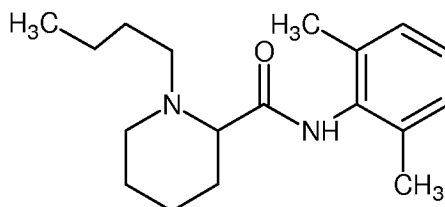
5 **Bupivacaine**

[0054] Bupivacaine or another local anesthetic may be contained in a drug depot. A drug depot comprises a physical structure to facilitate implantation and retention in a desired site (*e.g.*, a synovial joint, a disc space, a spinal canal, abdominal area, a tissue of the patient, *etc.*). The drug depot also comprises the drug. The term “drug” as used herein is generally meant to refer to any substance that alters the physiology of a patient. The term “drug” may be used interchangeably herein with the terms “therapeutic agent”, “therapeutically effective amount”, and “active pharmaceutical ingredient” or “API”. It will be understood that a “drug” formulation may include more than one therapeutic agent, wherein exemplary combinations of therapeutic agents include a combination of two or more drugs. The drug depot provides a concentration gradient of the therapeutic agent for delivery to the site. In various embodiments, the drug depot provides an optimal drug concentration gradient of the therapeutic agent at a distance of up to about 1 cm to about 10 cm from the implant site.

[0055] A “therapeutically effective amount” or “effective amount” is such that when administered, the drug results in alteration of the biological activity, such as, for example, inhibition of inflammation, reduction or alleviation of pain, improvement in the condition, *etc.* In various embodiments, the therapeutically effective amount of bupivacaine comprises from about 0.5 mg to 1,000 mg/day. In some embodiments, the therapeutically effective amount of bupivacaine comprises from about 0.1 mg to 800 mg of bupivacaine per day. In some embodiments, the therapeutically effective amount of bupivacaine comprises from about 50 mg to 800 mg of bupivacaine per day or from about 200 mg to 800 mg of bupivacaine per day. In some embodiments, the therapeutically effective amount of bupivacaine comprises about 0.5 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, or 1,000 mg of bupivacaine per day and all subranges therebetween. In some embodiments, the therapeutically effective amount of bupivacaine comprises 0.5mg, 0.6mg, 0.7mg, 0.8mg, 0.9mg, 1mg, 1.1mg, 1.2mg, 1.3mg, 1.4mg, 1.5mg, 1.6mg, 1.7mg, 1.8mg, 1.9mg, 2mg, 3mg, 4mg, 5mg, 6mg, 7mg, 8mg, 9mg,

10mg, 11mg, 12mg, 13mg, 14mg, 15mg, 16mg, 17mg, 18mg, 19mg, 20mg, 21mg, 22mg,
23mg, 24mg, 25mg, 30mg, 35mg, or 40mg of bupivacaine per day. In one embodiment,
the dosage to a human is between 400 mg and 600 mg of bupivacaine per day. It will be
understood that the dosage administered to a patient can be as single depot or multiple
5 depots depending upon a variety of factors, including the drug's administered
pharmacokinetic properties, the route of administration, patient conditions and
characteristics (sex, age, body weight, health, size, *etc.*), extent of symptoms, concurrent
treatments, frequency of treatment and the effect desired. For example, lower daily doses
of bupivacaine may be needed when there is concurrent treatment with an opioid (*e.g.*,
10 morphine), alternatively, the patient may require higher doses of bupivacaine as the
dosage of the opioid (*e.g.*, morphine) is reduced or eliminated to control post-operative
pain.

[0056] In various embodiments, a therapeutically effective amount of bupivacaine is
provided to inhibit, treat and/or prevent post-operative pain or inflammation. In general,
15 the chemical name of bupivacaine is 1-butyl-*N*-(2,6-dimethylphenyl) piperidine-2-
carboxamide. Bupivacaine has a molecular weight of 288.43 and exhibits the following
general structure:



[0057] Bupivacaine includes, but is not limited to, (+/-)-1-butyl-*N*-(2,6-
20 dimethylphenyl) piperidine-2-carboxamide or pharmaceutically acceptable non-toxic
esters or salts thereof. Bupivacaine includes the racemic mixtures ((+)-*R* and (-)-*S*
enantiomers) or each of the dextro and levo isomers of bupivacaine individually.
Bupivacaine includes the free acid as well as any other pharmaceutically acceptable salt of
any one of the foregoing. Bupivacaine may also be pegylated for long acting activity.

[0058] Pharmaceutically acceptable esters of bupivacaine include but are not limited
25 to, alkyl esters derived from hydrocarbons of branched or straight chain having one to
about 12 carbon atoms. Examples of such esters are methyl, ethyl, propyl, isopropyl,
butyl, *t*-butyl, isoamyl, pentyl, isopentyl, hexyl, octyl, nonyl, isodecyl, 6-methyldecyl or
dodecyl esters.

[0059] Pharmaceutically acceptable salts of bupivacaine include salts derived from either inorganic or organic bases. Salts derived from inorganic bases include, but are not limited to, sodium, potassium, lithium, ammonium, calcium, magnesium, ferrous, zinc, copper, manganese, aluminum, ferric, manganic salts or the like. Salts derived from pharmaceutically acceptable organic non-toxic bases include, but are not limited to, salts of primary, secondary, or tertiary amines, substituted amines including naturally occurring substituted amines or cyclic amines or basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, tromethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins or the like.

[0060] In addition to bupivacaine, the drug depot may comprise one or more additional therapeutic agents. Examples of therapeutic agents include, those that are direct- and local-acting modulators of pro-inflammatory cytokines such as TNF- α and IL-1 including, but not limited to, soluble tumor necrosis factor α receptors, any pegylated soluble tumor necrosis factor α receptor, monoclonal or polyclonal antibodies or antibody fragments or combinations thereof. Examples of suitable therapeutic agents include receptor antagonists, molecules that compete with the receptor for binding to the target molecule, antisense polynucleotides, and inhibitors of transcription of the DNA encoding the target protein. Suitable examples include but are not limited to Adalimumab, Infliximab, Etanercept, Pegsunercept (PEG sTNF-R1), sTNF-R1, CDP-870, CDP-571, CNI-1493, RDP58, ISIS 104838, 1 \rightarrow 3- β -D-glucans, Lenercept, PEG-sTNFRII Fc Mutein, D2E7, Afelimomab, and combinations thereof. In other embodiments, a therapeutic agent includes metalloprotease inhibitors, glutamate antagonists, glial cell-derived neurotrophic factors (GDNF), B2 receptor antagonists, Substance P receptor (NK1) antagonists such as capsaicin and civamide, downstream regulatory element antagonistic modulator (DREAM), iNOS, inhibitors of tetrodotoxin (TTX)-resistant Na⁺ -channel receptor subtypes PN3 and SNS2, inhibitors of interleukins such as IL-1, IL-6 and IL-8, and anti-inflammatory cytokines, TNF binding protein, onercept (r-hTBP-1), recombinant adeno-associated viral (rAAV) vectors encoding inhibitors, enhancers, potentiators, or neutralizers, antibodies, including but not limited to naturally occurring or synthetic,

double-chain, single-chain, or fragments thereof. For example, suitable therapeutic agents include molecules that are based on single chain antibodies called Nanobodies™ (Ablynx, Ghent Belgium), which are defined as the smallest functional fragment of a naturally occurring, single-domain antibody. Alternatively, therapeutic agents include, agents that effect kinases and/or inhibit cell signaling mitogen-activated protein kinases (MAPK), p38 MAPK, Src or protein tyrosine kinase (PTK). Therapeutic agents include, kinase inhibitors such as, for example, Gleevec, Herceptin, Iressa, imatinib (STI571), herbimycin A, tyrphostin 47, erbstatin, genistein, staurosporine, PD98059, SB203580, CNI-1493, VX-50/702 (Vertex/Kissei), SB203580, BIRB 796 (Boehringer Ingelheim), Glaxo P38 MAP Kinase inhibitor, RWJ67657 (J&J), UO126, Gd, SCIO-469 (Scios), RO3201195 (Roche), Semipimod (Cytokine PharmaSciences), or derivatives thereof.

[0061] Therapeutic agents, in various embodiments, block the transcription or translation of TNF- α or other proteins in the inflammation cascade. Suitable therapeutic agents include, but are not limited to, integrin antagonists, alpha-4 beta-7 integrin antagonists, cell adhesion inhibitors, interferon gamma antagonists, CTLA4-Ig agonists/antagonists (BMS-188667), CD40 ligand antagonists, Humanized anti-IL-6 mAb (MRA, Tocilizumab, Chugai), HMGB-1 mAb (Critical Therapeutics Inc.), anti-IL2R antibodies (daclizumab, basilicimab), ABX (anti IL-8 antibodies), recombinant human IL-10, or HuMax IL-15 (anti-IL 15 antibodies).

[0062] Other suitable therapeutic agents include IL-1 inhibitors, such Kineret® (anakinra) which is a recombinant, non-glycosylated form of the human interleukin-1 receptor antagonist (IL-1Ra), or AMG 108, which is a monoclonal antibody that blocks the action of IL-1. Therapeutic agents also include excitatory amino acids such as glutamate and aspartate, antagonists or inhibitors of glutamate binding to NMDA receptors, AMPA receptors, and/or kainate receptors. Interleukin-1 receptor antagonists, thalidomide (a TNF- α release inhibitor), thalidomide analogues (which reduce TNF- α production by macrophages), bone morphogenetic protein (BMP) type 2 and BMP-4 (inhibitors of caspase 8, a TNF- α activator), quinapril (an inhibitor of angiotensin II, which upregulates TNF- α), interferons such as IL-11 (which modulate TNF- α receptor expression), and aurin-tricarboxylic acid (which inhibits TNF- α), for example, may also be useful as therapeutic agents for reducing inflammation. It is contemplated that where desirable a pegylated form of the above may be used. Examples of other therapeutic

agents include NF kappa B inhibitors such as glucocorticoids, clonidine; antioxidants, such as dithiocarbamate, and other compounds, such as, for example, sulfasalazine.

[0063] Specific examples of therapeutic agents suitable for use include, but are not limited to an anti-inflammatory agent, analgesic agent, or osteoinductive growth factor or a combination thereof. Anti-inflammatory agents include, but are not limited to, salicylates, diflunisal, sulfasalazine, indomethacin, ibuprofen, naproxen, tolmetin, diclofenac, ketoprofen, fenamates (mefenamic acid, meclofenamic acid), enolic acids (piroxicam, meloxicam), nabumetone, celecoxib, etodolac, nimesulide, apazone, gold, sulindac or tepoxalin; antioxidants, such as dithiocarbamate, and other compounds such as sulfasalazine [2-hydroxy-5-[-4-[C2-pyridinylamino)sulfonyl]azo]benzoic acid], steroids, such as fluocinolone, cortisol, cortisone, hydrocortisone, fludrocortisone, prednisone, prednisolone, methylprednisolone, triamcinolone, betamethasone, dexamethasone, beclomethasone, fluticasone or a combination thereof.

[0064] Suitable anabolic growth or anti-catabolic growth factors include, but are not limited to, a bone morphogenetic protein, a growth differentiation factor, a LIM mineralization protein, CDMP or progenitor cells or a combination thereof.

[0065] Additional analgesic agents may also be included in the depot. Suitable analgesic agents include, but are not limited to, acetaminophen, lidocaine, opioid analgesics such as buprenorphine, butorphanol, dextromoramide, dezocine, dextropropoxyphene, diamorphine, fentanyl, alfentanil, sufentanil, hydrocodone, hydromorphone, ketobemidone, levomethadyl, mepiridine, methadone, morphine, nalbuphine, opium, oxycodone, papaveretum, pentazocine, pethidine, phenoperidine, piritramide, dextropropoxyphene, remifentanil, tilidine, tramadol, codeine, dihydrocodeine, meptazinol, dezocine, eptazocine, flupirtine or a combination thereof.

[0066] Suitable analgesics also include agents with analgesic properties, such as for example, amitriptyline, carbamazepine, gabapentin, pregabalin, clonidine, or a combination thereof.

[0067] The depot may contain a muscle relaxant. Exemplary muscle relaxants include by way of example and not limitation, alcuronium chloride, atracurium besylate, baclofen, carbolonium, carisoprodol, chlorphenesin carbamate, chlorzoxazone, cyclobenzaprine, dantrolene, decamethonium bromide, fazadinium, gallamine triethiodide, hexafluorenium, meladrazine, mephensin, metaxalone, methocarbamol, metocurine iodide,

pancuronium, pridinol mesylate, styramate, suxamethonium, suxethonium, thiocolchicoside, tizanidine, tolperisone, tubocuarine, vecuronium, or combinations thereof.

5 [0068] The depot comprises the therapeutic agent or agents and may also contain other non-active ingredients. These non-active ingredients may have a multi-functional purpose including the carrying, stabilizing and controlling of the release of the therapeutic agent(s). The sustained release process, for example, may be by a solution-diffusion mechanism or it may be governed by an erosion-controlled process. Typically, the depot will be a solid or semi-solid formulation comprised of a biocompatible material, which can be biodegradable. The term “solid” is intended to mean a non-gel like material, while, 10 “semi-solid” is intended to mean a gel like material that has some degree of flowability, thereby allowing the depot to bend and conform to the surrounding tissue requirements. The term “gel” is intended to mean a material that is soft and deformable at any point in its application to the surgical site.

15 [0069] In various embodiments, the depot material will be durable within the tissue site for a period of time similar to (for biodegradable components) or greater than (for non-biodegradable components) the planned period of drug delivery. For example, the depot material may have a melting point or glass transition temperature close to or higher than body temperature, but lower than the decomposition or degradation temperature of 20 the therapeutic agent. However, the pre-determined erosion of the depot material can also be used to provide for slow release of the loaded therapeutic agent(s).

25 [0070] In various embodiments, the drug depot may be designed to release the local anesthetic such as bupivacaine when certain trigger points are reached (*e.g.*, temperature, pH, *etc.*) after implantation *in vivo*. For example, the drug depot may comprise polymers that will release more drug as the body temperature reaches greater than, for example, 102°F, particularly if the drug possesses antipyretic properties. In various embodiments, depending on the site of implantation, the drug depot may release more or less drug as a certain pH is reached. For example, the drug depot may be designed to release the drug as the bodily fluid having a certain pH contact the drug depot (*e.g.*, CSF having a pH of 30 about 7.35 to about 7.70, synovial fluid having a pH of about 7.29 to about 7.45; urine having a pH of about 4.6 to about 8.0, pleural fluids having a pH of about 7.2 to about 7.4, blood having a pH of about 7.35 to about 7.45, *etc.*).

[0071] In various embodiments, the depot may have a high drug loading, such that the local anesthetic such as bupivacaine and/or other therapeutic agent comprises about 5-99 wt.% of the depot, or 30-95 wt.% of the depot, 30-90 wt.% of the depot, or 50-75 wt.% of the depot, or 55-65 wt.% of the depot. In various embodiments, the amount of bupivacaine and/or other therapeutic agent are present in the depot in a range from about 40% to about 80% by weight of the depot (including 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, and any ranges between any two of these points, for instance, 40.1-50%, 50-60% and 60-70%, etc.).

[0072] In various embodiments, the drug depot may release 0.1mg, 0.2mg, 0.3mg, 0.4mg, 0.5mg, 0.6mg, 0.7mg, 0.8mg, 0.9mg, 1mg, 1.1mg, 1.2mg, 1.3mg, 1.4mg, 1.5mg, 1.6mg, 1.7mg, 1.8mg, 1.9mg, 2mg, 3mg, 4mg, 5mg, 6mg, 7mg, 8mg, 9mg, 10mg, 11mg, 12mg, 13mg, 14mg, 15mg, 16mg, 17mg, 18mg, 19mg, 20mg, 21mg, 22mg, 23mg, 24mg, 25mg, 30mg, 35mg, or 40mg, 45mg, 50mg, 55mg, 60mg, 65mg, 70mg, 75mg, 75mg, 80mg, 85mg, 90mg, 95mg, 100mg, 105mg, 110mg, 115mg, 120mg, 125mg, 130mg, 135mg, 140mg, 145mg, 150mg, 155mg, 160mg, 165mg, 170mg, 175mg, 180mg, 185mg, 190mg, 195mg, 200mg, 300mg, 400mg, 500mg, 600mg, 700mg 800mg, 900mg, or 1,000mg of bupivacaine per day and all subranges therebetween for a total of at least 4 days, at least 7 days, at least 8 days, 4 to 30 days, 4 to 10 days, 4 to 8 days, 5 to 7 days, or 7 to 10 days. In various embodiments, the drug depot may release 0.5mg to 20mg of bupivacaine per hour for a total of at least 4 days, 4 to 10 days, 5 to 7 days or 7 to 10 days to reduce, treat or prevent post-operative pain. In various embodiments, the drug depot releases 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or 100% of the bupivacaine over a period of 3 to 10 days, 4 to 10 days, or 5 to 7 days after the drug depot is administered to the target tissue site. The drug depot may have a "release rate profile" that refers to the percentage of active ingredient that is released over fixed units of time, *e.g.*, mg/hr, mg/day, 10% per day for ten days, *etc.* As persons of ordinary skill know, a release rate profile may be but need not be linear. By way of a non-limiting example, the drug depot may be a strip or a ribbon-like strip or fiber that releases the bupivacaine over a period of time.

[0073] In various embodiments, the drug depot comprises from about 40% to 80% by weight bupivacaine, 15% to 55% by weight of a polymer and 5% to 15% by weight of an excipient. mPEG may be used as an excipient or plasticizer for a polymer as it imparts malleability to the resulting formulation. PEG 300 may also be used as an excipient. In addition, a combination of PEG 300 and NMP may be used as the excipient.

[0074] Exemplary excipients that may be formulated with bupivacaine in addition to the biodegradable polymer include but are not limited to MgO (*e.g.*, 1 wt.%), 5050 DLG 6E, 5050 DLG 1A, mPEG, TBO-Ac, mPEG, Span-65, Span-85, pluronic F127, TBO-Ac, sorbital, cyclodextrin, maltodextrin and combinations thereof. In some embodiments, the excipient or excipients may comprise from about 0.001 wt.% to about 50 wt.% of the formulation. In some embodiments, the excipient(s) comprise from about 0.001 wt.% to about 40 wt.% of the formulation. In some embodiments, the excipient(s) comprise from about 0.001 wt.% to about 30 wt.% of the formulation. In some embodiments, the excipient(s) comprise from about 0.001 wt.% to about 20 wt.% of the formulation. In some embodiments, the excipient(s) comprise from about 0.5 wt.% to about 20 wt.% of the formulation. In some embodiments, the excipient(s) comprise from about 0.001 wt.% to about 10 wt.% of the formulation. In some embodiments, the excipient(s) comprise from about 0.001 wt.% to about 2 wt.% of the formulation.

[0075] In some embodiments, the drug depot may not be biodegradable. For example, the drug depot may comprise polyurethane, polyurea, polyether(amide), PEBA, thermoplastic elastomeric olefin, copolyester, and styrenic thermoplastic elastomer, steel, aluminum, stainless steel, titanium, metal alloys with high non-ferrous metal content and a low relative proportion of iron, carbon fiber, glass fiber, plastics, ceramics or combinations thereof. Typically, these types of drug depots may need to be removed after a certain amount of time.

[0076] In some instances, it may be desirable to avoid having to remove the drug depot after use. In those instances, the drug depot may comprise a biodegradable material. There are numerous materials available for this purpose and having the characteristic of being able to breakdown or disintegrate over a prolonged period of time when positioned at or near the target tissue. As function of the chemistry of the biodegradable material the mechanism of the degradation process can be hydrolytical or enzymatical in nature, or both. In various embodiments, the degradation can occur either at the surface

(heterogeneous or surface erosion) or uniformly throughout the drug delivery system depot (homogeneous or bulk erosion).

[0077] The drug depot may comprise a polymeric or non-polymeric material as well as a synthetic or naturally occurring material, or a combination thereof. Non-polymeric materials include, for example, cholesterol, stigmasterol, glycerol, estradiol, sucrose, distearate, sorbitan, sorbitan monooleate, sorbitan monopalmitate, sorbitan tristearate, or the like.

[0078] In various embodiments, the drug depot comprises a polymer and the polymer will degrade in vivo over a period of less than a year, with at least 50% of the polymer degrading within six months or less. In some embodiments, the polymer is capable of or will degrade in two months, one month or less. In some embodiments, the polymer will degrade significantly within a month, with at least 50% of the polymer degrading into non-toxic residues which are removed by the body, and 100% of the drug being released within a two week period. Polymers should also degrade by hydrolysis by surface erosion, rather than by bulk erosion, so that release is not only sustained but also linear. Polymers which meet this criteria include some of the polyanhydrides, copolymers of lactic acid and glycolic acid wherein the weight ratio of lactic acid to glycolic acid is no more than 4:1 (i.e., 80% or less lactic acid to 20% or more glycolic acid by weight), and polyorthoesters containing a catalyst or degradation enhancing compound, for example, containing at least 1% by weight anhydride catalyst such as maleic anhydride. Other polymers include protein polymers such as gelatin and fibrin and polysaccharides such as hyaluronic acid.

[0079] A “depot” includes but is not limited to capsules, microspheres, microparticles, microcapsules, microfibers particles, nanospheres, nanoparticles, coating, matrices, wafers, pills, pellets, emulsions, liposomes, micelles, sheets, strips, ribbon-like strips or fibers, mesh, a paste, a slab, pellets, gels, or other pharmaceutical delivery compositions. Suitable materials for the depot are ideally pharmaceutically acceptable biodegradable and/or any bioabsorbable materials that are preferably FDA approved or GRAS materials. These materials can be polymeric or non-polymeric, as well as synthetic or naturally occurring, or a combination thereof.

[0080] The term “biodegradable” includes that all or parts of the drug depot will degrade over time by the action of enzymes, by hydrolytic action and/or by other similar

mechanisms in the human body. In various embodiments, “biodegradable” includes that the depot (e.g., microparticle, microsphere, gel, *etc.*) can break down or degrade within the body to non-toxic components after or while a therapeutic agent has been or is being released. By “bioerodible,” it is meant that the depot and/or gel will erode or degrade over time due, at least in part, to contact with substances found in the surrounding tissue, fluids or by cellular action. By “bioabsorbable,” it is meant that the depot will be broken down and absorbed within the human body, for example, by a cell or tissue. “Biocompatible” means that the depot will not cause substantial tissue irritation or necrosis at the target tissue site.

5 [0081] In various embodiments, the depot may comprise a bioabsorbable, a bioabsorbable, and/or a biodegradable biopolymer that may provide immediate release, sustained release or controlled release of the drug. Examples of suitable sustained release biopolymers include but are not limited to poly (alpha-hydroxy acids), poly(lactide-co-glycolide) (PLGA or DLG) (which includes poly(lactide-co-glycolide), poly(D-lactide-co-glycolide), poly(L-lactide-co-glycolide) and poly(D,L-lactide-co-glycolide), polylactide (PLA), polyglycolide (PG), polyorthoester(s) (POE), polyethylene glycol (PEG), PEG 200, PEG 300, PEG 400, PEG 500, PEG 550, PEG 600, PEG 700, PEG 800, PEG 900, PEG 1000, PEG 1450, PEG 3350, PEG 4500, PEG 8000, conjugates of poly (alpha-hydroxy acids), polyaspirins, polyphosphagenes, collagen, starch, pre-gelatinized starch, 10 hyaluronic acid, chitosans, gelatin, alginates, albumin, fibrin, vitamin E analogs, such as alpha tocopheryl acetate, d-alpha tocopheryl succinate, D-lactide, D,L-lactide, L-lactide, D,L-lactide-caprolactone (DL-CL), D,L-lactide-glycolide-caprolactone (DL-G-CL), dextrans, vinylpyrrolidone, polyvinyl alcohol (PVA), PVA-g-PLGA, PEGT-PBT copolymer (polyactive), methacrylates, poly (N-isopropylacrylamide), PEO-PPO-PEO (plurionics), PEO-PPO-PAA copolymers, PLGA-PEO-PLGA, PEG-PLG, PLA-PLGA, poloxamer 407, PEG-PLGA-PEG triblock copolymers, SAIB (sucrose acetate isobutyrate) hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl methylcellulose, carboxymethylcellulose or salts thereof, Carbopol, poly(hydroxyethylmethacrylate), poly(methoxyethylmethacrylate), poly(methoxyethoxy-ethylmethacrylate), 25 polymethylmethacrylate (PMMA), methylmethacrylate (MMA), gelatin, polyvinyl alcohols, propylene glycol, or combinations thereof.

[0082] In various embodiments, the molecular weight of the polymer can be a wide range of values. The average molecular weight of the polymer can be from about 1000 to about 10,000,000; or about 1,000 to about 1,000,000; or about 5,000 to about 500,000; or about 10,000 to about 100,000; or about 20,000 to 50,000.

5 **[0083]** In some embodiments, the polymer comprises PLGA or POE or a combination thereof. The PLGA may comprise a mixture of polyglycolide and polylactide and in some embodiments, in the mixture, there is more polylactide than polyglycolide. In various embodiments, the PLGA may comprise: 100% polylactide and 0% polyglycolide; 95% polylactide and 5% polyglycolide; 90% polylactide and 10% polyglycolide; 85% polylactide and 15% polyglycolide; 80% polylactide and 20% polyglycolide; 75% polylactide and 25% polyglycolide; 70% polylactide and 30% polyglycolide; 65% polylactide and 35% polyglycolide; 60% polylactide and 40% polyglycolide; 55% polylactide and 45% polyglycolide; 50% polylactide and 50% polyglycolide; 45% polylactide and 55% polyglycolide; 40% polylactide and 60% polyglycolide; 35% polylactide and 65% polyglycolide; 30% polylactide and 70% polyglycolide; 25% polylactide and 75% polyglycolide; 20% polylactide and 80% polyglycolide; 15% polylactide and 85% polyglycolide; 10% polylactide and 90% polyglycolide; 5% polylactide and 95% polyglycolide; or 0% polylactide and 100% polyglycolide.

10 20 **[0084]** In various embodiments that comprise both polylactide and polyglycolide, there is at least 95% polylactide; at least 90% polylactide; at least 85% polylactide; at least 80% polylactide; at least 75% polylactide; at least 70% polylactide; at least 65% polylactide; at least 60% polylactide; at least 55%; at least 50% polylactide; at least 45% polylactide; at least 40% polylactide; at least 35% polylactide; at least 30% polylactide; at least 25% polylactide; at least 20% polylactide; at least 15% polylactide; at least 10% polylactide; or at least 5% polylactide; and the remainder of the biopolymer is polyglycolide.

25 30 **[0085]** In various embodiments, when the drug depot comprises a polymer, it is employed at about 10 wt.% to about 90 wt.%, about 10 wt.% to about 80 wt.%, about 10 wt.% to about 70 wt.%, about 10 wt.% to about 50 wt.%, or about 20 wt.% to about 40 wt.% based on the weight of the drug depot.

[0086] In some embodiments, at least 75% of the particles have a size from about 1 micrometer to about 200 micrometers. In some embodiments, at least 85% of the particles have a size from about 1 micrometer to about 200 micrometers. In some embodiments, at least 95% of the particles have a size from about 1 micrometer to about 200 micrometers. In some embodiments, all of the particles have a size from about 1 micrometer to about 200 micrometers.

[0087] In some embodiments, at least 75% of the particles have a size from about 20 micrometer to about 100 micrometers. In some embodiments, at least 85% of the particles have a size from about 20 micrometers to about 100 micrometers. In some embodiments, at least 95% of the particles have a size from about 20 micrometer to about 100 micrometers. In some embodiments, all of the particles have a size from about 20 micrometer to about 100 micrometers.

[0088] In some embodiments, the polymer comprises DL-CL or a combination thereof. The DL-CL may comprise a mixture of lactide and caprolactone. The molar ratio of lactide to caprolactone can be 10:90 to 90:10 and all subranges therebetween (e.g., 20:80, 30:70, 45:55, 65:35, 67:33, 89:11, etc.).

[0089] In some embodiments, the polymer comprises DL-G-CL or a combination thereof. The DL-G-CL may comprise a mixture of lactide, glycolide and caprolactone. In some embodiments, the molar ratio of lactide to glycolide to caprolactone may be 30:20:50. In some embodiments, the mixture may comprise 5-50% lactide, 5-50% glycolide, and 20-80% caprolactone.

[0090] In various embodiments, when the drug depot comprises a polymer, it may be employed at about 10 wt.% to about 90 wt.%, about 15 wt.% to about 55 wt.%, about 25 wt.% to about 45 wt.%, or about 30 wt.% to about 35 wt.% based on the weight of the drug depot.

[0091] The depot may optionally contain inactive materials such as buffering agents and pH adjusting agents such as potassium bicarbonate, potassium carbonate, potassium hydroxide, sodium acetate, sodium borate, sodium bicarbonate, sodium carbonate, sodium hydroxide or sodium phosphate; degradation/release modifiers; drug release adjusting agents; emulsifiers; preservatives such as benzalkonium chloride, chlorobutanol, phenylmercuric acetate and phenylmercuric nitrate, sodium bisulfite, sodium bisulfate, sodium thiosulfate, thimerosal, methyl and other paraben, polyvinyl alcohol and

phenylethyl alcohol; solubility adjusting agents; stabilizers; and/or cohesion modifiers. Typically, any such inactive materials will be present within the range of 0-75 wt.%, and more typically within the range of 0-30 wt.%. If the depot is to be placed in the spinal area or joint area, in various embodiments, the depot may comprise sterile preservative free material.

[0092] The depot can be different sizes, shapes and configurations. There are several factors that can be taken into consideration in determining the size, shape and configuration of the drug depot. For example, both the size and shape may allow for ease in positioning the drug depot at the target tissue site that is selected as the implantation or injection site. In addition, the shape and size of the system should be selected so as to minimize or prevent the drug depot from moving after implantation or injection. In various embodiments, the drug depot can be shaped like a sphere, a cylinder such as a rod or fiber, a flat surface such as a disc, film, ribbon, strip or sheet, a paste, a slab, microparticles, nanoparticles, pellets, mesh or the like. Flexibility may be a consideration so as to facilitate placement of the drug depot. In various embodiments, the drug depot can be different sizes, for example, the drug depot may be a length of from about 0.5 mm to 100 mm and have a diameter or thickness of from about 0.01 to about 5 mm. In various embodiments, the drug depot may have a layer thickness of from about 0.005 to 5.0 mm, such as, for example, from 0.05 to 2.0 mm. In some embodiments, the shape may be a strip or a ribbon-like strip and the strip or ribbon-like strip has a ratio of width to thickness in the range of 2 to 20 or greater.

[0093] Radiographic markers can be included on or in the drug depot to permit the user to accurately position the depot into the target site of the patient. These radiographic markers will also permit the user to track movement and degradation of the depot at the site over time. In this embodiment, the user may accurately position the depot in the site using any of the numerous diagnostic imaging procedures. Such diagnostic imaging procedures include, for example, X-ray imaging or fluoroscopy. Examples of such radiographic markers include, but are not limited to, barium, calcium, and/or metal beads or particles. Where present, the radiographic marker is typically present in an amount of from about 10% to about 40% (including 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39% and 40%, as well as ranges between any two of

these values, e.g., 10-15%, 15-20%, 20-25%, 25-30%, 30-35%, 35-40%, and so forth, with 15-30% being more typical, even more typically 20-25%). In various embodiments, the radiographic marker could be a spherical shape or a ring around the depot.

[0094] In some embodiments, the drug depot has pores that allow release of the drug from the depot. The drug depot will allow fluid in the depot to displace the drug. However, cell infiltration into the depot will be prevented by the size of the pores of the depot. In this way, in some embodiments, the depot will not function as a tissue scaffold and will not allow tissue growth. Rather, the drug depot will solely be utilized for drug delivery. In some embodiments, the pores in the drug depot will be less than 250 to 500 microns. This pore size will prevent cells from infiltrating the drug depot and laying down scaffolding cells. Thus, in this embodiment, drug will elute from the drug depot as fluid enters the drug depot, but cells will be prevented from entering. In some embodiments, where there are little or no pores, the drug will elute out from the drug depot by the action of enzymes, by hydrolytic action and/or by other similar mechanisms in the human body. In other embodiments, the drug depot may have pore sizes above 500 microns to allow influx of cells and drug release and the drug depot may function, in this embodiment, as a tissue scaffold.

[0095] In one exemplary embodiment, a drug depot for delivering a therapeutic agent to a target tissue site beneath the skin of a patient is provided, the drug depot comprising an effective amount of bupivacaine, wherein the target tissue site comprises at least one muscle, ligament, tendon, cartilage, spinal disc, spinal foraminal space near the spinal nerve root, facet or synovial joint, or spinal canal.

[0096] In various embodiments, the drug depot comprises a gel, which includes a substance having a gelatin, jelly-like, or colloidal properties at room temperature. The gel, in various embodiments, may have the bupivacaine and optionally one or more additional therapeutic agents dispersed throughout it or suspended within the gel. The dispersal of the therapeutic agent may be even throughout the gel. Alternatively, the concentration of the therapeutic agent may vary throughout it. As the biodegradable material of the gel or drug depot degrades at the site, the therapeutic agent is released.

[0097] When the drug depot is a gel, in contrast to a sprayable gel that typically employs a low viscosity polymer, a gel with a higher viscosity may be desirable for other applications, for example, a gel having a putty-like consistency may be more preferable

for bone regeneration applications. In various embodiments, when a polymer is employed in the gel, the polymeric composition includes about 10 wt.% to about 50 wt.% or about 15 wt.% to about 30 wt.% of the polymer.

5 [0098] In another exemplary embodiment, the gel in viscous form is loaded with one or more drug depots (*e.g.*, microspheres loaded with a therapeutic agent), wherein the viscous gel is positioned into a synovial joint, disc space, a spinal canal, or a soft tissue surrounding the spinal canal of a subject. The gel can also be used, in various
10 embodiments, to seal or repair tissue. In yet another exemplary embodiment, the gel is injectable, and/or an adherent gel that solidifies upon contact with tissue. For example, the gel may be administered as a liquid that gels *in situ* at the target tissue site. In various
15 embodiments, the gel can comprise a two part system where a liquid is administered and a gelling agent is added subsequently to cause the liquid to gel or harden.

[0099] In various embodiments, the gel is a hardening gel, where after the gel is applied to the target site, it hardens and the drug can be released as the bodily fluid
20 contacts the gel.

[00100] In various embodiments, the drug depot is loaded with bupivacaine and optionally one or more additional therapeutic agents, and delivered to the desired target
25 tissue site (*e.g.*, surgical wound site, inflamed tissue, degenerative tissue, *etc.*) and, in various embodiments, the drug depot may be held in place by a suture, barb, staple, adhesive gel, *etc.* which prevents the drug depot from being removed from that site by the venous systemic circulation or otherwise dispersed too widely, which reduces the desired
30 therapeutic effect. For example, after hours or days, the drug depot may degrade, thereby allowing the drug depots (*e.g.*, strips, ribbon-like strips, *etc.*) to begin releasing the therapeutic agent. The strips may be formed from an insoluble or inert substance, but soluble or active once it comes into contact with the target tissue site. Likewise, the drug depot may comprise a substance that dissolves or disperses within the tissue. As the drug depot begins to dissolve within hours to days, the drug depots (*e.g.*, strips) are exposed to body fluids and begin releasing their contents. The drug depot can be formulated to optimize exposure time of the drug depot and release of the therapeutic agent from the
35 drug depot.

[00101] In various embodiments, the drug depot (*e.g.*, gel) is flowable and can be injected, sprayed, instilled, and/or dispensed to, on or in the target tissue site. "Flowable"

means that the gel formulation is easy to manipulate and may be brushed, sprayed, dripped, painted, injected, shaped and/or molded at or near the target tissue site as it coagulates. "Flowable" includes formulations with a low viscosity or water-like consistency to those with a high viscosity, such as a paste-like material. In various 5 embodiments, the flowability of the formulation allows it to conform to irregularities, crevices, cracks, and/or voids in the tissue site. For example, in various embodiments, the gel may be used to fill one or more voids in an osteolytic lesion.

[00102] In various embodiments, the drug depot comprises poly (alpha-hydroxy acids), PLGA, D,L-lactide-glycolide-ε-caprolactone, PLA, PG, polyethylene glycol 10 conjugates of poly (alpha-hydroxy acids), polyorthoesters, poly(lactic acid-co-lysine), poly(lactide-co-urethane), poly(ester-co-amide), polyaspirins, polyphosphazenes, polyanhydrides; polyketals, collagen, starch, pre-gelatinized starch, hyaluronic acid, chitosans, gelatin, alginates, albumin, fibrin, vitamin E analogs, such as alpha tocopheryl acetate, d-alpha tocopheryl succinate, D,L-lactide, D-lactide, L-lactide, D,L-lactide- 15 caprolactone, D,L-lactide-glycolide-caprolactone, dextrans, vinylpyrrolidone, polyvinyl alcohol (PVA), PVA-g-PLGA, PEGT-PBT copolymer (polyactive), methacrylates, poly (N-isopropylacrylamide), PEO-PPO-PEO (pluronics), PEO-PPO-PAA copolymers, PLGA-PEO-PLGA, PEG-PLG (poly(d,l-lactide-co-glycolide), PLA-PLGA, poloxamer 407, PEG-PLGA-PEG triblock copolymers, SAIB (sucrose acetate isobutyrate) or 20 combinations thereof. These one or more components allow the therapeutic agent to be released from the drug depot in a controlled and/or sustained manner. For example, the drug depot containing the therapeutic agent and a polymer matrix can be injected at the target tissue site and the polymer matrix breaks down over time (e.g., hours, days) within the target tissue site releasing bupivacaine and optionally additional therapeutic agents. 25 Thus, the administration of the drug depot can be localized and occur over a period of time (e.g., at least one day to about 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 and 30 days).

[00103] The terms "sustained release" or "sustain release" (also referred to as 30 extended release or controlled release) are used herein to refer to one or more therapeutic agent(s) that is introduced into the body of a human or other mammal and continuously releases a stream of one or more therapeutic agents over a predetermined time period and at a therapeutic level sufficient to achieve a desired therapeutic effect throughout the

predetermined time period. Reference to a continuous release stream is intended to encompass release that occurs as the result of biodegradation *in vivo* of drug depot, or a matrix or component thereof, or as the result of metabolic transformation or dissolution of the therapeutic agent(s) or conjugates of therapeutic agent(s).

5 [00104] The phrase “immediate release” is used herein to refer to one or more therapeutic agent(s) that is introduced into the body and that is allowed to dissolve in or become absorbed at the location to which it is administered, with no intention of delaying or prolonging the dissolution or absorption of the drug.

10 [00105] The two types of formulations (sustain release and immediate release) may be used in conjunction. The sustained release and immediate release may be in or more of the same depots. In various embodiments, the sustained release and immediate release may be part of separate depots. For example, a bolus or immediate release formulation of bupivacaine may be placed at or near the target site and a sustain release formulation may also be placed at or near the same site. Thus, even after the bolus becomes completely
15 accessible, the sustain release formulation would continue to provide the active ingredient for the intended tissue.

[00106] In various embodiments, the drug depot is designed to cause an initial burst dose of therapeutic agent within the first 48 hours or 24 hours after implantation. “Initial burst” or “burst effect” or “bolus dose” refers to the release of therapeutic agent from the
20 drug depot during the first 48 hours or 24 hours after the drug depot comes in contact with an aqueous fluid (*e.g.*, synovial fluid, cerebral spinal fluid, *etc.*). In some embodiments, the drug depot is designed to avoid this initial burst effect.

[00107] In various embodiments, the drug depot contains one or more different release layer(s) that releases a bolus dose of bupivacaine or pharmaceutically acceptable salt thereof (*e.g.*, 100mg to 800mg, 400-800mg, or 100mg to 200mg at a target site
25 beneath the skin) and one or more sustain release layer(s) that releases an effective amount of bupivacaine or pharmaceutically acceptable salt thereof over a period of 3 to 30 days, 3 to 10 days, or 7 to 10 days. In various embodiments, the one or more immediate release layer(s) comprise PLGA, which degrades faster than the one or more sustain release layer(s), which comprises PLA, which degrades at a slower rate than the PLGA.
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[00108] In various embodiments, when the drug depot comprises a gel, the gel may have a pre-dosed viscosity in the range of about 1 to about 500 centipoise (cps), 1 to about

200 cps, or 1 to about 100 cps. After the gel is administered to the target site, the viscosity of the gel will increase.

5 [00109] In one embodiment, the gel may be an adherent gel, which comprises a therapeutic agent that is evenly distributed throughout the gel. The gel may be of any suitable type, as previously indicated, and should be sufficiently viscous so as to prevent the gel from migrating from the targeted delivery site once deployed; the gel should, in effect, “stick” or adhere to the targeted tissue site. The gel may, for example, solidify upon contact with the targeted tissue or after deployment from a targeted delivery system. The targeted delivery system may be, for example, a syringe, a catheter, needle or cannula
10 or any other suitable device. The targeted delivery system may inject or spray the gel into or on the targeted tissue site. The therapeutic agent may be mixed into the gel prior to the gel being deployed at the targeted tissue site. In various embodiments, the gel may be part of a two-component delivery system and when the two components are mixed, a chemical process is activated to form the gel and cause it to stick or adhere to the target tissue.

15 [00110] In various embodiments, for those gel formulations that contain a polymer, the polymer concentration may affect the rate at which the gel hardens (*e.g.*, a gel with a higher concentration of polymer may coagulate more quickly than gels having a lower concentration of polymer). In various embodiments, when the gel hardens, the resulting matrix is solid but is also able to conform to the irregular surface of the tissue (*e.g.*,
20 recesses and/or projections in bone).

[00111] The percentage of polymer present in the gel may also affect the viscosity of the polymeric composition. For example, a composition having a higher percentage by weight of polymer is typically thicker and more viscous than a composition having a lower percentage by weight of polymer. A more viscous composition tends to flow more slowly.
25 Therefore, a composition having a lower viscosity may be preferred in some instances, for example, when applying the formulation via spray.

[00112] In various embodiments, the molecular weight of the gel can be varied by many methods known in the art. The choice of method to vary molecular weight is typically determined by the composition of the gel (*e.g.*, polymer, versus non-polymer).
30 For example, in various embodiments, when the gel comprises one or more polymers, the degree of polymerization can be controlled by varying the amount of polymer initiators

(*e.g.* benzoyl peroxide), organic solvents or activator (*e.g.* DMPT), crosslinking agents, polymerization agent, and/or reaction time.

[00113] Suitable gel polymers may be soluble in an organic solvent. The solubility of a polymer in a solvent varies depending on the crystallinity, hydrophobicity, hydrogen-bonding and molecular weight of the polymer. Lower molecular weight polymers will normally dissolve more readily in an organic solvent than high-molecular weight polymers. A polymeric gel, which includes a high molecular weight polymer, tends to coagulate or solidify more quickly than a polymeric composition, which includes a low-molecular weight polymer. Polymeric gel formulations, which include high molecular weight polymers, also tend to have a higher solution viscosity than a polymeric gel, which include a low-molecular weight polymer.

[00114] In various embodiments, the gel has an inherent viscosity (abbreviated as "I.V." and units are in deciliters/gram), which is a measure of the gel's molecular weight and degradation time (*e.g.*, a gel with a high inherent viscosity has a higher molecular weight and longer degradation time). Typically, a gel with a high molecular weight provides a stronger matrix and the matrix takes more time to degrade. In contrast, a gel with a low molecular weight degrades more quickly and provides a softer matrix. In various embodiments, the gel has a molecular weight, as shown by the inherent viscosity, from about 0.10 dL/g to about 1.2 dL/g or from about 0.10 dL/g to about 0.40 dL/g. Other IV ranges include but are not limited to about 0.05 to about 0.15 dL/g, about 0.10 to about 0.20 dL/g, about 0.15 to about 0.25 dL/g, about 0.20 to about 0.30 dL/g, about 0.25 to about 0.35 dL/g, about 0.30 to about 0.35 dL/g, about 0.35 to about 0.45 dL/g, about 0.40 to about 0.45 dL/g, about 0.45 to about 0.50 dL/g, about 0.50 to about 0.70 dL/g, about 0.60 to about 0.80 dL/g, about 0.70 to about 0.90 dL/g, and about 0.80 to about 1.00 dL/g.

[00115] In various embodiments, the gel can have a viscosity of about 300 to about 5,000 centipoise (cp). In other embodiments, the gel can have a viscosity of from about 5 to about 300 cps, from about 10 cps to about 50 cps, from about 15 cps to about 75 cps at room temperature, which allows it to be sprayed at or near the target site.

[00116] In various embodiments, the drug depot may comprise material to enhance viscosity and control the release of the drug. Such material may include, for example, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl methylcellulose, carboxymethylcellulose and salts thereof, Carbopol, poly(hydroxyethylmethacrylate),

poly(methoxyethylmethacrylate), poly(methoxyethoxy-ethylmethacrylate), polymethylmethacrylate (PMMA), methylmethacrylate (MMA), gelatin, polyvinyl alcohols, propylene glycol, PEG 200, PEG 300, PEG 400, PEG 500, PEG 550, PEG 600, PEG 700, PEG 800, PEG 900, PEG 1000, PEG 1450, PEG 3350, PEG 4500, PEG 8000 or combinations thereof. For example, in various embodiments, the drug depot comprises from about 25% to 75% by weight bupivacaine, about 15% to 75% by weight D,L-lactide-glycolide-caprolactone, and about 5% to 10% by weight of PEG 300. The drug depot can also comprise from about 1% to 15% NMP.

[00117] The drug depot release profile can also be controlled, among other things, by controlling the particle size distribution of the components of the drug depot. In various embodiments, the particle size distribution of the components of the drug depot (*e.g.*, bupivacaine, gel, *etc.*) may be in the range of from about 10 μM to 200 μM so that the drug depot can easily be delivered to or at or near the target site by injection, spraying, instilling, *etc.* In various embodiments, the particle size may be 10 μM , 13 μM , 85 μM , 100 μM , 151 μM , 200 μM and all subranges therebetween.

[00118] In various embodiments, the drug depot may comprise a hydrogel made of high molecular weight biocompatible elastomeric polymers of synthetic or natural origin. A desirable property for the hydrogel to have is the ability to respond rapidly to mechanical stresses, particularly shears and loads, in the human body.

[00119] Hydrogels obtained from natural sources are particularly appealing since they are more likely to be biodegradable and biocompatible for *in vivo* applications. Suitable hydrogels include natural hydrogels, such as for example, gelatin, collagen, silk, elastin, fibrin and polysaccharide-derived polymers like agarose, and chitosan, glucomannan gel, hyaluronic acid, polysaccharides, such as cross-linked carboxyl-containing polysaccharides, or a combination thereof. Synthetic hydrogels include, but are not limited to those formed from polyvinyl alcohol, acrylamides such as polyacrylic acid and poly (acrylonitrile-acrylic acid), polyurethanes, polyethylene glycol (*e.g.*, PEG 3350, PEG 4500, PEG 8000), silicone, polyolefins such as polyisobutylene and polyisoprene, copolymers of silicone and polyurethane, neoprene, nitrile, vulcanized rubber, poly(N-vinyl-2-pyrrolidone), acrylates such as poly(2-hydroxy ethyl methacrylate) and copolymers of acrylates with N-vinyl pyrrolidone, N-vinyl lactams, polyacrylonitrile or combinations thereof. The hydrogel materials may further be cross-linked to provide

further strength as needed. Examples of different types of polyurethanes include thermoplastic or thermoset polyurethanes, aliphatic or aromatic polyurethanes, polyetherurethane, polycarbonate-urethane or silicone polyether-urethane, or a combination thereof.

5 [00120] In various embodiments, rather than directly admixing the therapeutic agent into the gel, microspheres may be dispersed within the gel, the microspheres being loaded with bupivacaine. In one embodiment, the microspheres provide for a sustained release of the bupivacaine. In yet another embodiment, the gel, which is biodegradable, prevents the microspheres from releasing the bupivacaine; the microspheres thus do not release the
10 bupivacaine until they have been released from the gel. For example, a gel may be deployed around a target tissue site (*e.g.*, a nerve root). Dispersed within the gel is a plurality of microspheres that encapsulate the desired therapeutic agent. Certain of these microspheres degrade once released from the gel, thus releasing the bupivacaine.

15 [00121] Microspheres, much like a fluid, may disperse relatively quickly, depending upon the surrounding tissue type, and hence disperse the bupivacaine. In some situations, this may be desirable; in others, it may be more desirable to keep the bupivacaine tightly constrained to a well-defined target site. The present invention also contemplates the use of adherent gels to so constrain dispersal of the therapeutic agent. These gels may be
20 deployed, for example, in a disc space, in a spinal canal, or in surrounding tissue.

Drug Delivery

25 [00122] It will be appreciated by those with skill in the art that the depot can be administered to the target site using a “cannula” or “needle” that can be a part of a drug delivery device *e.g.*, a syringe, a gun drug delivery device, or any medical device suitable for the application of a drug to a targeted organ or anatomic region. The cannula or needle of the drug depot device is designed to cause minimal physical and psychological trauma to the patient.

30 [00123] Cannulas or needles include tubes that may be made from materials, such as for example, polyurethane, polyurea, polyether(amide), PEBA, thermoplastic elastomeric olefin, copolyester, and styrenic thermoplastic elastomer, steel, aluminum, stainless steel, titanium, metal alloys with high non-ferrous metal content and a low relative proportion of iron, carbon fiber, glass fiber, plastics, ceramics or combinations thereof. The cannula or

needle may optionally include one or more tapered regions. In various embodiments, the cannula or needle may be beveled. The cannula or needle may also have a tip style vital for accurate treatment of the patient depending on the site for implantation. Examples of tip styles include, for example, Trepine, Courmand, Veress, Huber, Seldinger, Chiba, Francine, Bias, Crawford, deflected tips, Hustead, Lancet, or Tuohy. In various embodiments, the cannula or needle may also be non-coring and have a sheath covering it to avoid unwanted needle sticks.

[00124] The dimensions of the hollow cannula or needle, among other things, will depend on the site for implantation. For example, the width of the epidural space is only about 3-5 mm for the thoracic region and about 5-7 mm for the lumbar region. Thus, the needle or cannula, in various embodiments, can be designed for these specific areas. In various embodiments, the cannula or needle may be inserted using a transforaminal approach in the spinal foramen space, for example, along an inflamed nerve root and the drug depot implanted at this site for treating the condition. Typically, the transforaminal approach involves approaching the intervertebral space through the intervertebral foramina.

[00125] Some examples of lengths of the cannula or needle may include, but are not limited to, from about 50 to 150 mm in length, for example, about 65 mm for epidural pediatric use, about 85 mm for a standard adult and about 110 mm for an obese adult patient. The thickness of the cannula or needle will also depend on the site of implantation. In various embodiments, the thickness includes, but is not limited to, from about 0.05 to about 1.655. The gauge of the cannula or needle may be the widest or smallest diameter or a diameter in between for insertion into a human or animal body. The widest diameter is typically about 14 gauge, while the smallest diameter is about 22 gauge. In various embodiments the gauge of the needle or cannula is about 18 to about 22 gauge.

[00126] In various embodiments, like the drug depot and/or gel, the cannula or needle includes dose radiographic markers that indicate location at or near the site beneath the skin, so that the user may accurately position the depot at or near the site using any of the numerous diagnostic imaging procedures. Such diagnostic imaging procedures include, for example, X-ray imaging or fluoroscopy. Examples of such radiographic markers include, but are not limited to, barium, calcium, and/or metal beads or particles.

5 [00127] In various embodiments, the needle or cannula may include a transparent or translucent portion that can be visualizable by ultrasound, fluoroscopy, x-ray, or other imaging techniques. In such embodiments, the transparent or translucent portion may include a radiopaque material or ultrasound responsive topography that increases the contrast of the needle or cannula relative to the absence of the material or topography.

10 [00128] The drug depot, and/or medical device to administer the drug may be sterilizable. In various embodiments, one or more components of the drug depot, and/or medical device to administer the drug are sterilized by radiation in a terminal sterilization step in the final packaging. Terminal sterilization of a product provides greater assurance of sterility than from processes such as an aseptic process, which require individual product components to be sterilized separately and the final package assembled in a sterile environment.

15 [00129] Typically, in various embodiments, gamma radiation is used in the terminal sterilization step, which involves utilizing ionizing energy from gamma rays that penetrates deeply in the device. Gamma rays are highly effective in killing microorganisms, they leave no residues nor have sufficient energy to impart radioactivity to the device. Gamma rays can be employed when the device is in the package and gamma sterilization does not require high pressures or vacuum conditions, thus, package seals and other components are not stressed. In addition, gamma radiation eliminates the need for permeable packaging materials.

20 [00130] In various embodiments, electron beam (e-beam) radiation may be used to sterilize one or more components of the device. E-beam radiation comprises a form of ionizing energy, which is generally characterized by low penetration and high-dose rates. E-beam irradiation is similar to gamma processing in that it alters various chemical and molecular bonds on contact, including the reproducing cells of microorganisms. Beams produced for e-beam sterilization are concentrated, highly-charged streams of electrons generated by the acceleration and conversion of electricity. E-beam sterilization may be used, for example, when the drug depot is included in a gel.

25 [00131] Other methods may also be used to sterilize the depot and/or one or more components of the device, including, but not limited to, gas sterilization, such as, for example, with ethylene oxide or steam sterilization.

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[00132] In various embodiments, a kit is provided that may include additional parts along with the drug depot and/or medical device combined together to be used to implant the drug depot (*e.g.*, ribbon-like strips). The kit may include the drug depot device in a first compartment. The second compartment may include a canister holding the drug depot and any other instruments needed for the localized drug delivery. A third compartment may include gloves, drapes, wound dressings and other procedural supplies for maintaining sterility of the implanting process, as well as an instruction booklet. A fourth compartment may include additional cannulas and/or needles. Each tool may be separately packaged in a plastic pouch that is radiation sterilized. A cover of the kit may include illustrations of the implanting procedure and a clear plastic cover may be placed over the compartments to maintain sterility.

[00133] In various embodiments, a method for delivering bupivacaine into a target tissue site of a patient is provided. The method comprises inserting a cannula or needle at or near a target tissue site and implanting the drug depot containing the bupivacaine at the target site beneath the skin of the patient. In various embodiments, to administer the drug depot to the desired site, first the cannula or needle can be inserted through the skin and soft tissue down to the target tissue site and the drug depot administered (*e.g.*, injected, implanted, instilled, sprayed, *etc.*) at or near the target site. In those embodiments where the drug depot is separate from the gel, first the cannula or needle can be inserted through the skin and soft tissue down to the site of injection and one or more base layer(s) of gel can be administered to the target site. Following administration of the one or more base layer(s), the drug depot can be implanted on or in the base layer(s) so that the gel can hold the depot in place or reduce migration. If required, a subsequent layer or layers of gel can be applied on the drug depot to surround the depot and further hold it in place. Alternatively, the drug depot may be implanted or injected first and then the gel placed (*e.g.*, brushed, dripped, injected, or painted, *etc.*) around the drug depot to hold it in place. By using the gel, accurate and precise implantation of a drug depot can be accomplished with minimal physical and psychological trauma to the patient. In various embodiments, the drug depot can be sutured to the target site or alternatively the drug depot can be implanted, without suturing. For example, in various embodiments, the drug depot can be a strip-shaped or ribbon-shaped depot and placed at the target site, before, during or after surgery. As another example, the drug depot can be delivered in the form of a gel via a

syringe or other injectable delivery directly to the target site, before, during or after surgery.

[00134] In various embodiments, when the target tissue site comprises a spinal region, a portion of fluid (*e.g.*, spinal fluid, *etc.*) can be withdrawn from the target site through a cannula or needle first and then the depot administered (*e.g.*, placed, dripped, injected, or implanted, *etc.*). The target site will re-hydrate (*e.g.*, replenishment of fluid) and this aqueous environment will cause the drug to be released from the depot.

[00135] Treating or treatment of a disease or condition refers to executing a protocol, which may include administering one or more drugs to a patient (human, other normal or otherwise), in an effort to alleviate signs or symptoms of the disease. Alleviation can occur prior to signs or symptoms of the disease or condition appearing, as well as after their appearance. Thus, “treating” or “treatment” may include “preventing” or “prevention” of disease or undesirable condition. In addition, “treating” or “treatment” does not require complete alleviation of signs or symptoms, does not require a cure, and specifically includes protocols that have only a marginal effect on the patient. “Reducing pain” includes a decrease in pain and does not require complete alleviation of pain signs or symptoms, and does not require a cure. In various embodiments, reducing pain includes even a marginal decrease in pain. By way of example, the administration of one or more effective dosages of bupivacaine may be used to prevent, treat or relieve the symptoms of post-operative pain incidental to surgery.

[00136] “Localized” delivery includes delivery where one or more drugs are deposited within, at or near a tissue. For example, localized delivery includes delivery to a nerve root of the nervous system or a region of the brain, or in close proximity (within about 10 cm, or preferably within about 5 cm, for example) thereto. “Targeted delivery system” provides delivery of one or more drugs depots (*e.g.*, gels or depot dispersed in the gel, *etc.*) having a quantity of therapeutic agent that can be deposited at or near the target tissue site as needed for treatment of pain and/or inflammation incidental to surgery.

[00137] Figure 1 illustrates a number of common locations within a patient that may be sites at which surgery took place. It will be recognized that the locations illustrated in Figure 1 are merely exemplary of the many different locations within a patient that may be at which surgery took place. For example, surgery may be required at a patient's knees 21,

hips 22, fingers 23, thumbs 24, neck 25, and spine 26. Thus, during or following these surgeries, the patient may be experiencing post-operative pain and/or inflammation.

[00138] The term “pain” includes nociception and the sensation of pain, both of which can be assessed objectively and subjectively, using pain scores and other methods well-known in the art. In various embodiments, pain may include allodynia (*e.g.*, increased response to a normally non-noxious stimulus) or hyperalgesia (*e.g.*, increased response to a normally noxious or unpleasant stimulus), which can in turn be thermal or mechanical (tactile) in nature. In some embodiments, pain is characterized by thermal sensitivity, mechanical sensitivity and/or resting pain. In other embodiments, pain comprises mechanically-induced pain or resting pain. In still other embodiments, the pain comprises resting pain. The pain can be primary or secondary pain, as is well-known in the art. Exemplary types of pain reducible, preventable or treatable by the methods and compositions disclosed herein include, without limitation, include post-operative pain, for example, from the back in the lumbar regions (lower back pain) or cervical region (neck pain), leg pain, radicular pain (experienced in the lower back and leg from lumbar surgery in the neck and arm from cervical surgery), or abdominal pain from abdominal surgery, and neuropathic pain of the arm, neck, back, lower back, leg, and related pain distributions resulting from disk or spine surgery. Neuropathic pain may include pain arising from surgery to the nerve root, dorsal root ganglion, or peripheral nerve.

[00139] In various embodiments, the pain results from “post-surgical pain” or “post-operative pain” or “surgery-induced pain”, which are used herein interchangeably, and refer to pain arising in the recovery period of seconds, minutes, hours, days or weeks following a surgical procedure (*e.g.*, hernia repair, orthopedic or spine surgery, *etc.*). Surgical procedures include any procedure that penetrates beneath the skin and causes pain and/or inflammation to the patient. Surgical procedure also includes arthroscopic surgery, an excision of a mass, spinal fusion, thoracic, cervical, or lumbar surgery, pelvic surgery or a combination thereof.

[00140] The term “pain management medication” includes one or more therapeutic agents that are administered to reduce, prevent, alleviate or remove pain entirely. These include anti-inflammatory agents, muscle relaxants, analgesics, anesthetics, narcotics, *etc.*, or combinations thereof.

5 [00141] In various embodiments, the post-surgical pain or post-operative pain or surgery-induced pain, is accompanied by inflammation. Inflammation can be an acute response to trauma or surgery. When tissues are damaged, TNF- α attaches to cells to cause them to release other cytokines that cause inflammation. The purpose of the inflammatory cascade is to promote healing of the damaged tissue, but once the tissue is healed the inflammatory process does not necessarily end. Left unchecked, this can lead to degradation of surrounding tissues and associated pain. Thus, pain can become a disease state in itself. That is, when this pathway is activated, inflammation and pain ensue. Often a vicious and seemingly endless cycle of insult, inflammation, and pain sets in.

10 [00142] One exemplary embodiment where the depot is suitable for use in pain and/or inflammation management (*e.g.*, post-operative pain and/or inflammation management) is illustrated in Figure 2. Schematically shown in Figure 2 is a dorsal view of the spine and sites where the drug depot may be inserted using a syringe, cannula or needle beneath the skin 34 to a spinal site 32 (*e.g.*, spinal disc space, spinal canal, soft tissue surrounding the spine, nerve root, etc.) and one or more drug depots 28 and 32 are delivered to various sites along the spine. In this way, when several drug depots are to be implanted, they are implanted in a manner that optimizes location, accurate spacing, and drug distribution.

15 [00143] Although the spinal site is shown, as described above, the drug depot can be delivered to any site beneath the skin, including, but not limited to, at least one muscle, ligament, tendon, cartilage, spinal disc, spinal foraminal space, near the spinal nerve root, or spinal canal. In various embodiments, the drug depot containing bupivacaine can be administered to the patient intra-operatively, intravenously, intramuscularly, continuous or intermittent infusion, intraperitoneal, intrasternal, subcutaneously, intrathecally, 20 intradiskally, peridiskally, epidurally, perispinally, intraarticular injection, parenterally, or via combinations thereof. In some embodiments, the injection is intrathecal, which refers to an injection into the spinal canal (intrathecal space surrounding the spinal cord). An injection may also be into a muscle or other tissue.

25 [00144] In some embodiments, it is preferable to co-administer bupivacaine with an antagonist to counteract undesirable effects. Exemplary antagonists include but are not limited to phentolamine, yohimbine, tolazoline and piperoxane. Additionally, compounds such as 5-fluorodeoxyuridine (FUDR) and 3,4 dehydroprolene may also be included.

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These compounds may prevent or reduce glial and fibroblastic scar formation associated with some types of surgeries.

[00145] The bupivacaine-based formulations of the present application may be used as medicaments in the form of pharmaceutical preparations. The preparations may be formed in an administration with a suitable pharmaceutical carrier that may be solid or liquid and organic or inorganic, and placed in the appropriate form for parenteral or other administration as desired. As persons of ordinary skill are aware, known carriers include but are not limited to water, gelatine, lactose, starches, stearic acid, magnesium stearate, siccaryl alcohol, talc, vegetable oils, benzyl alcohols, gums, waxes, propylene glycol, polyalkylene glycols and other known carriers for medicaments.

[00146] Parenteral administration may additionally include, for example, an infusion pump that administers a pharmaceutical composition (*e.g.*, anesthetic and anti-inflammatory combination) through a catheter near the spine or one or more inflamed joints, an implantable mini-pump that can be inserted at or near the target site, an implantable controlled release device or sustained release delivery system that can release a certain amount of the statin per hour or in intermittent bolus doses. One example of a suitable pump for use is the SynchroMed® (Medtronic, Minneapolis, Minnesota) pump. This pump has three sealed chambers. One contains an electronic module and battery. The second contains a peristaltic pump and drug reservoir. The third contains an inert gas, which provides the pressure needed to force the pharmaceutical composition into the peristaltic pump. To fill the pump, the pharmaceutical composition is injected through the reservoir fill port to the expandable reservoir. The inert gas creates pressure on the reservoir, and the pressure forces the pharmaceutical composition through a filter and into the pump chamber. The pharmaceutical composition is then pumped out of the device from the pump chamber and into the catheter, which will direct it for deposit at the target site. The rate of delivery of pharmaceutical composition is controlled by a microprocessor. This allows the pump to be used to deliver similar or different amounts of pharmaceutical composition continuously, at specific times, or at set intervals between deliveries.

[00147] In various embodiments, where the target tissue site comprises blood vessels, a vasoconstrictor may be employed in the drug depot. When the vasoconstrictor is released, it lengthens the duration of the anesthetic response and reduces the systemic

uptake of the anesthetic agent. The anesthetic may be, for example, bupivacaine, and the vasoconstrictor may be, for example, epinephrine or phenylephrine.

[00148] The term “patient” refers to organisms from the taxonomy class “mammalian,” including but not limited to humans, other primates such as chimpanzees, apes orangutans and monkeys, rats, mice, cats, dogs, cows, horses, *etc.*

Method of Making Bupivacaine Depots

[00149] In various embodiments, the drug depot comprising the bupivacaine can be made by combining a biocompatible polymer and a therapeutically effective amount of bupivacaine or pharmaceutically acceptable salt thereof and forming the implantable drug depot from the combination.

[00150] Various techniques are available for forming at least a portion of a drug depot from the biocompatible polymer(s), therapeutic agent(s), and optional materials, including solution processing techniques and/or thermoplastic processing techniques. Where solution processing techniques are used, a solvent system is typically selected that contains one or more solvent species. The solvent system is generally a good solvent for at least one component of interest, for example, biocompatible polymer and/or therapeutic agent. The particular solvent species that make up the solvent system can also be selected based on other characteristics, including drying rate and surface tension.

[00151] Solution processing techniques include solvent casting techniques, spin coating techniques, web coating techniques, solvent spraying techniques, dipping techniques, techniques involving coating via mechanical suspension, including air suspension (e.g., fluidized coating), ink jet techniques and electrostatic techniques. Where appropriate, techniques such as those listed above can be repeated or combined to build up the depot to obtain the desired release rate and desired thickness.

[00152] In various embodiments, a solution containing solvent and biocompatible polymer are combined and placed in a mold of the desired size and shape. In this way, polymeric regions, including barrier layers, lubricious layers, and so forth can be formed. If desired, the solution can further comprise, one or more of the following: bupivacaine and other therapeutic agent(s) and other optional additives such as radiographic agent(s), *etc.* in dissolved or dispersed form. This results in a polymeric matrix region containing these species after solvent removal. In other embodiments, a solution containing solvent

with dissolved or dispersed therapeutic agent is applied to a pre-existing polymeric region, which can be formed using a variety of techniques including solution processing and thermoplastic processing techniques, whereupon the therapeutic agent is imbibed into the polymeric region.

5 [00153] Thermoplastic processing techniques for forming the depot or portions thereof include molding techniques (for example, injection molding, rotational molding, and so forth), extrusion techniques (for example, extrusion, co-extrusion, multi-layer extrusion, and so forth) and casting.

10 [00154] Thermoplastic processing in accordance with various embodiments comprises mixing or compounding, in one or more stages, the biocompatible polymer(s) and one or more of the following: bupivacaine, optional additional therapeutic agent(s), radiographic agent(s), and so forth. The resulting mixture is then shaped into an implantable drug depot. The mixing and shaping operations may be performed using any of the conventional devices known in the art for such purposes.

15 [00155] During thermoplastic processing, there exists the potential for the therapeutic agent(s) to degrade, for example, due to elevated temperatures and/or mechanical shear that are associated with such processing. For example, bupivacaine may undergo substantial degradation under ordinary thermoplastic processing conditions. Hence, processing is preferably performed under modified conditions, which prevent the
20 substantial degradation of the therapeutic agent(s). Although it is understood that some degradation may be unavoidable during thermoplastic processing, degradation is generally limited to 10% or less. Among the processing conditions that may be controlled during processing to avoid substantial degradation of the therapeutic agent(s) are temperature, applied shear rate, applied shear stress, residence time of the mixture containing the
25 therapeutic agent, and the technique by which the polymeric material and the therapeutic agent(s) are mixed.

[00156] Mixing or compounding the biocompatible polymer with therapeutic agent(s) and any additional additives to form a substantially homogenous mixture thereof may be performed with any device known in the art and conventionally used for mixing polymeric
30 materials with additives.

[00157] Where thermoplastic materials are employed, a polymer melt may be formed by heating the biocompatible polymer, which can be mixed with various additives (*e.g.*,

therapeutic agent(s), inactive ingredients, *etc.*) to form a mixture. A common way of doing so is to apply mechanical shear to a mixture of the biocompatible polymer(s) and additive(s). Devices in which the biocompatible polymer(s) and additive(s) may be mixed in this fashion include devices such as single screw extruders, twin screw extruders, banbury mixers, high-speed mixers, ross kettles, and so forth.

5 [00158] Any of the biocompatible polymer(s) and various additives may be premixed prior to a final thermoplastic mixing and shaping process, if desired (e.g., to prevent substantial degradation of the therapeutic agent among other reasons).

10 [00159] For example, in various embodiments, a biocompatible polymer is pre-compounded with a radiographic agent (*e.g.*, radio-opacifying agent) under conditions of temperature and mechanical shear that would result in substantial degradation of the therapeutic agent, if it were present. This pre-compounded material is then mixed with therapeutic agent under conditions of lower temperature and mechanical shear, and the resulting mixture is shaped into the bupivacaine containing drug depot. Conversely, in another embodiment, the biocompatible polymer can be pre-compounded with the therapeutic agent under conditions of reduced temperature and mechanical shear. This pre-compounded material is then mixed with, for example, a radio-opacifying agent, also under conditions of reduced temperature and mechanical shear, and the resulting mixture is shaped into the drug depot.

15 [00160] The conditions used to achieve a mixture of the biocompatible polymer and therapeutic agent and other additives will depend on a number of factors including, for example, the specific biocompatible polymer(s) and additive(s) used, as well as the type of mixing device used.

20 [00161] As an example, different biocompatible polymers will typically soften to facilitate mixing at different temperatures. For instance, where a depot is formed comprising PLGA or PLA polymer, a radio-opacifying agent (*e.g.*, bismuth subcarbonate), and a therapeutic agent prone to degradation by heat and/or mechanical shear, in various embodiments, the PGLA or PLA can be premixed with the radio-opacifying agent at temperatures of about, for example, 150^oC to 170^oC. The therapeutic agent is then combined with the premixed composition and subjected to further thermoplastic processing at conditions of temperature and mechanical shear that are substantially lower than is typical for PGLA or PLA compositions. For example, where extruders are used,

barrel temperature, volumetric output are typically controlled to limit the shear and therefore to prevent substantial degradation of the therapeutic agent(s). For instance, the therapeutic agent and premixed composition can be mixed/compounded using a twin screw extruder at substantially lower temperatures (e.g., 100-105^dC), and using substantially reduced volumetric output (e.g., less than 30% of full capacity, which generally corresponds to a volumetric output of less than 200 cc/min). It is noted that this processing temperature is well below the melting points of bupivacaine, because processing at or above these temperatures will result in substantial therapeutic agent degradation. It is further noted that in certain embodiments, the processing temperature will be below the melting point of all bioactive compounds within the composition, including the therapeutic agent. After compounding, the resulting depot is shaped into the desired form, also under conditions of reduced temperature and shear.

[00162] In other embodiments, biodegradable polymer(s) and one or more therapeutic agents are premixed using non-thermoplastic techniques. For example, the biocompatible polymer can be dissolved in a solvent system containing one or more solvent species. Any desired agents (for example, a radio-opacifying agent, a therapeutic agent, or both radio-opacifying agent and therapeutic agent) can also be dissolved or dispersed in the solvents system. Solvent is then removed from the resulting solution/dispersion, forming a solid material. The resulting solid material can then be granulated for further thermoplastic processing (for example, extrusion) if desired.

[00163] As another example, the therapeutic agent can be dissolved or dispersed in a solvent system, which is then applied to a pre-existing drug depot (the pre-existing drug depot can be formed using a variety of techniques including solution and thermoplastic processing techniques, and it can comprise a variety of additives including a radio-opacifying agent and/or viscosity enhancing agent), whereupon the therapeutic agent is imbibed on or in the drug depot. As above, the resulting solid material can then be granulated for further processing, if desired.

[00164] Typically, an extrusion process may be used to form the drug depot comprising a biocompatible polymer(s), therapeutic agent(s) and radio-opacifying agent(s). Co-extrusion may also be employed, which is a shaping process that can be used to produce a drug depot comprising the same or different layers or regions (for example, a structure comprising one or more polymeric matrix layers or regions that have

permeability to fluids to allow immediate and/or sustained drug release). Multi-region depots can also be formed by other processing and shaping techniques such as co-injection or sequential injection molding technology.

5 [00165] In various embodiments, the depot that may emerge from the thermoplastic processing (*e.g.*, ribbon, pellet, strip, *etc.*) is cooled. Examples of cooling processes include air cooling and/or immersion in a cooling bath. In some embodiments, a water bath is used to cool the extruded depot. However, where the therapeutic agent is water-soluble, the immersion time should be held to a minimum to avoid unnecessary loss of therapeutic agent into the bath.

10 [00166] In various embodiments, immediate removal of water or moisture by use of ambient or warm air jets after exiting the bath will also prevent re-crystallization of the drug on the depot surface, thus controlling or minimizing a high drug dose “initial burst” or “bolus dose” upon implantation or insertion if this is release profile is not desired.

15 [00167] In various embodiments, the drug depot can be prepared by mixing or spraying the drug with the polymer and then molding the depot to the desired shape. In various embodiments, bupivacaine is used and mixed or sprayed with PLGA, poly(D,L-lactide-caprolactone) polymer, and/or poly(D,L-lactide-glycolide-caprolactone) polymer and the resulting depot may be formed by extrusion and dried.

20 [00168] In some exemplary formulations, there may be 55-65% bupivacaine, 25-35% PLGA and 5-15% mPEG. Some of these formulations will release between 10 and 30% of the active ingredient on day 1 and all or substantially all of the active ingredient by day 10. Some of these formulations will release between 15 and 25% of the active ingredient on day 1 and all or substantially all of the product by day 10.

25 [00169] In still other exemplary formulations, there may be 55-65% bupivacaine, 25-35% DL-G-CL, 6% PEG 300 and 13% NMP. Some of these formulations will release between 10 and 30% of the active ingredient on day 1 and all or substantially all of the active ingredient by day 10. Some of these formulations will release between 10 and 15% of the active ingredient on day 1 and all or substantially all of the product by day 10.

30 [00170] In another exemplary embodiment, an implantable drug depot useful for reducing, preventing or treating post-operative pain in a patient in need of such treatment is provided. The implantable drug depot comprises a therapeutically effective amount of bupivacaine or pharmaceutically acceptable salt thereof. The depot is implantable at a site

beneath the skin to reduce, prevent or treat post-operative pain wherein the drug depot comprises (i) one or more immediate release layer(s) that is capable of releasing about 5% to about 50% of the bupivacaine or pharmaceutically acceptable salt thereof relative to a total amount of the bupivacaine or pharmaceutically acceptable salt thereof loaded in the drug depot over a first period of up to 48 hours, a first period of up to 24 hours, or a first period of about 24 to 48 hours and (ii) one or more sustain release layer(s) that is capable of releasing about 50% to about 95% of the bupivacaine or pharmaceutically acceptable salt thereof relative to a total amount of the bupivacaine or pharmaceutically acceptable salt thereof loaded in the drug depot over a subsequent period of up to 4 to 30 or 4 to 10 days. The one or more immediate release layer(s) comprise one or more of poly(lactide-co-glycolide), polylactide, polyglycolide, polyorthoester, D-lactide, D,L-lactide, poly(D,L-lactide), L-lactide, poly(D,L-lactide-co-caprolactone), poly(D,L-lactide-co-glycolide-co-caprolactone), polycaprolactone or a combination thereof, and the one or more sustain release layer(s) comprise one or more of poly(lactide-co-glycolide), polylactide, polyglycolide, polyorthoester, D-lactide, D,L-lactide, poly(D,L-lactide), L-lactide, poly(D,L-lactide-co-caprolactone), poly(D,L-lactide-co-glycolide-co-caprolactone), polycaprolactone or a combination thereof.

[00171] In yet another exemplary embodiment, an implantable drug depot is provided. The implantable drug depot comprises: (i) a therapeutically effective amount of bupivacaine or pharmaceutically acceptable salt thereof; (ii) one or more immediate release layer(s) that is capable of releasing a bolus dose of bupivacaine or pharmaceutically acceptable salt thereof at a site beneath the skin; and (iii) one or more sustain release layer(s) that is capable of releasing an effective amount of bupivacaine or pharmaceutically acceptable salt thereof over a period of 4 to 30 days, 4 to 10 days, or 5 to 7 days. The one or more immediate release layer(s) comprise one or more of poly(lactide-co-glycolide), polylactide, polyglycolide, polyorthoester, D-lactide, D,L-lactide, poly(D,L-lactide), L-lactide, poly(D,L-lactide-co-caprolactone), poly(D,L-lactide-co-glycolide-co-caprolactone), polycaprolactone or a combination thereof, and the one or more sustain release layer(s) comprise one or more of poly(lactide-co-glycolide), polylactide, polyglycolide, polyorthoester, D-lactide, D,L-lactide, poly(D,L-lactide), L-lactide, poly(D,L-lactide-co-caprolactone), poly(D,L-lactide-co-glycolide-co-caprolactone), polycaprolactone or a combination thereof. The drug depot is capable of releasing about

40% to about 70% of the bupivacaine or pharmaceutically acceptable salt thereof relative to a total amount of bupivacaine loaded in the drug depot over the sustained release period.

[00172] Having now generally described the invention, the same may be more readily understood through the following reference to the following examples, which are provided by way of illustration and are not intended to limit the present invention unless specified.

EXAMPLES

Example 1

[00173] Implants comprising bupivacaine were prepared according to the following procedures:

[00174] Materials: Poly (D,L-lactide-co-caprolactone) having a 25:75 lactide to caprolactone molar ratio (25:75 DL-CL), an intrinsic viscosity of 0.8 dL/g and a molecular weight of 95 kDa was purchased from Lakeshore Biomaterials (Birmingham, Alabama). Poly (D,L-lactide-co-glycolide-co-caprolactone) having a 30:20:50 lactide to glycolide to caprolactone molar ratio (30:20:50 DL-G-CL), an intrinsic viscosity of 0.05 dL/g to 0.15dL/g and a molecular weight of 10kDa was purchased from Lakeshore Biomaterials (Birmingham, Alabama). Bupivacaine Base was purchased from Orgamol (Switzerland). Polyethylene glycol (PEG) having an average molecular weight of 300-400 g/mol was purchased from Spectrum Chemicals, n-methylpyrrolidone (NMP) having an average molecular weight of 99 g/mol was purchased from Fisher, and acetone was also purchased from Sigma-Aldrich.

[00175] Methods:

[00176] Preparation of Bupivacaine base / 25:75 DL-CL strip implant: The 25:75 DL-CL polymer was added to a glass vial and heated to either 100°C (below drug melt temp) or 110°C (above drug melt temp). Bupivacaine base was added to the melted polymer and mixed with a spatula until visually homogeneous. The resulting blend was removed from the glass vial and pressed into a thin film (0.4-0.6 mm thickness) using a Carver Press. The Carver Press was operated at 45°C and 6000-8000 psi pressure. The thin film was cut to form a strip of the desired dimensions with a sharp blade. The dimensions of the implant were 9mm in length, 0.4 to 1mm in thickness and 1.5 to 3mm in width. The

dimensions of the implant were chosen for *in vivo* testing in the Brennan rat post-operative pain model.

[00177] Preparation of Bupivacaine base / 30:20:50 DL-G-CL injectable paste/gel formulation: The polymer (318mg), PEG 300 (92 mg) and NMP (199mg) were added to a glass vial and heated to 93°C for approximately 10 minutes. Bupivacaine (911 mg) was added to the mixture and maintained at 93°C for 20 minutes while being stirred/vortexed to get the drug to dissolve. Vial was removed from the heat and the mixture was stirred as it cooled to room temperature. The formulation was collected from the vial and added to a 1 mL syringe. The mixture was easily expelled from the syringe (no needle attached) when heated to 40°C.

[00178] *In Vitro* Drug Elution Testing of Bupivacaine base / 25:75 DL-CL ribbon implant and Bupivacaine base/30:20:50 DL-G-CL injectable gel formulation: The purpose of this procedure was to measure the release of bupivacaine from a polymer implant and a gel formulation into a receiving fluid PBS buffer, pH 7.4. The *in vitro* release procedure consisted of placing a known mass of implant or gel into an apparatus containing the receiving fluid. The *in vitro* release apparatus consisted of a 60ml glass bottle. A receiving fluid in the amount of 30ml was added to each sample bottle. During the release study, the apparatus was placed in an incubator maintained at 37 ± 2 °C. At predetermined intervals, samples of the receiving fluid were removed and analyzed for bupivacaine concentration by HPLC.

[00179] Elution profile and *in vivo* data: Implants of these formulations of bupivacaine were tested in Brennan rats to determine their *in vitro* elution and *in vivo* performance. Figures 3 and 4 show the average cumulative release profiles of these bupivacaine formulations. Also, the elution profiles and *in vivo* data for these formulations are summarized below in Table 1:

Table 1

Formulation Number	Polymer	Active Wt. % of Bupivacaine	Excipient	Handling Property	<i>In vitro</i> elution profile	<i>In vivo</i> data
bupivacaine 1	2575 DL-CL 8E	63% (bupivacaine base)	None	Malleable	Day 1 burst release of 22%. 97% eluted by day 10.	Some efficacy in Brennan rat

bupivacaine 2	30:20:50 DL-G-CL 1E	60% (bupivacaine base)	6% PEP 300, 13% NMP	Injectable Paste	Day 1 release of 12%, 75% of the drug eluted by day 10	Could not demonstrate
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[00180] DL-CL is an abbreviation for poly(DL-lactide-co-caprolactone) polymer.

[00181] Figures 5 and 6 show the efficacy data for *in vivo* testing for bupivacaine 1 and 2 formulations. In Figures 5 and 6, “n” represents the number of animals evaluated. In Figure 6, for each of the 4 groups (surgery, control paste, bupivacaine paste and bupivacaine polymer), eight time points are provided. The time points are from left to right baseline, day 1 post-surgery, day 2 post-surgery, day 3 post-surgery, day 4 post-surgery, day 7 post-surgery, day 8 post-surgery and day 10 post-surgery.

[00182] For the bupivacaine 1 formulation, there was a concern that the co-polymer could take up to 6-8 months to fully degrade. No excipient was needed because the bupivacaine was melted before it was mixed with the polymer. The malleability was of sufficient flexibility to permit extrusion to a strip or ribbon dosage form. As a preliminary evaluation, the efficacy of this formulation was tested in the Brennan rat model of post-incisional pain. Mechanical allodynia was used as the behavioral endpoint to assess the presence/absence of pain in the animal model following treatment with these formulations. The Brennan rat incision was made on the plantar aspect of the rat paw. The depth and length of the incision was a limiting factor in this model as the implant size was a bit bigger for the incision and became bulky in the rats’ paw following implantation. This in turn affected wound healing. Some implants were lost from the incised paw at different timepoints following administration. Due to this issue, some animals were excluded from the study due to the loss of implants and a complete evaluation of the efficacy of these formulations with only the few rats remaining in the study was not possible. However, of the few rats that proceeded through the study, some efficacy in reversing mechanical allodynia following the administration of the bupivacaine 1 formulation was noted.

[00183] For the bupivacaine 2 formulation, the degradation of the polymer was less than one month. The effect of the bupivacaine 2 formulation was not able to be demonstrated due to the fact that the handling property of the injectable formulation was changed at the time for administration. The formulation stability was affected during shipping. In the *in vivo* tests, although only some efficacy was seen (such as that with the

bupivacaine 1 formulation), it is understood that in the Brennan rat model, efficacy is affected by the absence of an effective drug dose in the formulation strip dimension cut to fit the incision in the model.

5 **Example 2**

[00184] A number of implants comprising bupivacaine were prepared according to the following procedures:

10 [00185] Materials: Poly(D,L-lactide-co-glycolide) having a 50:50 lactide to glycolide molar ratio (PLGA 50501A), an intrinsic viscosity of 0.12 and acid end capped polymer chain ends was purchased from Lakeshore Biomaterials (Birmingham, Alabama). Bupivacaine Base was purchased from Orgamol (Switzerland). Bupivacaine HCl was purchased from Spectrum Chemicals (Gardena, CA). Methoxy polyethylene glycol (mPEG) having an average molecular weight of 550 was purchased from Sigma-Aldrich. Methanol and acetone was also purchased from Sigma-Aldrich.

15 [00186] Methods:

[00187] Preparation of Spray Dried Bupivacaine base / PLGA50501A: Bupivacaine base and PLGA50501A were both dissolved in acetone to yield a 10% (w/w) solution. A mixture of 65.2% bupivacaine base solution and 34.8% PLGA50501A solution was spray dried in the Buchi Spray Dryer. The processing parameters were set as follows: inlet temp. (70°C), aspirator (80%), nitrogen inlet (50 mm), spray flow rate (80 mL/hr) and ultrasonic generator (0.8 watts). The spray dried powder was collected and dried for an additional 24 hours at 30°C and 15 mmHg vacuum.

20 [00188] Preparation of Spray Dried Bupivacaine HCl: Bupivacaine HCl was dissolved in methanol to yield a 10% (w/w) solution and the solution was spray dried in the Buchi Spray Dryer. The processing parameters were set as follows: inlet temp. (70°C), aspirator (80%), nitrogen inlet (50 mm), spray flow rate (80 mL/hr) and ultrasonic generator (0.8 watts). The spray dried powder was collected and dried for additional 24 hours at 70°C and 15 mm Hg vacuum.

25 [00189] Preparation of Melt Extruded Rods: Three formulations were prepared for melt extrusion. All three formulations contained PLGA50501A ground into powder using a Retsch (Retsch GmbH, Germany) rotor mill with an 80 micrometer sieve filter. The first such formulation contained 30% (w/w) ground PLGA50501A, 60% (w/w) spray dried

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bupivacaine HCl, and 10% (w/w) mPEG (60% bupivacaine HCl). The second formulation contained 90% (w/w) spray dried bupivacaine base / PLGA50501A and 10% (w/w) mPEG (60% bupivacaine base). The last formulation contained 90% (w/w) ground PLGA50501A and 10% (w/w) mPEG (vehicle polymer). The last formulation was not tested.

5 [00190] The first two formulations were dry mixed with a spatula prior to being feed into a Haake Mini-Lab twin screw extruder (Thermo Fischer Scientific, Waltham, MA). The extruder settings were as follows: 105°C and 30 RPM for the 60% bupivacaine HCl formulation, and 85°C and 30 RPM for the 60% bupivacaine base formulation. The first 10 two formulations were extruded out of a 1.5mm diameter die.

[00191] Strip Preparation: Extruded formulations were pressed into sheets of a desired thickness using a Carver Laboratory Heat Press (Carver, Inc., Wabash, IN) set at 50°C. The sheets were cut by razor blades to form strips (or ribbons) or implants of the desired dimensions. The dimensions of each implant were as follows (length by width by 15 height or L x W x H): for the 60% bupivacaine base formulation, the implants were 9mm x 3mm x 1mm and for the 60% bupivacaine HCl formulation, the implants were 9mm x 3mm x 1mm.

[00192] *In Vitro* Drug Elution Testing: Each strip or implant was tested in triplicate and placed in 20mL scintillation vials for drug elution testing. The 60% bupivacaine HCl 20 and 60% bupivacaine base strips (or ribbons) were incubated in 10mL of phosphate buffer with 0.5% (w/w) sodium dodecyl sulfate pH 7.4 at 37°C under mild agitation. At pre-selected times, the buffer was removed for analysis and replaced with fresh buffer medium. The drug content was quantified at 260 nm for bupivacaine by Molecular Devices SpectraMax M2 (Sunnyvale, CA) plate reader.

25 [00193] Elution profile and *in vivo* data: The implants of bupivacaine were tested in Brennan rats to determine their *in vitro* elution and *in vivo* performance. Figures 7 and 8 show the average release rate of a bupivacaine 3 implant (labeled as Bupivacaine HCl in the figures) and a bupivacaine 4 implant (labeled as Bupivacaine Base in the figures) from Table 2 in micrograms and percentages. Figure 9 shows the thermal paw withdrawal 30 threshold in grams per days post-surgery for bupivacaine 3 and 4 implants. The results are also summarized below in Table 2:

Table 2

Implant Number	Polymer (wt.%)	Active wt. % of Bupivacaine	Excipient (wt.%)	Handling Property	<i>In vitro</i> elution profile	<i>In vivo</i> data
bupivacaine 3	30% PLGA 50501 A	60% (bupivacaine HCl)	10% mPEG	Sticky, malleable	Day 1 release of 47%; by day 7, 100% released	No statistical reduction in hyperalgesia
bupivacaine 4	30% PLGA 50501 A	60% (bupivacaine base)	10% mPEG	Sticky, malleable	Day 1 release of 20%; by day 9, 70% released	Statistically significant reduction in mechanical hyperalgesia on Day 2
bupivacaine 5	PLA-C12 gel	30% (bupivacaine base)	None	Injectable	Day 1 burst release of 30%; by day 10, 70% of the drug eluted	Not tested

[00194] For the bupivacaine 3 and 4 implants, the polymer degraded in less than one month. The handling property was of a nature to enable a malleable and formable formulation product that could be extruded to a strip-like (ribbon) dosage form. As a preliminary evaluation, the efficacy of these implant formulations was tested in the Brennan rat model of post-incisional pain. Mechanical hyperalgesia was used as the behavioral endpoint to assess the presence/absence of pain in the animal model following treatment with these drug formulations. The Brennan rat incision was made on the plantar aspect of the rat paw. The depth and length of the incision was a limiting factor in this model as an implant was a little bigger than the incision and it became bulky in the rats paw following implantation. This in turn affected wound healing. Some implants were lost from the incised paw at different timepoints following administration. Due to this issue, some animals were excluded from the study due to the loss of implants and a complete evaluation of the efficacy of these implants with the few rats remaining in the study was not able to be conducted. However, of the few rats that proceeded through the study, a statistically significant reduction in mechanical hyperalgesia on day 2 post-surgery, following the administration of a bupivacaine 4 implant, was noted whereas there was no statistical effect with the administration of a bupivacaine 3 implant.

[00195] For the bupivacaine 5 implant, the degradation of the polymer took at least a couple of months.

Example 3

[00196] A number of implants comprising bupivacaine base were prepared and their cumulative *in vitro* release profiles were measured.

[00197] Materials: Poly(D,L-lactide-co-caprolactone) having a 25:75 lactide to caprolactone molar ratio (25:75 DL-CL), an intrinsic viscosity of 0.8 dL/g and a molecular weight of 95 kDa was purchased from Lakeshore Biomaterials (Birmingham, Alabama). Poly(D,L-lactide-co-glycolide-co-caprolactone) having a 30:20:50 lactide to glycolide to caprolactone molar ratio (30:20:50 DL-G-CL), an intrinsic viscosity of 0.05 dL/g to 0.15 dL/g and a molecular weight of 10kDa was purchased from Lakeshore Biomaterials (Birmingham, Alabama). Bupivacaine base was purchased from Orgamol (Switzerland). The PEG polymers having average molecular weights of 300, 1,500 and 8,000 were purchased from Spectrum Chemicals, n-methylpyrrolidone (NMP) having an average molecular weight of 99 g/mol was purchased from Fisher, and acetone was also purchased from Sigma-Aldrich. Labrosol consisting of PEG-8 caprylic/capric glycerides was purchased from Gattefosse, USA (Paramus, NJ). Trehalose having an average molecular weight of 324g/mol was purchased from Sigma-Aldrich (St. Louis, MO).

[00198] Methods:

[00199] Preparation of Bupivacaine base / DL-CL strip implants: The 10:90, 25:75 or 65:35 DL-CL polymer were each added to glass vials and heated to either 100°C (below drug melt temp) or 110°C (above drug melt temp). Bupivacaine base was added to the melted polymers and mixed with a spatula until visually homogeneous. The resulting blend was removed from the glass vial and pressed into a thin film (0.4-0.6 mm thickness) using a Carver Press. The Carver Press was operated at 45°C and 6000-8000 psi pressure. The thin film was cut to form strips (ribbons) of the desired dimensions with a sharp blade. The dimensions of the implants were 9mm in length, 1.5 to 3mm in width and 0.5 to 1mm in thickness.

[00200] *In Vitro* Drug Elution Testing of Bupivacaine base / 25:75 DL-CL ribbon implants: The purpose of this procedure was to measure the release of bupivacaine from a polymer implant formulation into a receiving fluid PBS buffer, pH 7.4. The *in vitro* release procedure consisted of placing a known mass of implant or gel into an apparatus containing the receiving fluid. The *in vitro* release apparatus consisted of a 60ml glass bottle. A receiving fluid in the amount of 30ml was added to each sample bottle. During

the release study, the apparatus was placed in an incubator maintained at 37 ± 2 °C. At predetermined intervals, samples of the receiving fluid were removed and analyzed for bupivacaine concentrations by HPLC. The drug loadings for these implants are summarized in Table 3 below. In addition, Table 3 provides a description for each of these bupivacaine implants.

Table 3

Batch Number	Polymer	Molar Ratio of Polymers	Excipient	Drug Load (wt.%)	Description/Shape
00180-25	DL-CL	10:90	None	62.16	extruded, ribbon shaped
00180-26	5050 4C PEG 1500	-	None	71.34	extruded, ribbon shaped
00180-27	5050 2C PEG 1500	-	None	58.96	extruded, ribbon shaped
00180-28	DL-CL 8E	25:75	None	53.83	maleable, formable product
00180-36	DL-CL 8E	25:75	None	70.88	maleable, formable product
00180-38	DL-CL 8E	25:75	100mg NMP	57.5	maleable, formable product
00180-39	DL-CL 8E	25:75	None	61.7	maleable, formable product
00180-40	DL-CL 8E	25:75	None	60.6	maleable, formable product
00180-53	DL-CL 4A	65:35	None	70	very hard, not very formable product
00180-54	DL-CL 5A	25:75	None	70	brittle, crumbly, not formable product
00180-55	DL-CL 5A	25:75	118mg NMP	65.92	maleable, formable product- investigation of lower MW polymers with acid end group chemistry
00180-56	DL-CL 4A	65:35	118mg NMP	66.19	
00180-57	DL-CL 5A	25:75	20.5mg NMP	60.11	
00180-58	DL-CL 4A	65:35	45.6mg NMP	58.37	
00180-79-01	DL-CL 8E	25:75	2% PEG 1500	62.69	somewhat tacky, easily formable initially, after handling for a few minutes, the material becomes crumbly
00180-79-02	DL-CL 8E	25:75	2% PEG 8000	61.9	somewhat tacky, easily formable, holds together much better than PEG1500 formulation (180-79-01), does not crumble after prolonged handling
00180-80-01	DL-CL 8E	25:75	2% trehalose, 4% NMP	61.57	easy to handle, smooth texture, formable
00180-80-03	DL-CL 8E	25:75	2% CMC, 4 % NMP	61.03	tacky, easy to handle, formable
00180-80-04	DL-CL 8E	25:75	4% labrosol	58.91	tacky, easy to handle, formable
00180-80-05	DL-CL 8E	25:75	5% 5050 2C PEG 1500	60.49	flaky and crumbly, did not hold together well
00180-112	DL-CL 8E	25:75	None	62.03	maleable, formable product

Example 4

[00201] Several bupivacaine gel formulations were prepared.

[00202] Preparation of PLA Gel: Depolymerization of Polylactic Acid with Dodecanol

[00203] Polylactic acid (intrinsic viscosity of 5.71 and weight of 15.0 grams), 4-dimethylaminopyridine (weight of 9.16 grams), and dodecanol (weight of 5.59 grams) were added into a 100mL round bottom flask, charged, capped with a rubber septum and placed in an oil bath at 140°C. The materials were heated at that temperature for 30 minutes after everything was melted and was stirred freely with a magnetic stir bar. After cooling, 15 mL of tetrahydrofuran was added into the flask to dissolve the materials and precipitated by adding heptane. After decanting off the solvents, the material was dissolved in chloroform (30 mL) and washed with hydrochloride (1 molar, 20 mL, three times) and brined once. The solution was dried over anhydrous sodium sulfate. Yellow oil was obtained after solvent removal by rota-evaporation. (Mn about 800 g/mol by end group analysis by H-NMR)

[00204] Method of Preparation of Bupivacaine Gel Formulations: The formulations were prepared to contain 70% (w/w) PLA gel and 30% (w/w) spray dried bupivacaine. For each formulation, the two components were added to a 2cc transfer cup and mixed in a Flacktek, Inc. Speedmixer DAC 150 FVZ for 2 minutes. The mixed formulations were each then back loaded into a 1mL BD syringe with a 18G 1.5 inch blunt tip needle.

[00205] *In Vitro* Drug Elution Testing: 100 μ L of each of the gel formulations was injected in a 20mL scintillation vial for drug elution testing. The formulations were each tested in triplicate and incubated in 10mL of phosphate buffer with 0.5% (w/w) sodium dodecyl sulfate pH 7.4 at 37°C under mild agitation. At pre-selected times, the buffer was removed for analysis and replaced with fresh buffer medium. The drug content was quantified for bupivacaine by a Molecular Devices SpectraMax M2 (Sunnyvale, CA) plate reader. The resulting formulations included 30% bupivacaine. Figures 10-12 show the average *in vitro* cumulative percentage release of bupivacaine per day for the formulations which are listed below in Table 4.

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Table 4

Formulation ID	Drug Load (%)
13335-80-1	30
13335-80-2	30
13335-80-3	30
13335-80-4	30
13335-80-5	30
13335-80-6	30
13335-80-7	30
13335-88-1	30
13335-88-2	30
13335-88-3	30
13335-88-4	30
13335-88-5	30
13699-13-1	30

5

Example 5

[00206] A number of implants comprising bupivacaine were prepared according to the following procedures:

10

[00207] Materials: Poly(D,L-lactide-co-glycolide) having a 50:50 lactide to glycolide molar ratio (DLG 50501A), an intrinsic viscosity of 0.12 and acid end capped polymer chain ends was purchased from Lakeshore Biomaterials (Birmingham, Alabama). Bupivacaine base was purchased from Orgamol (Switzerland). Methoxy polyethylene glycol (mPEG) having an average molecular weight of 550 was purchased from Sigma-Aldrich. Methanol and acetone was also purchased from Sigma-Aldrich.

15

[00208] Methods:

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[00209] Preparation of Spray Dried Bupivacaine base / DLG 50501A: Bupivacaine base and DLG5 0501A were both dissolved in acetone to yield a 10% (w/w) solution. A mixture of 65.2% bupivacaine base solution and 34.8% DLG 50501A solution was spray dried in the Buchi Spray Dryer. The processing parameters were set as follows: inlet temp. (70°C), aspirator (80%), nitrogen inlet (50 mm), spray flow rate (80 mL/hr) and ultrasonic generator (0.8 watts). The spray dried powder was collected and dried for an additional 24 hours at 30°C and 15 mm Hg vacuum.

[00210] Preparation of Melt Extruded Rods: Several formulations were prepared for melt extrusion. All formulations contained DLG 50501A ground into powder using a Retsch (Retsch GmbH, Germany) rotor mill with an 80 micrometer sieve filter. All formulations contained 60% (w/w) spray dried bupivacaine base / PLGA50501A.

5 [00211] The formulations were each dry mixed with a spatula prior to being fed into a Haake Mini-Lab twin screw extruder (Thermo Fischer Scientific, Waltham, MA). The extruder settings were as follows: 105°C and 30 RPM for the 60% bupivacaine HCl formulation, and 85°C and 30 RPM for the 60% bupivacaine base formulation. The formulations were extruded out of a 1.5mm diameter die.

10 [00212] Strip Preparation: Extruded formulations were pressed into sheets of a desired thickness using a Carver Laboratory Heat Press (Carver, Inc., Wabash, IN) set at 50°C. The sheets were cut by razor blades to form strips of the desired dimensions. The dimensions of each of the implants or strips were 9mm in length by 3mm in width by 1mm in height.

15 [00213] *In Vitro* Drug Elution Testing: Each strip or implant was tested in triplicate and placed in 20mL scintillation vials for drug elution testing. The 60% bupivacaine base strips (or ribbons) were incubated in 10mL of phosphate buffer with 0.5% (w/w) sodium dodecyl sulfate pH 7.4 at 37°C under mild agitation. At pre-selected times, the buffer was removed for analysis and replaced with fresh buffer medium. The drug content was
20 quantified at 260 nm for bupivacaine by Molecular Devices SpectraMax M2 (Sunnyvale, CA) plate reader. Figures 13 and 14 show the average *in vitro* cumulative percentage release of bupivacaine per day for the implants which are listed below in Table 5.

Table 5

ID Number	Polymer	Drug Load (%)	Excipient	Ribbon Size (mm) (L x W x H)
13335-76-1	5050 DLG 1A	60	5% mPEG	9 x 3 x 1
13335-76-2	5050 DLG 2A	60	5% mPEG	9 x 3 x 1
13335-76-3	5050 DLG 1A	60	7% mPEG	9 x 3 x 1
13335-83-1	5050 DLG 1A	60	8% mPEG	9 x 3 x 1
13335-83-2	5050 DLG 1A	60	10% mPEG	9 x 3 x 1
13335-83-5	5050 DLG 1A	60	8% mPEG	9 x 3 x 1

Example 6

[00214] Bupivacaine implants were prepared according to the procedure described in Example 5 above. The formulation used to prepare the implants is described below in Table 6. In particular, the formulation contained 50 wt% bupivacaine base, 42 wt% 5050DLG 1A, and 8 wt% mPEG. The inherent viscosity of the 5050DLG was 0.05-0.15 and it had an acid end group.

Table 6

Polymer	% Polymer	Drug Load (%)	Excipient	Ribbon Size (mm) (L x W x H)
5050 DLG 1A	42	50	8% mPEG	9 x 3 x 1

[00215] The *in vitro* cumulative and daily release profile was tested before sterilization using three strip implants from the formulation described in Table 6. Figures 15A and 15B are *in vitro* graphic representations of the percentage cumulative release of three sterilized bupivacaine strips. As is readily apparent in these figures, each formulation released between 65% to 85% of the bupivacaine over 14 days with an average of 5%-10% of drug released every day. The average cumulative drug release of the three strips is shown in Figure 15B, where 75% of the drug released in 14 days.

[00216] Figures 16A and 16B are *in vitro* graphic representations of the daily release profile of the three sterilized bupivacaine strips and their cumulative average daily release in micrograms per day. As is readily apparent in these figures, each drug depot had an initial burst effect with a release of bupivacaine at a dose of about 3500 mcg within 2 days. After the two days, each drug depot released about 500-1000 mcg per day until the drug depot was exhausted at day 14.

Example 7: *In vivo* efficacy evaluation of bupivacaine implants in the pig surgical model

[00217] *Induction of Post-Operative Pain in piglets:* Piglets were anesthetized by Isoflurane/Oxygen mixture, which was delivered through a face mask. A 5 cm long skin and fascia incision was made to the right femur at the groin keeping the muscle intact. The skin incision was closed with metal clamps. The duration of the anesthesia was kept

at less than 10 minutes. Immediately after the incision, the animals were administered with either control or drug implants into the incisional space. Morphine (Mor) was administered subcutaneously in the animals in a morphine group as a positive control.

5 [00218] *Analgesia evaluation:* The analgesic effect of bupivacaine implants was assessed using pain behavior scoring. The pain scoring system was the summation of 3 major categories:

1. Animal solitary performance (walking and vocalization)
2. Animal social behavior
3. The length of time in which the pigs stayed on a sling

10 [00219] All animals were observed at baseline (3 days prior to surgery) and at 1 and 3 hours post-surgery (study day 0). Pain behavior was then assessed daily for 4 more days (study days 1, 2, 3 and 4). The implants were administered into the surgical wound bed on study day 0 immediately right after surgery. Morphine was administered one hour prior to pain assessment in animals in the morphine group (Mor).

15 [00220] *Results:* Figure 17 shows an *in vivo* efficacy evaluation of bupivacaine high dose (250 mcg loaded in the depot, designed to release 25 mcg/day) formulations and bupivacaine low dose (125 mcg loaded in the depot, designed to release 12.5 mcg/day) formulations as measured by pain scores at 1 hour, 3 hours, day 1, day 2, day 3, and day 4, post-surgery. The increase in the pain behavior score reached a peak at 3 hours post-surgery on study day 0 (control group: 7.83 ± 0.9 points). The high mean group pain score of the control treated animals was observed also on study day 1. On study day 2 spontaneous recovery of pain behavior was observed and 4 days post-surgery the pain behavior score was not statistically different from baseline value.

20 [00221] Treatment with bupivacaine implants using a high level dose was effective in reducing pain 3 hours post-surgery and 1 day post-surgery. This effect was not dose related.

[00222] *Conclusion:* In view of the findings obtained under the conditions of this study and confined to the in-life data, treatment with bupivacaine implants at high levels was effective in reducing post-operative pain in pigs.

30 [00223] It will be apparent to those skilled in the art that various modifications and variations can be made to various embodiments described herein without departing from the spirit or scope of the teachings herein. Thus, it is intended that various embodiments

cover other modifications and variations of various embodiments within the scope of the present teachings.

WHAT IS CLAIMED IS:

1. An implantable drug depot useful for reducing, preventing or treating post-operative pain in a patient in need of such treatment, the implantable drug depot comprising a polymer and a therapeutically effective amount of a local anesthetic or pharmaceutically acceptable salt thereof, the depot being implantable at a site beneath the skin to reduce, prevent or treat post-operative pain, wherein the drug depot is capable of releasing (i) a bolus dose of the local anesthetic or pharmaceutically acceptable salt thereof at a site beneath the skin and (ii) a sustained release dose of an effective amount of the local anesthetic or pharmaceutically acceptable salt thereof over a period of at least 4 days.
2. An implantable drug depot according to claim 1, wherein the local anesthetic is at least one of bupivacaine, ropivacaine, mepivacaine, etidocaine, levobupivacaine, trimecaine, carticaine or articaine.
3. An implantable drug depot according to claim 1, wherein the local anesthetic is bupivacaine and the bupivacaine is in the form of a salt.
4. An implantable drug depot according to claim 1, wherein the local anesthetic is bupivacaine and the bupivacaine is in the form of a base.
5. An implantable drug depot according to claim 1, wherein the polymer comprises one or more of poly(lactide-co-glycolide), polylactide, polyglycolide, polyorthoester, D-lactide, D,L-lactide, poly(D,L-lactide), L-lactide, poly(D,L-lactide-co-caprolactone), poly(D,L-lactide-co-glycolide-co-caprolactone), polycaprolactone or a combination thereof.
6. An implantable drug depot according to claim 1, wherein the polymer is capable of degrading in 30 days or less after the drug depot is implanted at the site.
7. An implantable drug depot according to claim 1, wherein the local anesthetic is released in an amount between 50 and 800 mg per day for a period of 4 to 10 days.
8. An implantable drug depot according to claim 1, wherein the local anesthetic is present in an amount of about 30 to about 90 wt.% of the implantable drug depot and the polymer is present in an amount of about 10 to about 80 wt.% of the depot, and the depot further comprises about 0.5 to about 20 wt.% of an excipient.
9. A method of treating or preventing post-operative pain in a patient in need of such treatment, the method comprising administering one or more biodegradable drug depots

comprising a therapeutically effective amount of a local anesthetic or pharmaceutically acceptable salt thereof to a target tissue site beneath the skin before, during or after surgery, wherein the drug depot is capable of releasing an initial bolus dose of the local anesthetic or pharmaceutically acceptable salt thereof at a site beneath the skin followed by a sustained release dose of an effective amount of the local anesthetic or pharmaceutically acceptable salt thereof over a period of at least 4 days.

10. A method of treating or preventing post-operative pain according to claim 9, wherein the local anesthetic is at least one of bupivacaine, ropivacaine, mepivacaine, etidocaine, levobupivacaine, trimecaine, carticaine or artocaine.

11. A method of treating or preventing post-operative pain according to claim 9, wherein the drug depot is capable of releasing about 40% to about 70% of the local anesthetic or pharmaceutically acceptable salt thereof relative to a total amount of the local anesthetic loaded in the drug depot over a period of 4 to 10 days after the drug depot is administered to the target tissue site.

12. A method of treating or preventing post-operative pain according to claim 9, wherein the drug depot is capable of releasing between 50 and 800 mg/day of the local anesthetic or pharmaceutically acceptable salt thereof for a period of 4 to 10 days.

13. A method of treating or preventing post-operative pain according to claim 9, wherein the drug depot comprises a polymer comprising one or more of poly(lactide-co-glycolide), polylactide, polyglycolide, polyorthoester, D-lactide, D,L-lactide, poly(D,L-lactide), L-lactide, poly(D,L-lactide-co-caprolactone), poly(D,L-lactide-co-glycolide-co-caprolactone), polycaprolactone or a combination thereof.

14. An implantable drug depot useful for reducing, preventing or treating post-operative pain in a patient in need of such treatment, the implantable drug depot comprising a therapeutically effective amount of bupivacaine or pharmaceutically acceptable salt thereof and a polymer; wherein the depot is implantable at a site beneath the skin to reduce, prevent or treat post-operative pain, and the depot is capable of releasing (i) about 2% to about 50% of the bupivacaine or pharmaceutically acceptable salt thereof relative to a total amount of the bupivacaine or pharmaceutically acceptable salt thereof loaded in the drug depot over a first period of up to 48 hours and (ii) about 50% to about 98% of the bupivacaine or pharmaceutically acceptable salt thereof relative to a total

amount of the bupivacaine or pharmaceutically acceptable salt thereof loaded in the drug depot over a subsequent period of up to 3 to 10 days.

15. An implantable drug depot according to claim 14, wherein the polymer comprises one or more of poly(lactide-co-glycolide), polylactide, polyglycolide, polyorthoester, D-lactide, D,L-lactide, poly(D,L-lactide), L-lactide, poly(D,L-lactide-co-caprolactone),
5 poly(D,L-lactide-co-glycolide-co-caprolactone), polycaprolactone or a combination thereof.

16. An implantable drug depot according to claim 14, wherein the polymer comprises about 15% to about 55% of the total wt.% of the drug depot.

10 17. An implantable drug depot according to claim 14, wherein the drug depot is capable of releasing between 50 and 800 mg/day of bupivacaine or pharmaceutically acceptable salt thereof.

18. An implantable drug depot according to claim 14, wherein the polymer is capable of degrading in 30 days or less after the drug depot is implanted at the site.

15 19. A method of making an implantable drug depot of claim 14, the method comprising combining a biocompatible polymer and a therapeutically effective amount of bupivacaine or pharmaceutically acceptable salt thereof and forming the implantable drug depot from the combination.

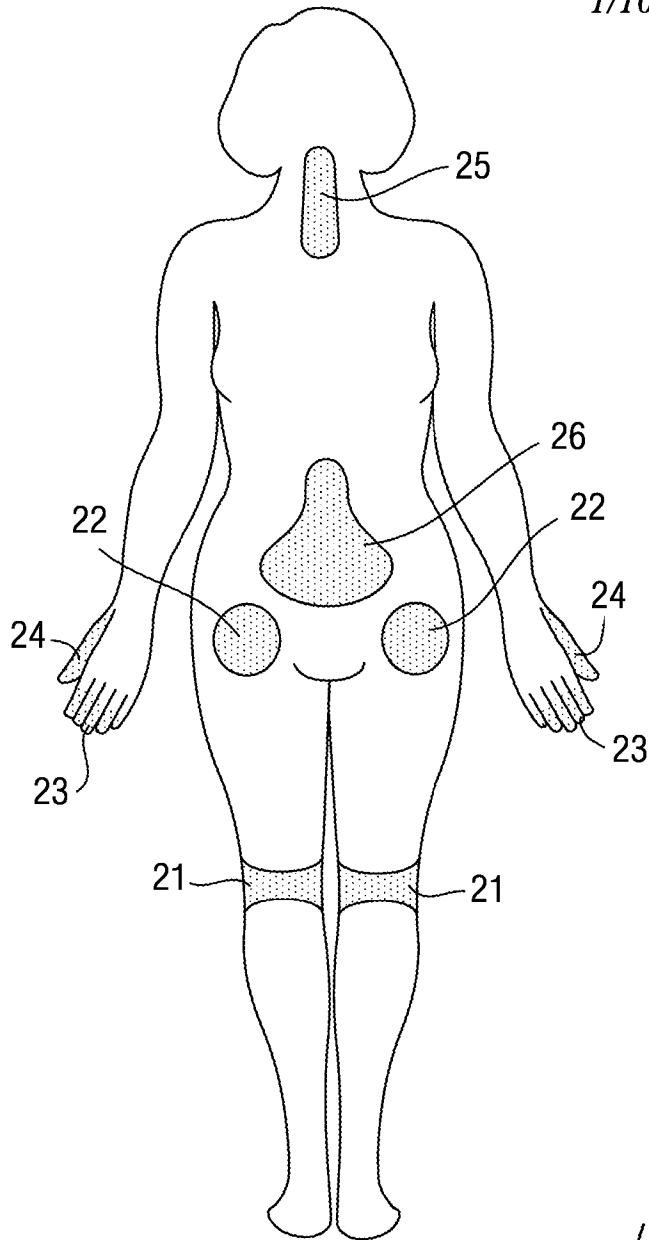


FIG. 1

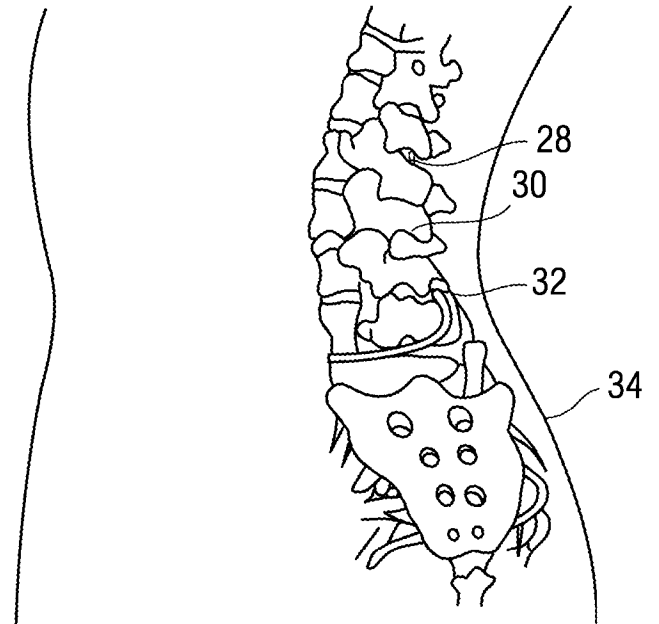


FIG. 2

2/10

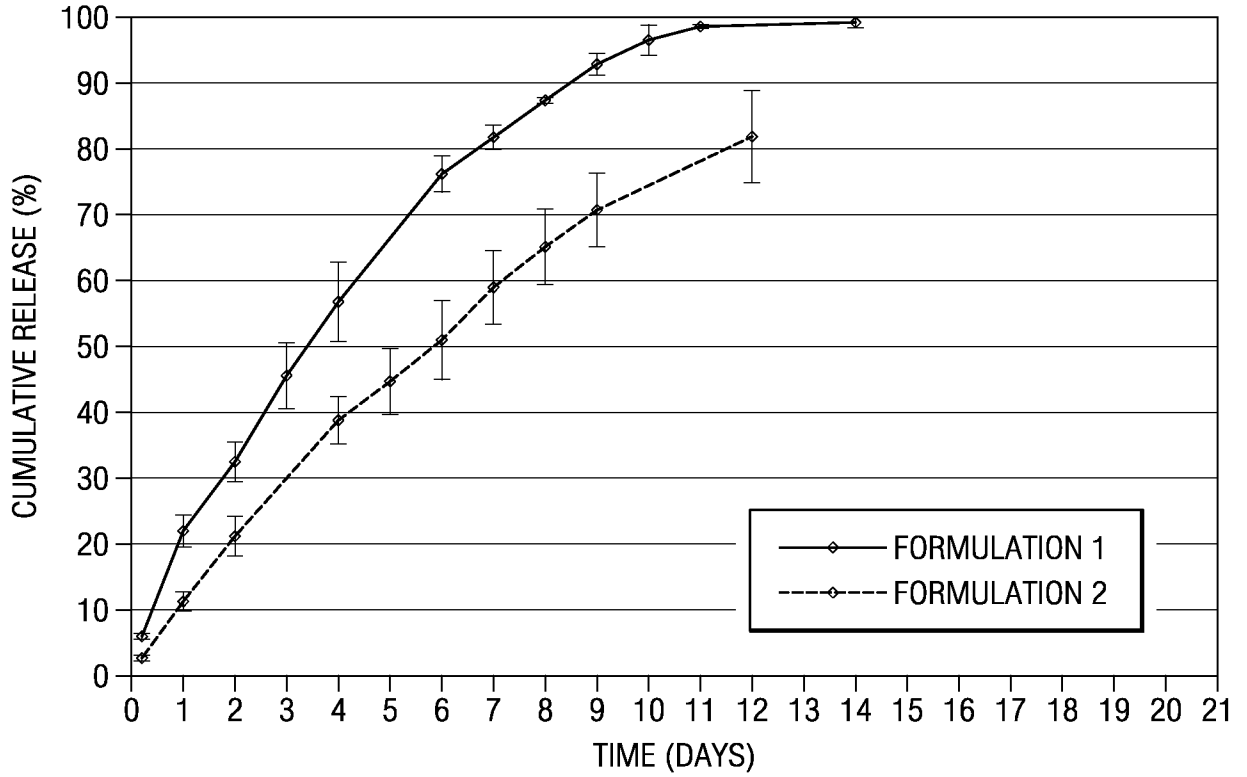


FIG. 3

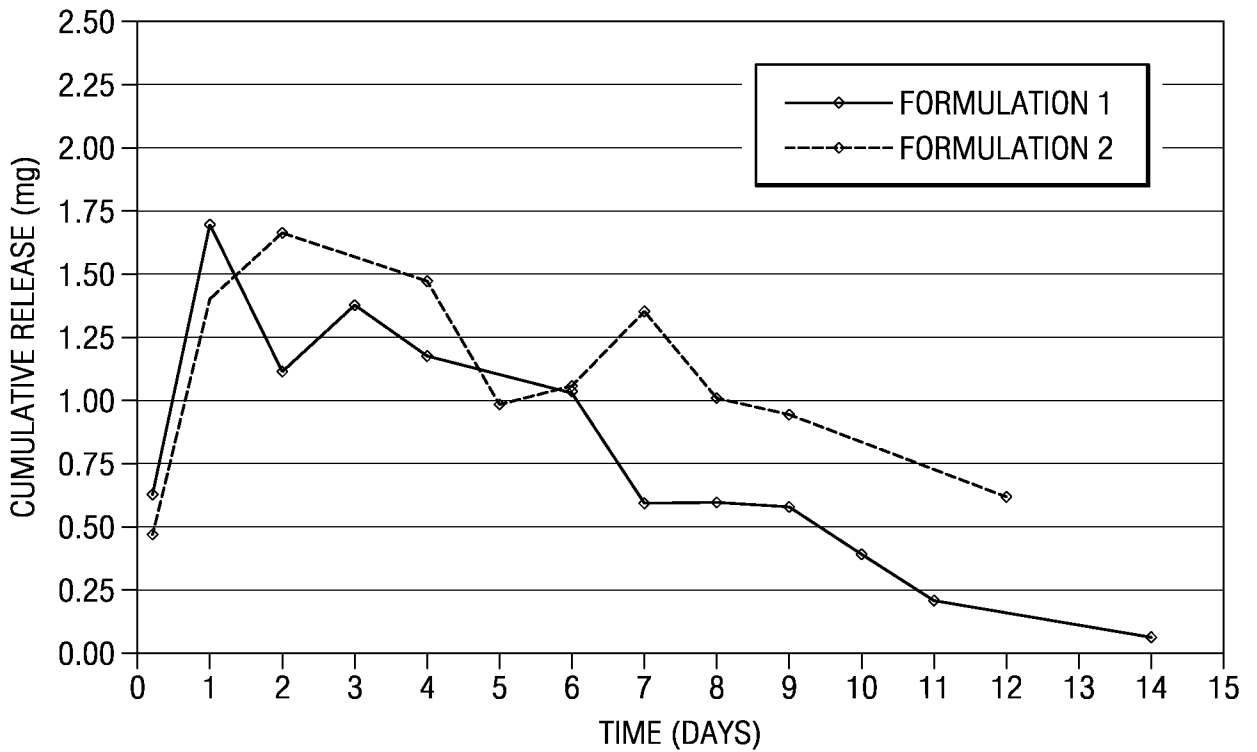


FIG. 4

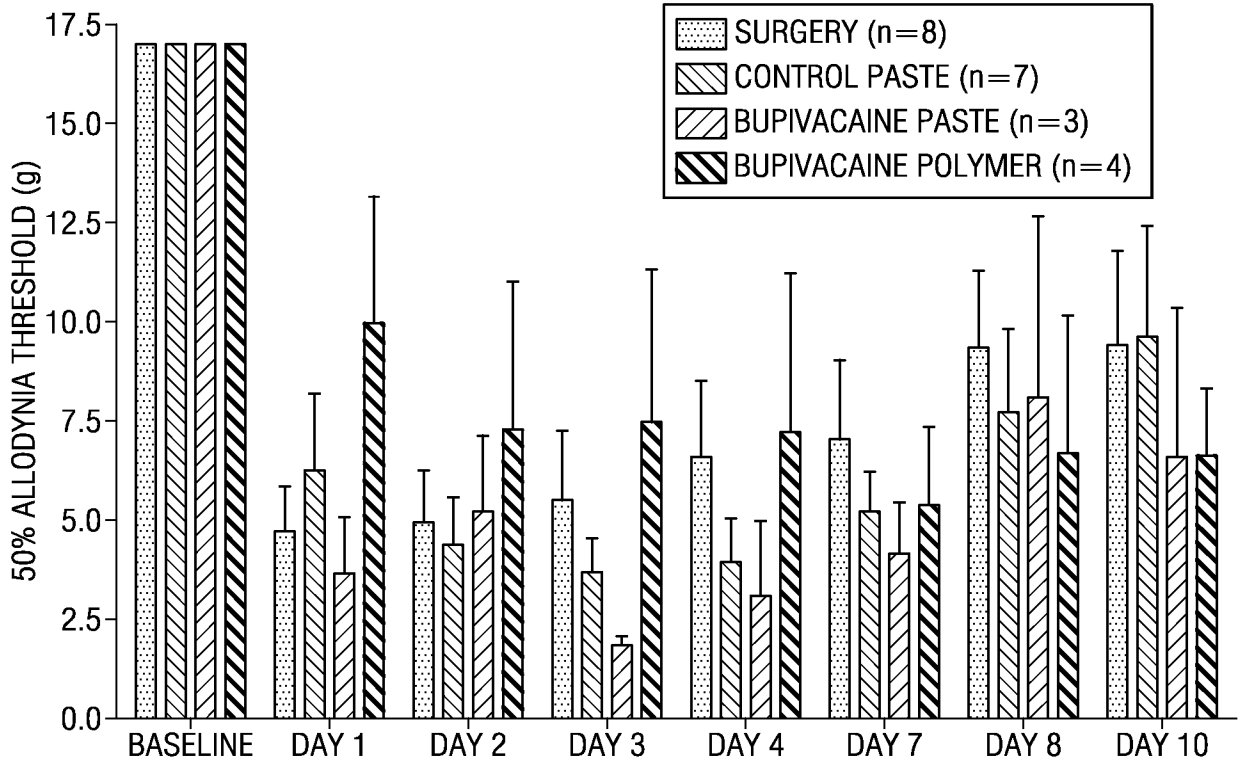


FIG. 5

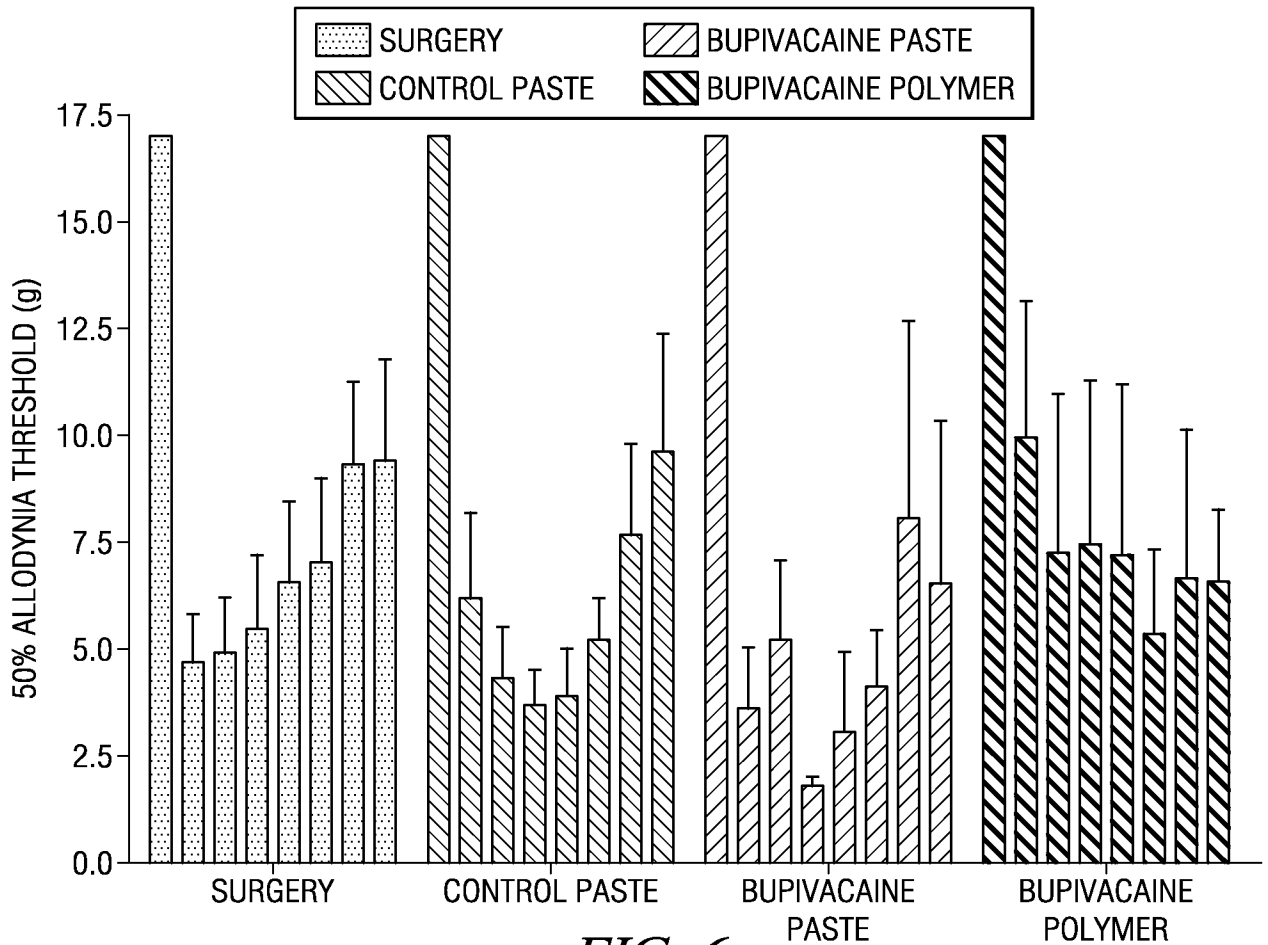


FIG. 6

4/10

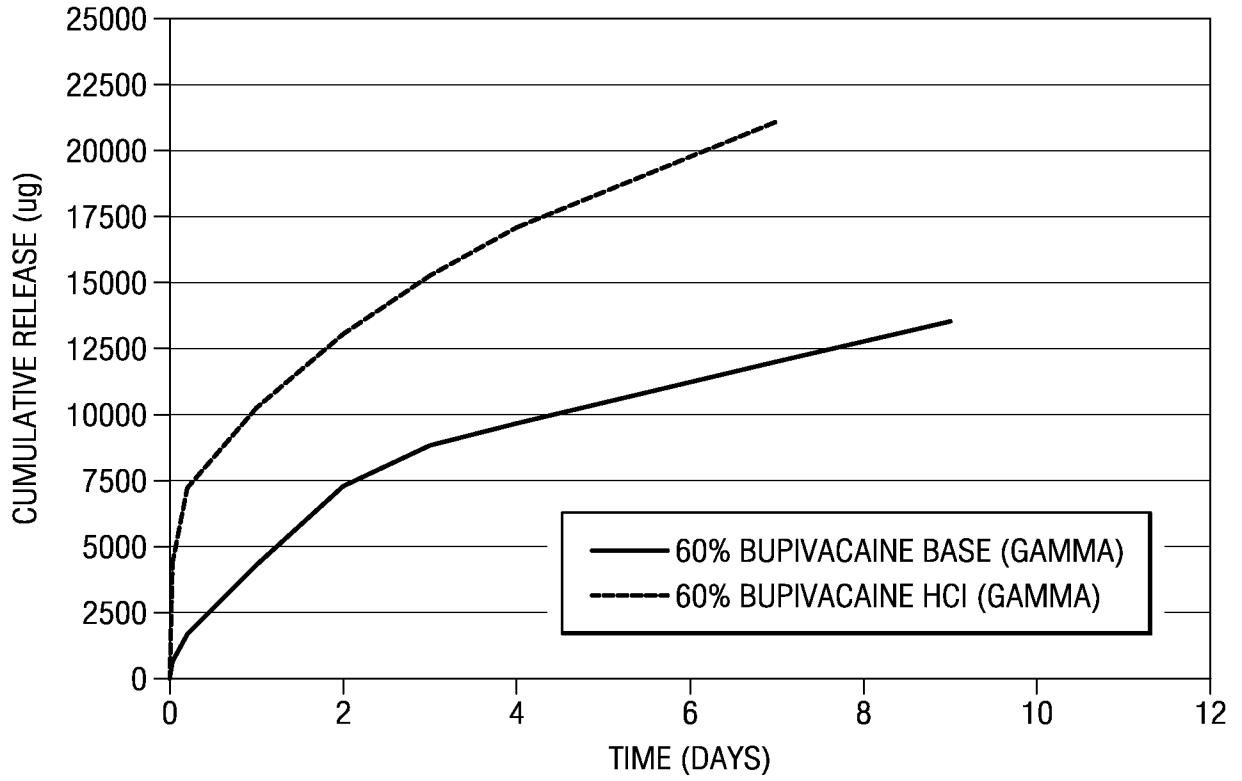


FIG. 7

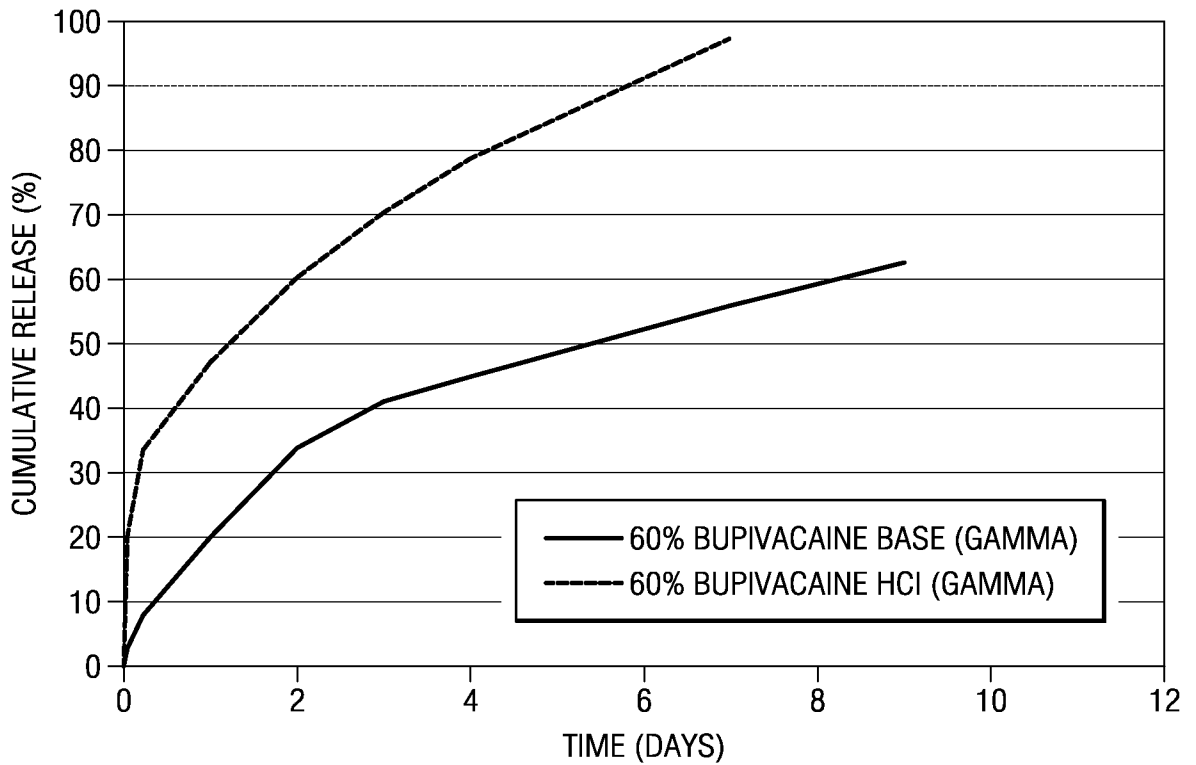


FIG. 8

5/10

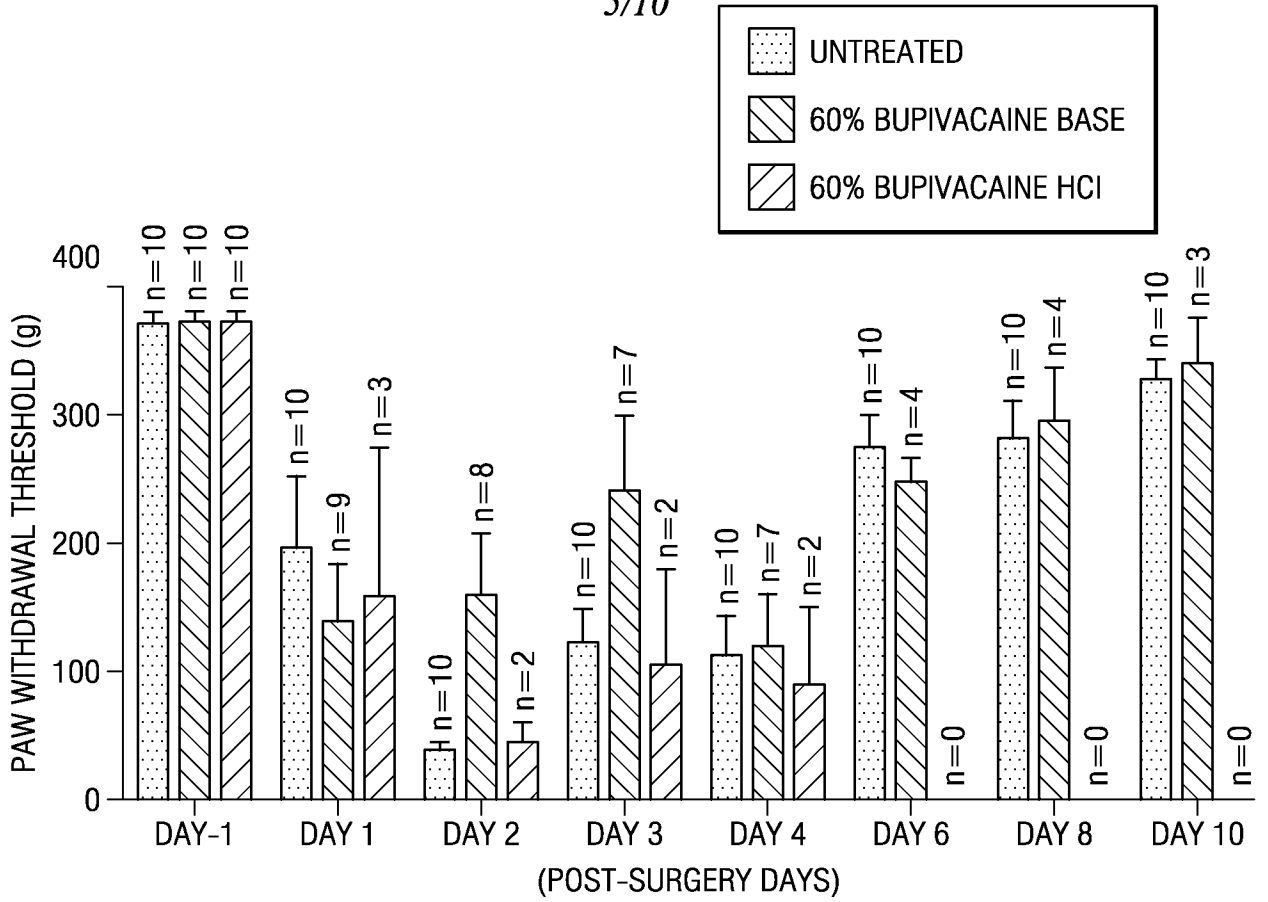


FIG. 9

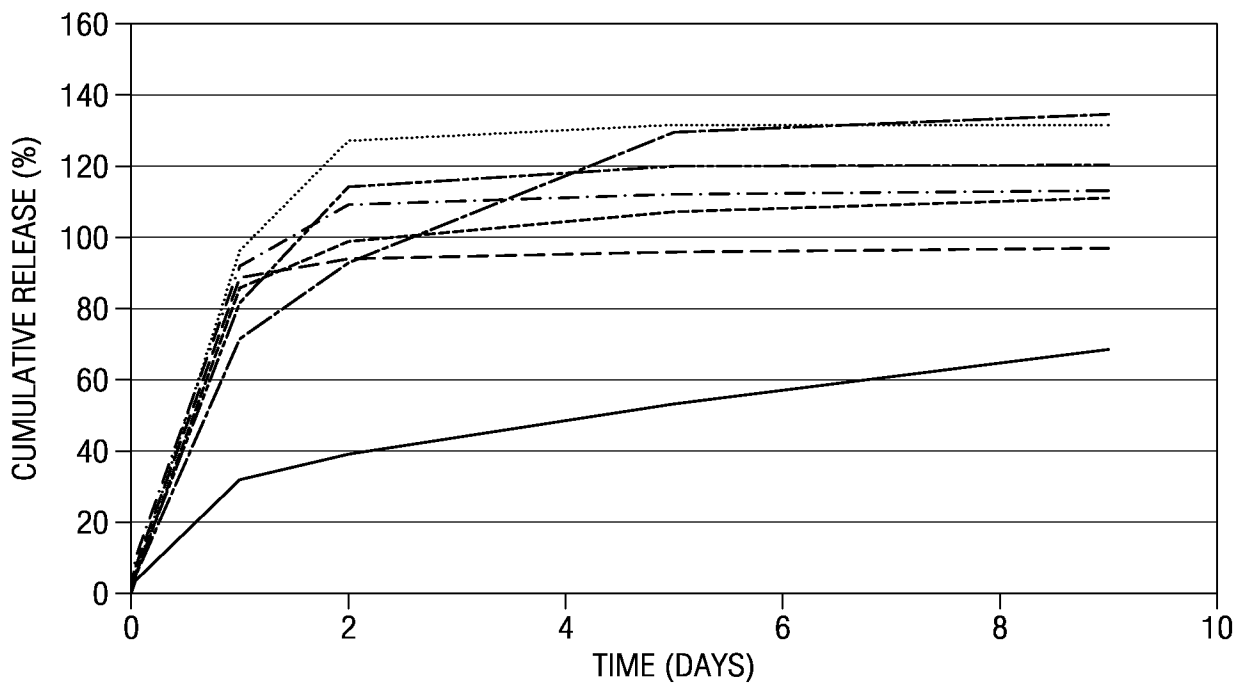
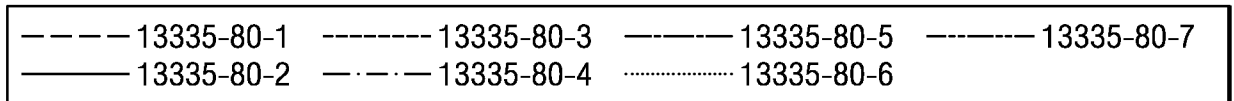


FIG. 10

6/10

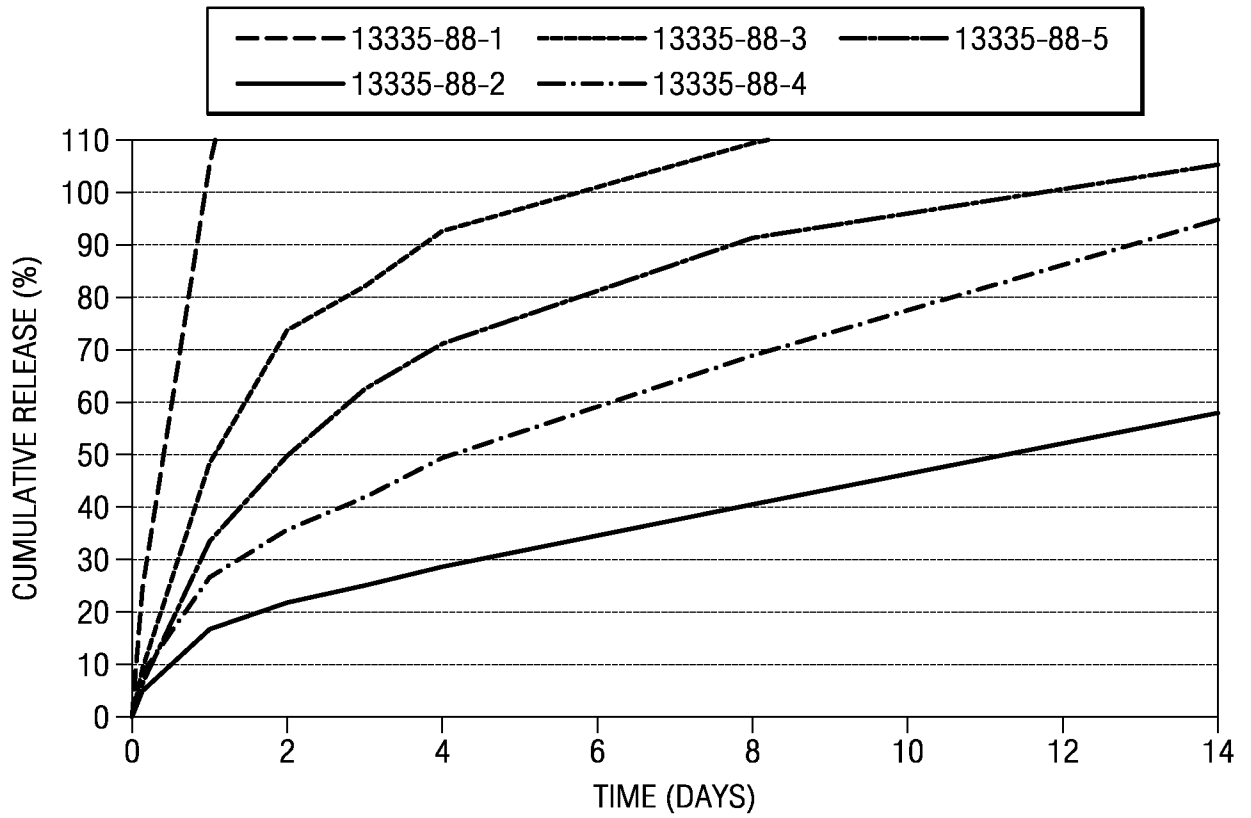


FIG. 11

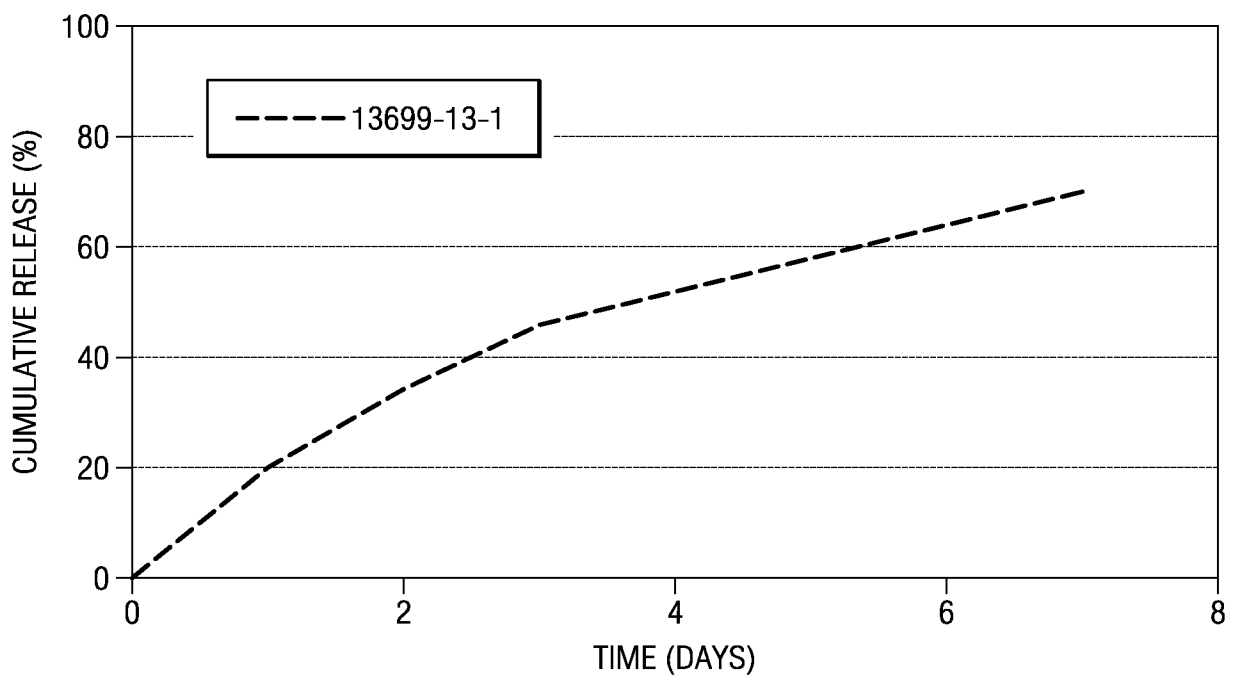


FIG. 12

7/10

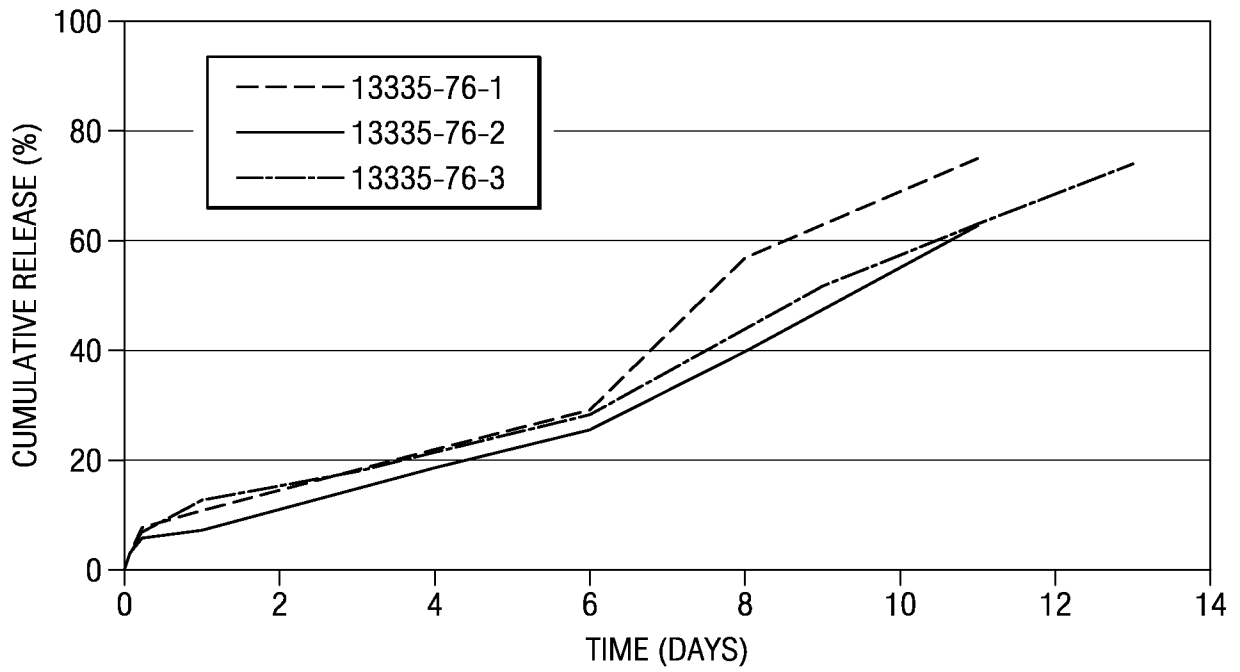


FIG. 13

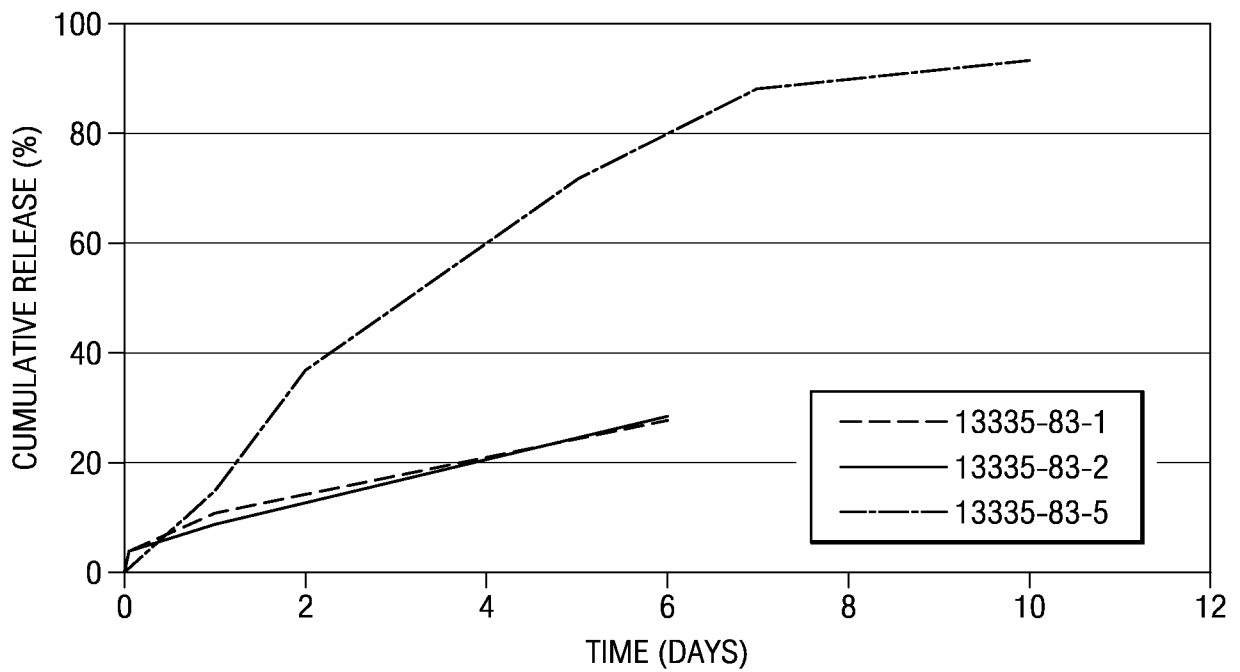


FIG. 14

8/10

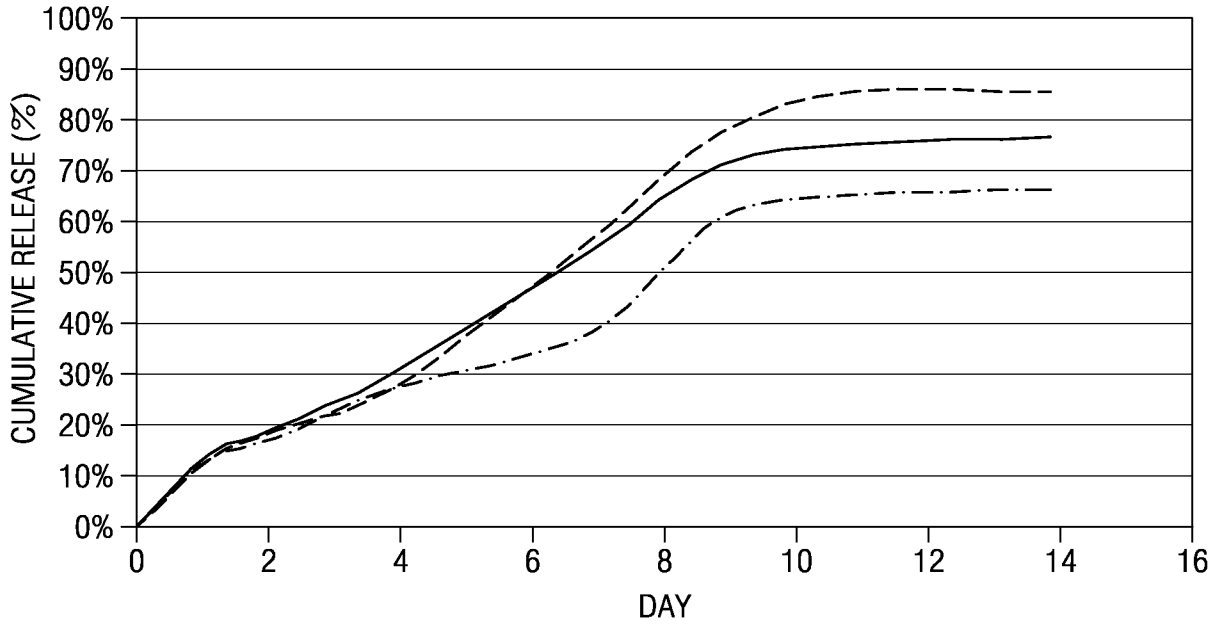


FIG. 15A

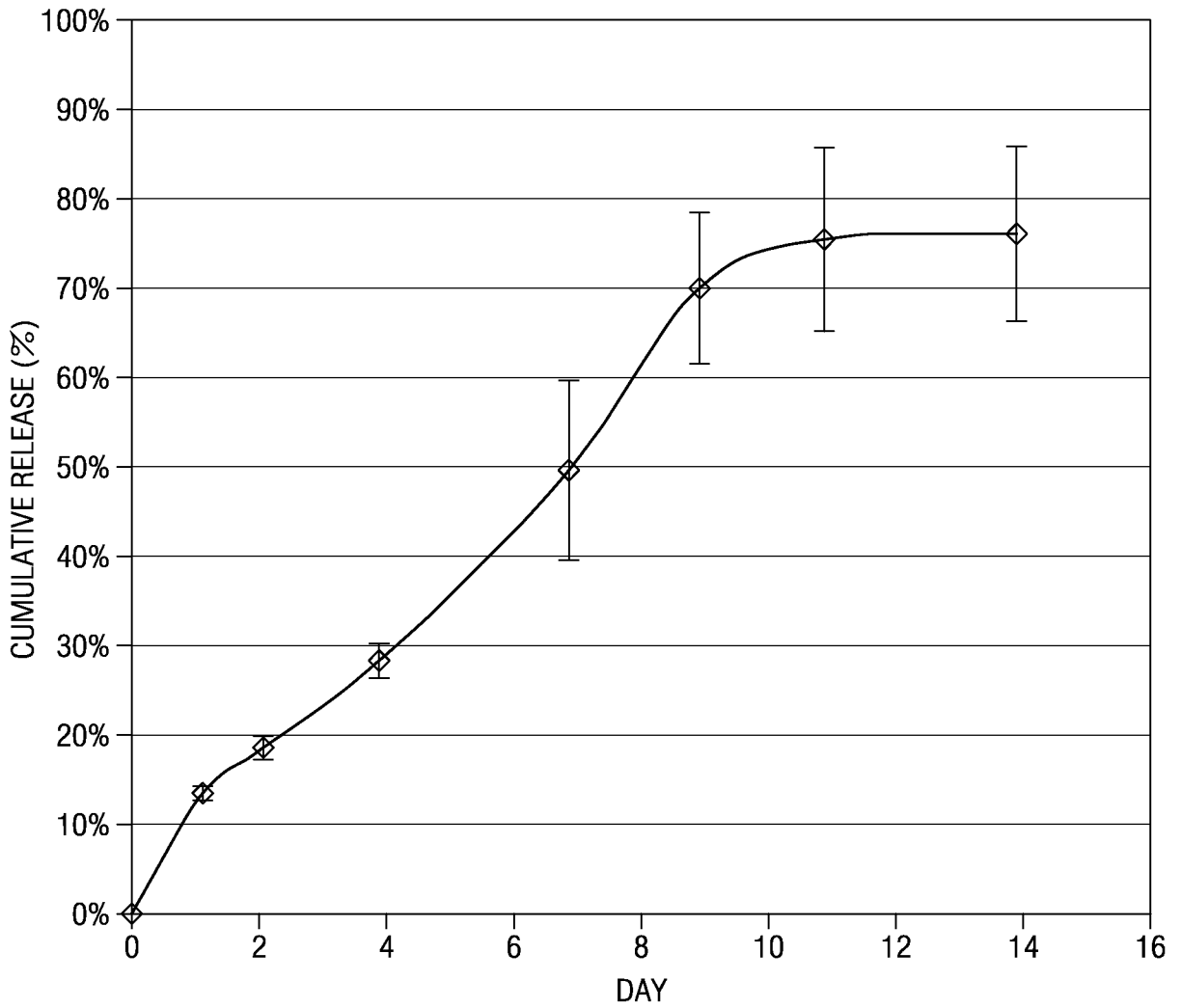


FIG. 15B

9/10

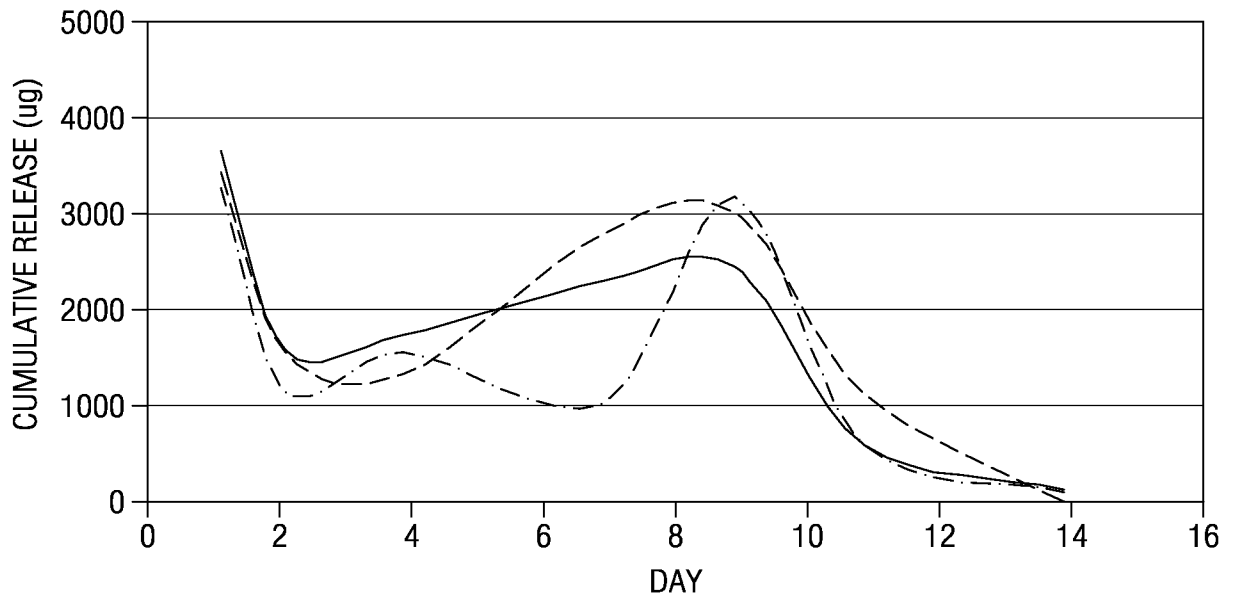


FIG. 16A

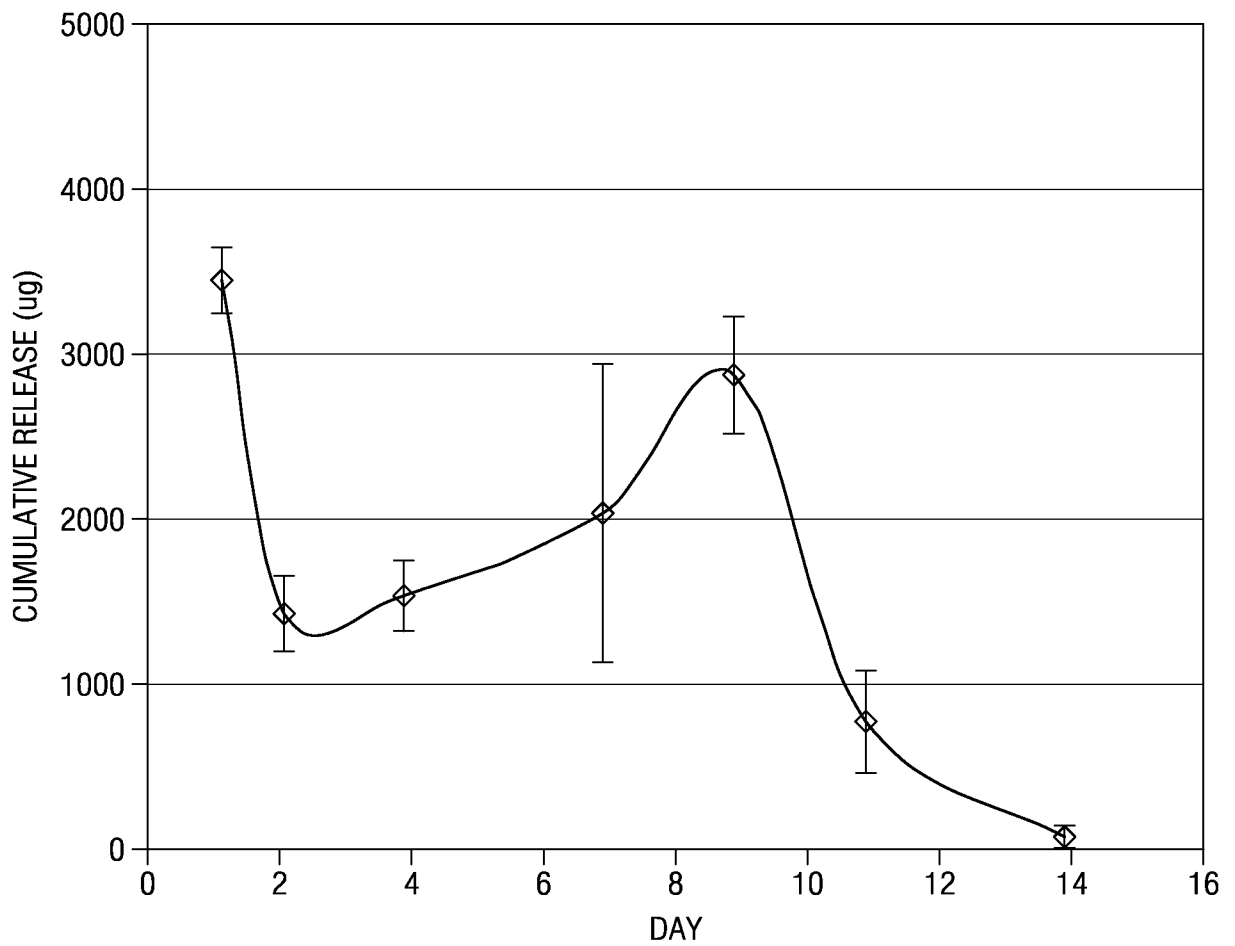


FIG. 16B

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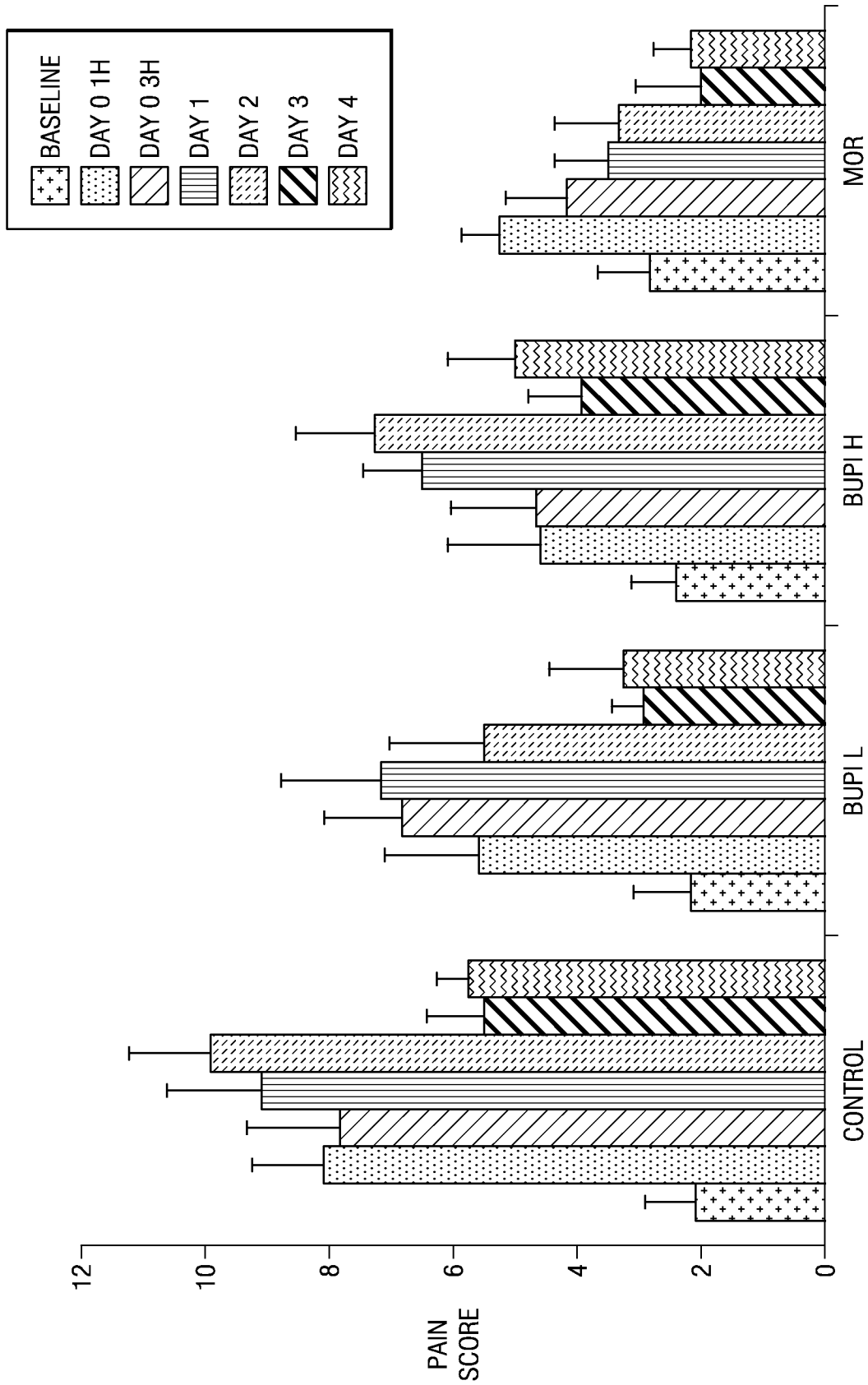


FIG. 17