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[Continued on next page]

(54) **Title**: CLONIDINE COMPOUNDS IN A BIODEGRADABLE FIBER

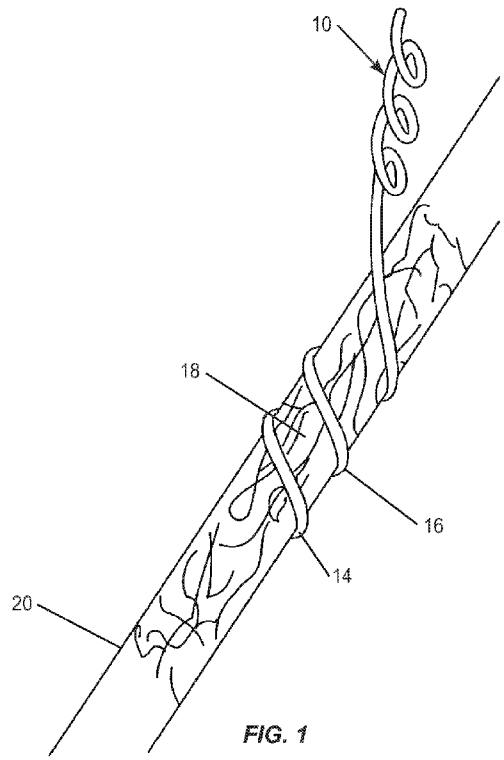

FIG. 1

(57) **Abstract**: Effective treatments of pain for extended periods of time are provided. Through the administration of an effective amount of clonidine in a fiber at or near a target site, one can relieve pain caused by diverse sources, including but not limited to spinal disc herniation (i.e. sciatica), spondilothesis, stenosis, discogenic back pain and joint pain, as well as pain that is incidental to surgery. When appropriate fiber formulations are provided within biodegradable polymers, this pain relief can be continued for at least three days.

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— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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CLONIDINE COMPOUNDS IN A BIODEGRADABLE FIBER

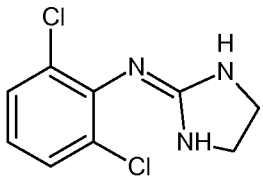
BACKGROUND

[0001] Pain is typically experienced when the free nerve endings of pain receptors are subject to mechanical, thermal, chemical or other noxious stimuli. These pain receptors can transmit signals along afferent neurons to the central nervous system and then to the brain. When a person feels pain, any one or more of a number of problems can be associated with this sensation, including but not limited to reduced function, reduced mobility, complication of sleep patterns, and decreased quality of life.

[0002] The causes of pain include but are not limited to inflammation, injury, disease, muscle stress, the onset of a neuropathic event or syndrome, and damage that can result from surgery or an adverse physical, chemical or thermal event or from infection by a biologic agent. When a tissue is damaged, a host of endogenous pain inducing substances, for example, bradykinin and histamine can be released from the injured tissue. The pain inducing substances can bind to receptors on the sensory nerve terminals and thereby initiate afferent pain signals. After activation of the primary sensory afferent neurons, the projection neurons may be activated. These neurons carry the signal via the spinothalamic tract to higher parts of the central nervous system.

[0003] One known class of pharmaceuticals to treat pain is opioids. This class of compounds is well-recognized as being among the most effective type of drugs for controlling pain, such as 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. Consequently, physicians typically limit the administration of opioids to within the first twenty-four hours post-surgery. Thus, it would be preferable to use non-narcotic drugs that deliver direct, localized pain control at a surgical site.

[0004] One pharmaceutical that is known to the medical profession is clonidine, which is widely recognized as an antihypertensive agent that acts as an agonist on the alpha-2-adrenergic receptor and as a neural receptor agonist. In general, clonidine, also referred to as 2,6-dichloro-*N*-2-imidazolidinyldenebenzenamine ($C_9H_9Cl_2N_3$) may be represented by the following chemical structure:



[0005] However, to date clonidine compounds have not been widely appreciated as a localized and effective treatment for pain. Thus, there is a need to develop effective devices and compositions containing clonidine compounds for this application.

SUMMARY

[0006] Compositions and methods are provided comprising clonidine or its pharmaceutically acceptable salts that are administered in order to treat pain and/or inflammation. The compositions and methods may for example be used to treat pain due to post operative pain, a spinal disc herniation (*i.e.,* sciatica), spondilothesis, stenosis, osteoarthritis, carpal/tarsal tunnel syndrome, tendonitis, temporomandibular joint disorder (TMJ), discogenic back pain, joint pain or inflammation.

[0007] In some embodiments, there is an implantable fiber for reducing or treating pain in a patient in need of such treatment, the implantable fiber comprising clonidine in an amount from about 0.1 wt.% to about 40 wt.% of the implantable fiber, and at least one biodegradable polymer, wherein the implantable fiber is configured to release clonidine over a period of at least three days.

[0008] In some embodiments, there is an implantable fiber or reducing or treating pain in a patient in need of such treatment, the implantable fiber comprising clonidine hydrochloride in an amount of from about 0.1 wt.% to about 30 wt.% of the fiber and at least one polymer comprising one or more of poly(lactide-co-glycolide) (PLGA), polylactide (PLA), polyglycolide (PGA), D-lactide, D,L-lactide, L-lactide, L-lactide-co-ε-caprolactone, D,L-lactide-co-ϵ-caprolactone, D,L-lactide-co-glycolide-co-ϵ-caprolactone, collagen, polyester(amide) copolymers, or a combination thereof.

[0009] In some embodiments, there is a method for treating acute pain, the method comprising implanting an implantable fiber into a mammal at or near a target tissue site, the implantable fiber comprising clonidine in an amount from about 0.1 wt.% to about 40 wt.% of the implantable fiber, and at least one biodegradable polymer, wherein the implantable fiber is configured to release clonidine over a period of at least three days.

[0010] In some embodiments, the fiber is a drug fiber that may: (i) consist of only the clonidine (or one or more of its pharmaceutically acceptable salts) and the biodegradable polymer(s); or

(ii) consist essentially of the clonidine (and/or one or more of its pharmaceutically acceptable salts) and the biodegradable polymer(s); or (iii) comprise the clonidine (and/or one or more of its pharmaceutically acceptable salts), and the biodegradable polymer(s) and one or more other active ingredients, surfactants, excipients or other ingredients or combinations thereof. When there are other active ingredients, surfactants, excipients or other ingredients or combinations thereof in the formulation, in some embodiments these other compounds or combinations thereof comprise less than 50 wt.%, less than 40 wt.%, less than 30 wt.%, less than 20 wt.%, less than 19 wt.%, less than 18 wt.%, less than 17 wt.%, less than 16 wt.%, less than 15 wt.%, less than 14 wt.%, less than 13 wt.%, less than 12 wt.%, less than 11 wt.%, less than 10 wt.%, less than 9 wt.%, less than 8 wt.%, less than 7 wt.%, less than 6 wt.%, less than 5 wt.%, less than 4 wt.%, less than 3 wt.%, less than 2 wt.%, less than 1 wt. % or less than 0.5 wt.%.

[0011] 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

[0012] 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:

[0013] FIG. 1 provides a perspective view of an exemplary fiber that is memory shaped, disposed about and anchored to a ligament;

[0014] FIG. 2 depicts a perspective view of an embodiment of a fiber comprising a first end configured to be sutured to a target tissue site and a second end configured to be sutured at or near a target tissue site;

[0015] FIG. 3 provides a chart of the cumulative release percentages of clonidine released per day; and

[0016] FIG. 4 provides a chart of the release profile of clonidine in μg/day.

[0017] 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

[0018] 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 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.

[0019] 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.

Definitions

[0020] 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 fiber" includes one, two, three or more matrices.

[0021] A "drug depot" is the composition in which the clonidine is administered to the body. Thus, a drug depot may comprise a physical structure (e.g., fiber) to facilitate implantation and retention in a desired site (*e.g.,* a disc space, a spinal canal, a tissue of the patient, particularly at or near a site of chronic pain, *etc.*). The drug depot (e.g., fiber) may also comprise the drug itself. 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 unless otherwise specified 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 provides a concentration gradient of the therapeutic agent for delivery to the site. In various embodiments, the drug depot (e.g., fiber) provides an optimal drug concentration gradient of the therapeutic agent at a distance of up to about 0.01 cm to about 20 cm from the administration site and comprises clonidine. A drug depot (e.g., fiber) may also include a pump or pellet.

[0022] 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 or spasticity, improvement in the condition through muscle relaxation, *etc*. The dosage administered to a patient can be as single or multiple doses 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. In some embodiments the formulation is designed for immediate release. In other embodiments the formulation is designed for sustained release. In other embodiments, the formulation comprises one or more immediate release surfaces and one or more sustained release surfaces.

[0023] A "depot" includes but is not limited to capsules, microspheres, microparticles, microcapsules, microfibers particles, nanospheres, nanoparticles, coating, matrices, wafers, pills, pellets, emulsions, liposomes, micelles, gels, or other pharmaceutical delivery compositions or a combination thereof. Suitable materials for the depot (e.g., fiber) 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.

[0024] The "fiber" of the present application provides a 3-D fiber of interconnecting pores, which acts as a pliant scaffold for cell migration and/or drug release.

[0025] As used herein, "fiber" refers to any flexible structure that can be stretched between two points and includes, without limitation, traditional fiber material, single or multiple stranded threads, or a mesh structure. A fiber may also be a strap-like structure with a number of holes in it. A "fiber" may also take the form of an acellular, collagen membrane or other biologic tissue augment, which may provide a scaffold or support matrix for cellular ingrowth to allow soft tissue to reconstruct itself. Fibers may include silk, nylon, linen, cotton, chromic gut, plain gut, cat gut, vicryl, polyglactin, polyester, polypropylene, stainless steel, synthetic polymers having lactic acid or glycolic acid ester linkages subject to hydrolytic degradation to non-toxic tissue compatible absorbable components, including polylactic acid or polyglycolic acid. The fiber may be monofilamentary or braided, absorbable or non-absorbable.

[0026] The term "biodegradable" includes that all or parts of the drug depot (e.g., fiber) 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.*, fiber) 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 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 (e.g., fiber) will be broken down and absorbed within the human body, for example, by a cell or tissue. "Biocompatible" means that the depot (e.g., fiber) will not cause substantial tissue irritation or necrosis at the target tissue site.

[0027] In some embodiments, the drug depot (e.g., fiber) has pores that allow release of the drug from the depot (e.g., fiber). The drug depot (e.g., fiber) will allow fluid in the depot (e.g., fiber) to displace the drug. However, cell infiltration into the depot (e.g., fiber) will be prevented by the size of the pores of the depot (e.g., fiber). In this way, in some embodiments, the depot (e.g., fiber) should not function as a tissue scaffold and allow tissue growth. Rather, the drug depot (e.g., fiber) will solely be utilized for drug delivery. In some embodiments, the pores in the drug depot (e.g., fiber) will be less than 250 to 500 microns. This pore size will prevent cells from infiltrating the drug depot (e.g., fiber) and laying down scaffolding cells. Thus, in this embodiment, the drug will elute from the drug depot (e.g., fiber) as fluid enters the drug depot (e.g., fiber), 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 (e.g., fiber) by the action of enzymes, by hydrolytic action and/or by other similar mechanisms in the human body. In some embodiments, the drug depot (e.g., fiber) will function to allow influx of cells and tissue and it will function as a scaffold.

[0028] The phrases "sustained release" and "sustain release" (also referred to as 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 or continually 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 or continual release stream is intended to encompass release that occurs as the result of biodegradation *in vivo* of the drug depot, or a fiber or component thereof, or as the result of metabolic transformation or dissolution of the therapeutic agent(s) or conjugates of therapeutic agent(s).

[0029] 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.

[0030] The two types of formulations (sustain release and immediate release) may be used in conjunction. The sustained release and immediate release may be in one or more of the same fiber. In various embodiments, the sustained release and immediate release may be part of separate fibers. For example a bolus or immediate release formulation of clonidine 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 accessible, the sustain release formulation would continue to provide the active ingredient for the intended tissue.

[0031] In various embodiments, the fiber can be designed to cause an initial burst dose of therapeutic agent within the first twenty-four to seventy-two hours after implantation. "Initial burst" or "burst effect" "burst release" or "bolus dose" refers to the release of therapeutic agent from the depot (e.g., fiber) during the first twenty-four hours to seventy-two hours after the depot (e.g., fiber) comes in contact with an aqueous fluid (*e.g.*, interstitial fluid, synovial fluid, cerebral spinal fluid, *etc.*). The "burst effect" is believed to be due to the increased release of therapeutic agent from the fiber. In some embodiments, the fiber has one or more burst release surfaces that releases about 10%, 15%, 20%, 25%, 30%, 35%, 45%, to about 50% of the drug over 24 or 48 hours.

[0032] In alternative embodiments, the fiber is designed to avoid or reduce this initial burst effect (e.g., by applying an outer polymer coating to the fiber).

[0033] "Treating" or "treatment" of a disease or condition refers to executing a protocol that may include administering one or more drugs to a patient (human, other normal or otherwise or other mammal), in an effort to alleviate signs or symptoms of the disease or condition. Alleviation can occur prior to signs or symptoms of the disease or condition appearing, as well as after their appearance. Thus, treating or treatment includes 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 and/or inflammation" includes a decrease in pain and/or inflammation and does not require complete alleviation of pain and/or inflammation signs or symptoms, and does not require a cure. In various embodiments, reducing pain and/or inflammation includes even a marginal decrease in pain and/or inflammation. By way of example, the administration of the effective dosage of clonidine may be used to prevent, treat or relieve the symptoms of pain and/or inflammation for different diseases or conditions. These disease/conditions may comprise post-operative pain, oral-facial diseases, bursitis, tendonitis, chronic inflammatory diseases, including, but not limited to

autoimmune diseases, such as multiple sclerosis, rheumatoid arthritis, osteoarthritis, insulin dependent diabetes (type I diabetes), systemic lupus erythrematosis and psoriasis, immune pathologies induced by infectious agents, such as helminthic (e.g., leishmaniasis) and certain viral infections, including HIV, and bacterial infections, including Lyme disease, tuberculosis and lepromatous leprosy, tissue transplant rejection, graft versus host disease and atopic conditions, such as asthma and allergy, including allergic rhinitis, gastrointestinal allergies, including food allergies, eosinophilia, conjunctivitis or glomerular nephritis. In some embodiments, the fiber containing the therapeutic agent is not administered in, to or near the eye.

[0034] One chronic condition is sciatica. In general, sciatica is an example of pain that can transition from acute to neuropathic pain. Sciatica refers to pain associated with the sciatic nerve which runs from the lower part of the spinal cord (the lumbar region), down the back of the leg and to the foot. Sciatica generally begins with a herniated disc. The herniated disc itself leads to local immune system activation. The herniated disc also may damage the nerve root by pinching or compressing it, leading to additional immune system activation in the area. In various embodiments, the clonidine may be used to reduce, treat, or prevent sciatic pain and/or inflammation by locally administering the clonidine at one or more target tissue sites (e.g., nerve root, dorsal root ganglion, focal sites of pain, at or near the spinal column, etc.).

[0035] In some embodiments, the fiber can be used to treat one or more target tissue sites that are involved in conditions/diseases, such as for example, 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, a surgical wound site or an incision site, postoperative pain or the like.

[0036] The term "implantable" as utilized herein refers to a biocompatible device (e.g., fiber) retaining potential for successful placement within a mammal. The expression "implantable device" and expressions of the like import as utilized herein refers to an object implantable through surgery, injection, or other suitable means whose primary function is achieved either through its physical presence or mechanical properties.

[0037] "Localized" delivery includes delivery where one or more drugs are deposited within a tissue, for example, a nerve root of the nervous system or a region of the brain, or in close proximity (within about 0.1 cm, or preferably within about 10 cm, for example) thereto. For example, the drug dose delivered locally from the fiber may be, for example, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 99%, or 99.9% less than the oral dosage or injectable

dose. In turn, systemic side effects, such as for example, liver transaminase elevations, hepatitis, liver failure, myopathy, constipation, etc. may be reduced or eliminated.

[0038] The term "mammal" 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.*

[0039] The phrase "pain management medication" includes one or more therapeutic agents that are administered to prevent, alleviate or remove pain entirely. These include anti-inflammatory agents, muscle relaxants, analgesics, anesthetics, narcotics, and so forth, and combinations thereof.

[0040] The phrase "release rate profile" refers to the percentage of active ingredient that is released over fixed units of time, *e.g.,* mcg/hr, mcg/day, 10% per day for ten days, *etc.* As persons of ordinary skill know, a release rate profile may, but need not, be linear. By way of a non-limiting example, the fiber may be a ribbon-like fiber that releases the clonidine over a period of time.

[0041] The term "solid" is intended to mean a rigid material, while, "semi-solid" is intended to mean a material that has some degree of flexibility, thereby allowing the depot (e.g., fiber) to bend and conform to the surrounding tissue requirements.

[0042] "Targeted delivery system" provides delivery of one or more drugs depots (e.g., fibers) at or near the target site as needed for treatment of pain, inflammation or other disease or condition.

[0043] The abbreviation "DLG" refers to poly(DL-lactide-co-glycolide).

[0044] The abbreviation "DL" refers to poly(DL-lactide).

[0045] The abbreviation "LG" refers to poly(L-lactide-co-glycolide).

[0046] The abbreviation "CL" refers to polycaprolactone.

[0047] The abbreviation "DLCL" refers to poly(DL-lactide-co-caprolactone).

[0048] The abbreviation "LCL" refers to poly(L-lactide-co-caprolactone).

[0049] The abbreviation "G" refers to polyglycolide.

[0050] The abbreviation "PEG" refers to poly(ethylene glycol).

[0051] The abbreviation "PLGA" refers to poly(lactide-co-glycolide) also known as poly(lactic-co-glycolic acid), which are used interchangeably.

[0052] The abbreviation "PLA" refers to polylactide.

[0053] The abbreviation "PEA" refers to poly(ester) amides.

[0054] The abbreviation "POE" refers to poly(orthoester). The above polymers or combination of polymers can be in the drug depot (e.g., fiber).

[0055] 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 that may be included within the invention as defined by the appended claims.

[0056] Clonidine Compounds

[0057] When referring to clonidine, unless otherwise specified or apparent from context it is understood that the inventors are also referring to pharmaceutically acceptable salts. One well-known commercially available salt for clonidine is its hydrochloride salt. Some other examples of potentially pharmaceutically acceptable salts include those salt-forming acids and bases that do not substantially increase the toxicity of a compound, such as, salts of alkali metals such as magnesium, potassium and ammonium, salts of mineral acids such as hydriodic, hydrobromic, phosphoric, metaphosphoric, nitric and sulfuric acids, as well as salts of organic acids such as tartaric, acetic, citric, malic, benzoic, glycollic, gluconic, gulonic, succinic, arylsulfonic, *e.g.,* p-toluenesulfonic acids, and the like.

[0058] Further, when referring to clonidine, the active ingredient may not only be in the salt form, but also in the base form (*e.g.,* free base). In various embodiments, if it is in the base form, it may be combined with polymers under conditions in which there is not severe polymer degradation, as may be seen upon heat or solvent processing that may occur with PLGA or PLA. By way of a non-limiting example, when formulating clonidine with poly(orthoesters) it may be desirable to use the clonidine base formulation. By contrast, when formulating clonidine with PLGA, it may be desirable to use the HCl salt form. In some embodiments, the clonidine may be incorporated into a polymer core with a polymer and then coated with the same or different polymer.

[0059] Pharmaceutically acceptable salts of clonidine include salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases, inorganic or organic acids and fatty acids. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2- dimethylaminoethanol, ethanolamine, ethylenediamine,

N-ethyl-morpholine, N- ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethyl amine, tripropylamine, tromethamine, and the like. When the compound of the current application is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, formic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, malonic, mucic, nitric, pamoic, pantothenic, phosphoric, propionic, succinic, sulfuric, tartaric, p-toluenesulfonic acid, trifluoroacetic acid, and the like. Fatty acid salts may also be used, e.g., fatty acid salts having greater than 2 carbons, greater than 8 carbons or greater than 16 carbons, such as butyric, caprioc, caprylic, capric, lauric, mystiric, palmitic, stearic, arachidic or the like.

[0060] In some embodiments, in order to reduce the solubility of the clonidine to assist in obtaining a controlled release depot (e.g., fiber) effect, clonidine is utilized as the free base or utilized in a salt which has relatively lower solubility. For example, the present application can utilize an insoluble salt such as a fatty acid salt. Representative fatty acid salts include salts of oleic acid or linoleic acid. In preferred embodiments fatty acid salts with between 8 to 20 carbons are used to produce salts with low solubility, such as clonidine palmeate and clonidine stearate. Most preferably, fatty acid salts with between 12 to 18 carbons are used. Other embodiments can utilize a lipid soluble salt of clonidine.

[0061] In some embodiments, clonidine can be used with a GABA compound in the fiber. The GABA compounds used in the treatment methods and in the device include compounds of gamma-aminobutyric acid. Such compounds include gabapentin (2-[1-(aminomethyl)cyclohexyl]acetic acid), pregabalin ((S)-3-(aminomethyl)-5-methylhexanoic acid), vigabatrin (4-aminohex-5-enoic acid), and baclofen (4-amino-3-(4-chlorophenyl)butanoic acid), which are 3'-alkylated GABA compounds. Additional GABA compounds that may be used are described in Satzinger et al., U.S. Pat. No. 4,024,175; Silverman et al., U.S. Pat. No. 5,563,175; Horwell et al., U.S. Pat. No. 6,020,370; Silverman et al., U.S. Pat. No. 6,028,214; Horwell et al., U.S. Pat. No. 6,103,932; Silverman et al., U.S. Pat. No. 6,117,906; WO 02/00209); Silverman et al., PCT Publication No. WO 92/09560; Silverman et al., PCT Publication No. WO 93/23383; Horwell et al., PCT Publication No. WO 97/29101, Horwell et al., PCT Publication No. WO 97/33858; Horwell et al., PCT Publication No. WO 97/33859; Bryans et al., PCT Publication No. WO 98/17627; Guglietta et al., PCT Publication No. WO 99/08671; Bryans et al., PCT Publication No. WO 99/21824; Bryans et al., PCT Publication No. WO 99/31057; WO 98/23383; Bryans et al., J. Med. Chem. 1998, 41, 1838-1845; Bryans et al.,

Med. Res. Rev. 1999, 19, 149-177, US Guglietta et al., WO 99/08670; Bryans et al., WO 99/21824; US Bryans et al., UK GB 2 374 595), Belliotti et al., PCT Publication No. WO 99/31074; Bryans et al., PCT Publication No. WO 99/31075; Bryans et al., PCT Publication No. WO 99/61424; Bryans et al., PCT Publication No. WO 00/15611; Bryans, PCT Publication No. WO 00/31020; Bryans et al., PCT Publication No. WO 00/50027; and Bryans et al., PCT Publication No. WO 02/00209). New classes of GABA compounds, which are bicyclic amino acid derivatives, have been recently described by Bryans et al., PCT Publication No. WO 01/28978; Blakemore et al., PCT Pub. No. WO 02/085839; Blakemore et al., U.S. Pat. No. 5,596,900; and Blakemore et al., PCT Pub. No. WO 02/090318.

[0062] In one embodiment, the GABA compound comprises 1-{[(alpha-isobutanoyloxyethoxy)carbonyl]aminomethyl}-1-cyclohexane acetic acid, baclofen, vigabatrin, gabapentin, pregabalin, gamma-amino-phosphinic acid or 1-{[(alpha-isobutanoyloxyethoxy)carbonyl]aminomethyl}-1-cyclohexane acetic acid, fengabine, GBL (gamma-Butyrolactone), GHB (gamma-Hydroxybutyric acid, 4-hydroxybutanoic acid or sodium oxybate), picamilon and progabide,(s)-(+)-4-amino-3-(2-methylpropyl) butanoic acid

[0063] In another embodiment, GABA compounds include pharmaceuticals that can increase locally the available amount of endogenous GABA or GABA analogs following their local or systemic administration. These include pharmaceuticals that interfere with GABA or GABA analog reuptake such as tiagabine, stiripentol, deramciclane, hyperforin or a combination thereof. GABA compounds also include pharmaceuticals that interfere with the degradation of GABA or GABA analogs such as phenelzine, gabaculine, valproate, vigabatrin, lemon balm or a combination thereof.

[0064] In some embodiments, the GABA compound is released locally from the device at a dose of from about 0.3 mg/day or about 1.8 mg/day or about 3.6 mg/day to about 180mg/day or about 360 mg/day. In some embodiments, the GABA compound is released from the device at a dose of 0.75 mg to 16 mg per day. In some embodiments, the initial burst or bolus release is about 2 to 20 times higher from 1 hour to about two weeks than the sustained release daily dose released from the device.

[0065] In some embodiments, the GABA compound comprises gabapentin, which is released from the device at a dosage of from about 0.3mg or 1mg to about 8mg, 10mg, 16mg or 32mg per day. In some embodiments, the GABA compound comprises pregabalin, which is released from the device at a dosage of from about 0.1mg or 0.3mg to about 1mg, 3mg, 5mg or 10mg per day. In some embodiments, the clonidine can be released from the depot (e.g., fiber) at a dose of 0.002mg to 16mg per day.

[0066] In some embodiments, the ratio of gabapentin to clonidine would be 300:1. For pregabalin, the ratio would be approximately 100:1. In some embodiments, the fiber releases 300mg of pregabalin per day.

[0067] The GABA compound compliments the anti-inflammatory and analgesic effect of clonidine in the fiber.

[0068] In some embodiments, the fiber comprises clonidine that is in the fiber in an amount of from about 0.1% to about 75% by weight.

[0069] In some embodiments, the fiber comprises both a GABA compound and clonidine in a single formulation. In some embodiments, the GABA compound can be in a separate depot (e.g., fiber) from the clonidine.

[0070] In some embodiments, a GABA compound, a steroid, bupivacaine, lidocaine and/or clonidine can be administered in an immediate release or sustained release liquid by injection before, after, or during the administration of the clonidine depot (e.g., fiber).

[0071] The clonidine and GABA compound or its pharmaceutically acceptable salt may be administered with a muscle relaxant. Exemplary muscle relaxants include by way of example and not limitation, alcuronium chloride, atracurium bescylate, carbamate, carbolonium, carisoprodol, chlorphenesin, 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.

[0072] The fiber may comprise other therapeutic agents in addition to the clonidine and GABA compound as well. These 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).

[0073] Other suitable therapeutic agents include IL-1 inhibitors, such Kineret® (anakinra) which is a recombinant, non-glycosylated form of the human inerleukin-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 analogs (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), may also be useful as therapeutic agents for reducing inflammation. It is further contemplated that where desirable a pegylated form of the above may be used. Examples of still other therapeutic agents include NF kappa B inhibitors such as glucocorticoids, antioxidants, such as dithiocarbamate, and other compounds, such as, for example, sulfasalazine.

[0074] Examples of therapeutic agents suitable for use also include, but are not limited to an anti-inflammatory agent, an analgesic agent, or an osteoinductive growth factor or a combination thereof. Anti-inflammatory agents include, but are not limited to, apazone, celecoxib, diclofenac, diflunisal, enolic acids (piroxicam, meloxicam), etodolac, fenamates (mefenamic acid, meclofenamic acid), gold, ibuprofen, indomethacin, ketoprofen, ketorolac, nabumetone, naproxen, nimesulide, salicylates, sulfasalazine [2-hydroxy-5-[-4-[C2-pyridinylamino)sulfonyl]azo]benzoic acid, sulindac, tepoxalin or tolmetin; as well as antioxidants, such as dithiocarbamate, steroids, such as fluocinolone, cortisol, cortisone, hydrocortisone, fludrocortisone, prednisone, prednisolone, methylprednisolone, triamcinolone, betamethasone, dexamethasone, beclomethasone, fluticasone or a combination thereof.

[0075] Suitable anabolic growth or anti-catabolic growth factors include, but are not limited to, a bone morphogenetic protein, a growth differentiation factor (e.g., GDF-5), a LIM mineralization protein, CDMP or progenitor cells or a combination thereof.

[0076] Suitable analgesic agents include, but are not limited to, acetaminophen, bupivacaine, 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, amitriptyline, carbamazepine, gabapentin, pregabalin, or a combination thereof.

[0077] The therapeutic agent in the fiber may include, but is not limited to, members of the fibroblast growth factor family, including acidic and basic fibroblast growth factor (FGF-1 and FGF-2) and FGF-4, members of the platelet-derived growth factor (PDGF) family, including PDGF-AB, PDGF-BB and PDGF-AA; EGFs; the TGF-β superfamily, including TGF- β1, 2 or 3; osteoid-inducing factor (OIF); angiogenin(s); endothelins; hepatocyte growth factor or

keratinocyte growth factor; members of the bone morphogenetic proteins (BMP's) BMP-1, BMP-3, BMP-2; OP-1, BMP-2A, BMP-2B, or BMP-7; HBGF-1 or HBGF-2; growth differentiation factors (GDF's); members of the hedgehog family of proteins, including indian, sonic and desert hedgehog; ADMP-1; other members of the interleukin (IL) family; or members of the colony-stimulating factor (CSF) family, including CSF-1, G-CSF, and GM-CSF, or isoforms thereof; or VEGF, NELL-1 (neural epidermal growth factor-like 1), CD-RAP (cartilage-derived retinoic acid-sensitive protein) or combinations thereof.

[0078] In some embodiments, the fiber comprises osteogenic proteins. Exemplary osteogenic proteins include, but are not limited to, OP-1, OP-2, OP-3, BMP-2, BMP-3, BMP-3b, BMP-4, BMP-5, BMP-6, BMP-9, BMP-10, BMP-11, BMP-12, BMP-13, BMP-14, BMP-15, GDF-1, GDF-2, GDF-3, GDF-5, GDF-6, GDF-7, GDF-8, GDF-9, GDF-10, GDF-11, GDF-12, CDMP-1, CDMP-2, CDMP-3, DPP, Vg-1, Vgr-1, 60A protein, NODAL, UNIVIN, SCREW, ADMP, NEURAL, and TGF-beta. As used herein, the terms "morphogen, " "bone morphogen, " "BMP, " "osteogenic protein" and "osteogenic factor" embrace the class of proteins typified by human osteogenic protein 1 (hOP-1).

[0079] Exemplary growth factors include, but are not limited to, members of the transforming growth factor beta family, including bone morphogenetic protein 2 (BMP-2); bone morphogenetic protein 4 (BMP-4); and transforming growth factors beta-1, beta-2, and beta-3 (potent keratinocyte growth factors). Other useful members of the transforming growth factor beta family include BMP-3, BMP-5, BMP-6, BMP-9, DPP, Vg1, Vgr, 60A protein, GDF-1, GDF-3, GDF-5, GDF-6, GDF-7, CDMP-1, CDMP-2, CDMP-3, BMP-10, BMP-11, BMP-13, BMP-15, Univin, Nodal, Screw, ADMP, Neural, and amino acid sequence variants thereof. Other growth factors include epidermal growth factor (EGF), which induces proliferation of both mesodermal and ectodermal cells, particularly keratinocytes and fibroblasts; platelet-derived growth factor (PDGF), which exerts proliferative effects on mesenchymal cells; fibroblast growth factor (FGF), both acidic and basic; and insulin-like growth factor 1 (IGF-1) or 2 (IGF-2), which mediate the response to growth hormone, particularly in bone growth. Further growth factors include osteogenic proteins. A particularly preferred osteogenic protein is OP-1, also known as bone morphogenetic protein 7 (BMP-7). OP-1 is a member of the transforming growth factor beta gene superfamily.

[0080] The clonidine may also be administered with non-active ingredients. These non-active ingredients may have multi-functional purposes including the carrying, stabilizing and controlling 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-sustained

process. Typically, the depot (e.g., fiber) will be a solid or semi-solid formulation comprised of a biocompatible material that can be biodegradable.

[0081] Exemplary excipients, plasticizers, and/or pore forming agents that may be formulated with clonidine in addition to the biodegradable polymer include but are not limited to MgO (*e.g.,* 1 wt.%), mPEG, propylene glycol, mannitol, trehalose, TBO-Ac, mPEG, Span-65, Span-85, pluronic F127, sorbitol, cyclodextrin, maltodextrin, pluronic F68, CaCl, dextran, dextran sulphate, dextran phosphate, hydroxypropylcellulose, ethylcellulose, PEG 1500, PEG 400, PEG3350 or combinations thereof. In some embodiments, the excipients comprise from about 0.001 wt.% to about 50 wt.% of the formulation. In some embodiments, the excipients comprise from about 0.001 wt.% to about 40 wt.% of the formulation. In some embodiments, the excipients comprise from about 0.001 wt.% to about 30 wt.% of the formulation. In some embodiments, the excipients comprise from about 0.001 wt.% to about 20 wt.% of the formulation. In some embodiments, the excipients comprise from about 0.001 wt.% to about 10 wt.% of the formulation. In some embodiments, the excipients comprise from about 0.001 wt.% to about 50 wt.% of the formulation. In some embodiments, the excipients comprise from about 0.001 wt.% to about 2 wt.% of the formulation.

[0082] In some embodiments, the fiber 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 the therapeutic agent. However, the pre-determined erosion of the depot (e.g., fiber) material can also be used to provide for slow release of the loaded therapeutic agent(s). Non-biodegradable polymers include but are not limited to PVC and polyurethane. In some embodiments, a plasticizer is used to lower glass translation temperature in order to affect stability of the fiber.

[0083] In various embodiments, the fiber comprises clonidine, bupivacaine or lidocaine and a biodegradable polymer in amorphous, crystalline or semicrystalline form; where the crystalline form may include polymorphs, solvates or hydrates.

[0084] In some embodiments, the clonidine can be in powdered form having a particle sizes predominantly in a range from about 3.5 to about 10 micrometers that can be reconstituted with the polymer for delivery.

[0085] In some embodiments, the fiber has a modulus of elasticity in the range of about 1 x 10^2 to about 6 x 10^5 dyn/cm^2, or 2 x 10^4 to about 5 x 10^5 dyn/cm^2, or 5 x 10^4 to about 5 x 10^5 dyn/cm^2. In some embodiments, the fiber is in the form of a solid. In some embodiments, the fiber comprises clonidine, bupivacaine or lidocaine.

[0086] In some embodiments, the clonidine, bupivacaine, lidocaine, and/or GABA compound is administered in a fiber that is solid or in semi-solid form. The solid or semi-solid form of the

fiber may have a pre-dosed viscosity in the range of about 1 to about 2000 centipoise (cps), 1 to about 200 cps, or 1 to about 100 cps. After the solid or semi-solid fiber is administered to the target site, the viscosity of the semi-solid or solid fiber will increase and the semi-solid will have a modulus of elasticity in the range of about 1 x -10^2 to about 6 x 10^5 dynes/cm^2, or 2 x 10^4 to about 5 x 10^5 dynes/cm^2, or 5 x 10^4 to about 5 x 10^5 dynes/cm^2.

[0087] In various embodiments, the semi-solid or solid fiber may comprise a polymer having a molecular weight, as shown by the inherent viscosity, from about 0.10 dL/g to about 1.2 dL/g or from about 0.20 dL/g to about 0.50 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 0.55 dL/g, about 0.50 to about 0.70 dL/g, about 0.55 to about 0.6 dL/g, about 0.60 to about 0.80 dL/g, about 0.70 to about 0.90 dL/g, about 0.80 to about 1.00 dL/g, about 0.90 to about 1.10 dL/g, about 1.0 to about 1.2 dL/g, about 1.1 to about 1.3 dL/g, about 1.2 to about 1.4 dL/g, about 1.3 to about 1.5 dL/g, about 1.4 to about 1.6 dL/g, about 1.5 to about 1.7 dL/g, about 1.6 to about 1.8 dL/g, about 1.7 to about 1.9 dL/g, or about 1.8 to about 2.1 dL/g.

[0088] In some embodiments, the fiber may comprise an 8% loaded 60:40 LCL 5A with a 6.5% content having a 0.4 mm diameter; an 8% loaded 60:40 LCL 5A with a 6.6% content having a 0.8 mm diameter; or a 16% loaded 60:40 LCL 5A with a 13.2% content having a 0.6 mm diameter.

[0089] In some embodiments, the fiber may not be fully biodegradable. For example, the fiber 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, methacrylates, poly (N-isopropylacrylamide), PEO-PPO-PEO (pluronics) or combinations thereof. Typically, these types of matrices may need to be removed after a certain amount of time.

[0090] In some instances, it may be desirable to avoid having to remove the fiber after use. In those instances, the fiber 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 a 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 (e.g., fiber) (homogeneous or bulk erosion).

[0091] In various embodiments, the depot (e.g., fiber) may comprise a bioerodible, a bioabsorbable, and/or a biodegradable biopolymer that may provide immediate release, or sustained release of the clonidine. Examples of suitable sustained release biopolymers include but are not limited to poly (alpha-hydroxy acids), poly (lactide-co-glycolide) (PLGA), polylactide (PLA), polyglycolide (PG), polyethylene glycol (PEG) conjugates of poly (alpha-hydroxy acids), poly(orthoester)s (POE), poly(esteramide)s, polyaspirins, polyphosphagenes, collagen, starch, pre-gelatinized starch, hyaluronic acid, chitosans, gelatin, alginates, albumin, fibrin, vitamin E compounds, such as alpha tocopheryl acetate, d-alpha tocopheryl succinate, D,L-lactide, or L-lactide, ,-caprolactone, dextrans, vinylpyrrolidone, polyvinyl alcohol (PVA), PVA-g-PLGA, PEGT-PBT copolymer (polyactive), PEO-PPO-PAA copolymers, PLGA-PEO-PLGA, PEG-PLG, PLA-PLGA, poloxamer 407, PEG-PLGA-PEG triblock copolymers, SAIB (sucrose acetate isobutyrate) or combinations thereof.

[0092] In some embodiments, the fiber comprises biodegradable polymers comprising wherein the at least one biodegradable polymer comprises one or more of poly(lactide-co-glycolide) (PLGA), polylactide (PLA), polyglycolide (PGA), D-lactide, D,L-lactide, L-lactide, D,L-lactide-co-ε-caprolactone, L-lactide-co-ε-caprolactone, D,L-lactide-co-glycolide-co-ε-caprolactone, poly(D,L-lactide-co-caprolactone), poly(L-lactide-co-caprolactone), poly(D-lactide-co-caprolactone), poly(D,L-lactide), poly(D-lactide), poly(L-lactide), poly(esteramide) or a combination thereof.

[0093] Mannitol, trehalose, dextran, mPEG and/or PEG may be used as a plasticizer for polymer. These plasticizers impart malleability to the resulting formulations. In some embodiments, the polymer and/or plasticizer may also be coated on the fiber to provide the desired release profile. In some embodiments, the coating thickness may be thin, for example, from about 5, 10, 15, 20, 25, 30, 35, 40, 45 or 50 microns to thicker coatings 60, 65, 70, 75, 80, 85, 90, 95, 100 microns to delay release of the drug from the depot (e.g., fiber). In some embodiments, the range of the coating on the fiber ranges from about 5 microns to about 250 microns or 5 microns to about 200 microns to delay release from the fiber.

[0094] In various embodiments, the fiber comprises poly(lactide-co-glycolide) (PLGA), polylactide (PLA), polyglycolide (PGA), D-lactide, D,L-lactide, L-lactide, D,L-lactide-co-ε-caprolactone, L-lactide-co-ε-caprolactone, D,L-lactide-co-glycolide-co-ε-caprolactone, poly(D,L-lactide-co-caprolactone), poly(L-lactide-co-caprolactone), poly(D-lactide-co-caprolactone), poly(D,L-lactide), poly(D-lactide), poly(L-lactide), poly(esteramide) or a combination thereof and has an inherent viscosity of 0.2 to about 0.5 dl/gm or 0.6 to about 1.0 dL/gm and a MW of 30,000 to about 125,000 Da.

[0095] In some embodiments, the fiber comprises one or more polymers (e.g., PLA, PLGA, etc.) having a MW of from about 15,000 to about 150,000 Da, from about 25,000 to about 100,000 Da or from about 30,000 to about 50,000 Da.

[0096] As persons of ordinary skill in the art are aware, an implantable depot (e.g., fiber) compositions having a blend of polymers with different end groups are used the resulting formulation will have a lower burst index and a regulated duration of delivery. For example, one may use polymers with acid (*e.g.*, carboxylic acid) and ester end groups (e.g., methyl or ethyl ester end groups).

[0097] Additionally, by varying the comonomer ratio of the various monomers that form a polymer (e.g., the L/G (lactic acid/glycolic acid) or G/CL (glycolic acid/polycaprolactone) ratio for a given polymer) there will be a resulting depot (e.g., fiber) composition having a regulated burst index and duration of delivery. For example, a depot (e.g., fiber) composition having a polymer with a L/G ratio of 50:50 may have a short duration of delivery ranging from about two days to about one month; a depot (e.g., fiber) composition having a polymer with a L/G ratio of 65:35 may have a duration of delivery of about two months; a depot (e.g., fiber) composition having a polymer with a L/G ratio of 75:25 or L/CL ratio of 75:25 may have a duration of delivery of about three months to about four months; a depot (e.g., fiber) composition having a polymer ratio with a L/G ratio of 85:15 may have a duration of delivery of about five months; a depot (e.g., fiber) composition having a polymer with a L/CL ratio of 25:75 or PLA may have a duration of delivery greater than or equal to six months; a depot (e.g., fiber) composition having a terpolymer of CL/G/L with G greater than 50% and L greater than 10% may have a duration of delivery of about one month and a depot (e.g., fiber) composition having a terpolymer of CL/G/L with G less than 50% and L less than 10% may have a duration months up to six months. In general, increasing the G content relative to the CL content shortens the duration of delivery whereas increasing the CL content relative to the G content lengthens the duration of delivery. Thus, among other things, depot (e.g., fiber) compositions having a blend of polymers having different molecular weights, end groups and comonomer ratios can be used to create a depot (e.g., fiber) formulation having a lower initial burst and a regulated duration of delivery.

[0098] The depot (e.g., fiber) 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 bisulfate, sodium bisulfite, sodium thiosulfate, thimerosal, methylparaben, polyvinyl alcohol and phenylethyl alcohol; solubility adjusting agents;

stabilizers; and/or cohesion modifiers. If the depot (e.g., fiber) is to be placed in the spinal area, in various embodiments, the depot (e.g., fiber) may comprise sterile preservative free material.

[0099] The depot (e.g., fiber) 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 fiber. For example, both the size and shape may allow for ease in positioning the fiber at the target tissue site that is selected as the implantation. In addition, the shape and size of the system should be selected so as to minimize or prevent the fiber from moving after implantation. In various embodiments, the fiber can be shaped like a rod or a flat surface such as a film or sheet (*e.g.*, ribbon-like) or the like. Flexibility may be a consideration so as to facilitate placement of the fiber.

[00100] In various embodiments, the fiber can be different sizes, for example, the fiber may be a length of from about 0.5 mm to 50 mm and have a diameter of from about 0.01 to about 4 mm. In various embodiments, as the diameter decreases, the surface area that comes in contact with the bodily fluid of the depot (e.g., fiber) increases and therefore release of the drug from the depot (e.g., fiber) increases. In various embodiments, the fiber may have a layer thickness of from about 0.005 to 1.0 mm, such as, for example, from 0.05 to 0.75 mm. In various embodiments, the length of the fiber is determined based on the length needed to treat the target tissue site.

[00101] Radiographic markers can be included on the fiber to permit the user to position the depot (e.g., fiber) accurately into the target site of the patient. These radiographic markers will also permit the user to track movement and degradation of the depot (e.g., fiber) at the site over time. In this embodiment, the user may accurately position the depot (e.g., fiber) 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 phosphate, bismuth, iodine, tantalum, tungsten, and/or metal beads or particles. In various embodiments, the radiographic marker could be a spherical shape or a ring around the depot (e.g., fiber).

Drug Depot In Fiber Form

[00102] In some embodiments, a drug depot is provided that controls delivery of therapeutic agents to local, target tissues and secures itself to a target tissue site. In some embodiments, the drug depot is a flexible, drug loaded fiber that attaches to a target tissue site, such as, for example, muscle and/or fascia. In various embodiments, the fiber attaches to the target tissue site via adhesives that are applied to the entire fiber or at the ends of the fiber. In some embodiments, the drug depot is a suture that is woven through a target tissue site via a needle

and acts as its own attachment device. In some embodiments, the drug depot is flexible, biodegradable fibers or strands that are drug loaded and/or drug coated to provide sustained release of a therapeutic to a local tissue site. In some embodiments, drug release is in days to months. In some embodiments, the drug depot comprises polymers, such as, for example, 10:90 poly(D,L-lactide-co-caprolactone), 85:15 poly(D,L-lactide-co-caprolactone), or 60:40 poly(L,lactide-co-caprolactone). Degradation times for the polymers could be weeks to months. In some embodiments, drugs are used such as, for example, an analgesic, anti-inflammatory and/or steroids, which are coated on the fiber or uniformly distributed throughout the fiber.

[00103] In various embodiments, the fiber is memory shape fiber and can comprise shape memory polymers including various polyethers, polyacrylates, polyamides, polysiloxanes, polyurethanes, polyether amides, polyurethane/ureas, polyether esters, or urethanelbutadiene copolymers or a combination thereof.

[00104] The fiber provides a scaffold to release clonidine in vivo in three dimensions. In some embodiments, one or more fibers may be stacked on one another.

[00105] In some embodiments, the fiber comprises a plurality of pores. In some embodiments, at least 10% of the pores are between about 10 micrometers and about 500 micrometers at their widest points. In some embodiments, at least 20% of the pores are between about 50 micrometers and about 150 micrometers at their widest points. In some embodiments, at least 30% of the pores are between about 30 micrometers and about 70 micrometers at their widest points. In some embodiments, at least 50% of the pores are between about 10 micrometers and about 500 micrometers at their widest points. In some embodiments, at least 90% of the pores are between about 50 micrometers and about 150 micrometers at their widest points. In some embodiments, at least 95% of the pores are between about 100 micrometers and about 250 micrometers at their widest points. In some embodiments, 100% of the pores are between about 10 micrometers and about 300 micrometers at their widest points.

[00106] In some embodiments, the fiber has a porosity of at least about 30%, at least about 50%, at least about 60%, at least about 70%, at least about 90%. The pore enhances release of the clonidine and may support ingrowth of cells, formation or remodeling of bone, cartilage and/or vascular tissue.

[00107] In some embodiments, the fiber may comprise natural and/or synthetic material. For example, the fiber may comprise poly (alpha-hydroxy acids), poly (lactide-co-glycolide) (PLGA), polylactide (PLA), polyglycolide (PG), polyethylene glycol (PEG) conjugates of poly (alpha-hydroxy acids), polyorthoesters (POE), polyaspirins, polyphosphagenes, collagen, hydrolyzed collagen, gelatin, hydrolyzed gelatin, fractions of hydrolyzed gelatin, elastin, starch, pre-gelatinized starch, hyaluronic acid, chitosan, alginate, albumin, fibrin, vitamin E analogs,

such as alpha tocopheryl acetate, d-alpha tocopheryl succinate, polyglycolide (PGA), D-lactide, D,L-lactide, L-lactide, D,L-lactide-co-ε-caprolactone, L-lactide-co-ε-caprolactone, D,L-lactide-co-glycolide-co-ε-caprolactone, poly(D,L-lactide-co-caprolactone), poly(L-lactide-co-caprolactone), poly(D-lactide-co-caprolactone), poly(D,L-lactide), poly(D-lactide), poly(L-lactide), poly(esteramide), 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, PLA-PLGA, poloxamer 407, PEG-PLGA-PEG triblock copolymers, SAIB (sucrose acetate isobutyrate), polydioxanone, methylmethacrylate (MMA), MMA and N-vinylpyyrolidone, polyamide, oxycellulose, copolymer of glycolic acid and trimethylene carbonate, polyesteramides, polyetheretherketone, polymethylmethacrylate, silicone, hyaluronic acid, chitosan, or combinations thereof.

[00108] In some embodiments, the fiber comprises collagen. Exemplary collagens include human or non-human (bovine, ovine, and/or porcine), as well as recombinant collagen or combinations thereof. Examples of suitable collagen include, but are not limited to, human collagen type I, human collagen type II, human collagen type III, human collagen type IV, human collagen type V, human collagen type VI, human collagen type VII, human collagen type VIII, human collagen type IX, human collagen type X, human collagen type XI, human collagen type XII, human collagen type XIII, human collagen type XIV, human collagen type XV, human collagen type XVI, human collagen type XVII, human collagen type XVIII, human collagen type XIX, human collagen type XXI, human collagen type XXII, human collagen type XXIII, human collagen type XXIV, human collagen type XXV, human collagen type XXVI, human collagen type XXVII, and human collagen type XXVIII, or combinations thereof. Collagen further may comprise hetero- and homo-trimers of any of the above-recited collagen types. In some embodiments, the collagen comprises hetero- or homo-trimers of human collagen type I, human collagen type II, human collagen type III, or combinations thereof.

[00109] In some embodiments, the fiber may be seeded with harvested bone cells and/or bone tissue, such as for example, cortical bone, autogenous bone, allogenic bones and/or xenogenic bone. In some embodiments, the fiber may be seeded with harvested cartilage cells and/or cartilage tissue (e.g., autogenous, allogenic, and/or xenogenic cartilage tissue). For example, before insertion into the target tissue site, the fiber can be wetted with the graft bone tissue/cells, usually with bone tissue/cells aspirated from the patient, at a ratio of about 3:1, 2:1, 1:1, 1:3 or 1:2 by volume. The bone tissue/cells are permitted to soak into the fiber provided, and the fiber may implanted at the target tissue site.

[00110] The fiber may contain an inorganic material, such as an inorganic ceramic and/or bone substitute material. Exemplary inorganic materials or bone substitute materials include but are not limited to aragonite, dahlite, calcite, amorphous calcium carbonate, vaterite, weddellite, whewellite, struvite, urate, ferrihydrate, francolite, monohydrocalcite, magnetite, goethite, dentin, calcium carbonate, calcium sulfate, calcium phosphosilicate, sodium phosphate, calcium aluminate, calcium phosphate, hydroxyapatite, alpha-tricalcium phosphate, dicalcium phosphate, β-tricalcium phosphate, tetracalcium phosphate, amorphous calcium phosphate, octacalcium phosphate, BIOGLASS™, fluoroapatite, chlorapatite, magnesium-substituted tricalcium phosphate, carbonate hydroxyapatite, substituted forms of hydroxyapatite (e.g., hydroxyapatite derived from bone may be substituted with other ions such as fluoride, chloride, magnesium sodium, potassium, etc.), or combinations or derivatives thereof.

[00111] In some embodiments, the fiber has a thickness of from 0.25 mm to 5 mm, or from about 0.4 mm to about 2 mm, or 0.4 mm to about 1 mm. In some embodiments, the fiber has a length of about 1 mm to about 300 mm or about 5 mm to 200 mm or about 5 mm to about 150 mm.

[00112] In some embodiments, the fiber has a density of between about 1.6 g/cm^3, and about 0.05 g/cm^3. In some embodiments, the fiber has a density of between about 1.2 g/cm^3, and about 0.07 g/cm^3. For example, the density may be less than about 1 g/cm^3, less than about 0.7 g/cm^3, less than about 0.6 g/cm^3, less than about 0.5 g/cm^3, less than about 0.4 g/cm^3, less than about 0.3 g/cm^3, less than about 0.2 g/cm^3, or less than about 0.1 g/cm^3.

[00113] In some embodiments, the diameter of the fiber can range from 0.1 mm to 10 mm. In some embodiments, the diameter of the fiber can range from 0.1 mm to 5 mm, 0.1 mm to 3 mm or 0.1 mm to 1 mm.

[00114] In some embodiments, the fiber may be monofilamentary or braided, absorbable or non-absorbable. The fiber may be of any length. In various embodiments, the fiber is long enough to reach from the site of placement.

[00115] In some embodiments, a variety of bioabsorbable polymers can be used to make the fiber. Examples of suitable biocompatible, bioabsorbable polymers include aliphatic polyesters, poly(amino acids), copoly(ether-esters), polyalkylenes oxalates, polyamides, tyrosine derived polycarbonates, poly(iminocarbonates), polyorthoesters, polyoxaesters, polyamidoesters, polyoxaesters containing amine groups, poly(anhydrides), polyphosphazenes, biomolecules (i.e., biopolymers such as collagen, elastin, bioabsorbable starches, etc.) or blends thereof. Polyesters include, but are not limited to, homopolymers and copolymers of lactide (which includes lactic acid, D-,L- and meso lactide), glycolide (including glycolic acid), caprolactone, p-dioxanone (1,4-dioxan-2-one), trimethylene carbonate (1,3-dioxan-2-one), alkyl derivatives of trimethylene

carbonate, delta-valerolactone, beta-butyrolactone, gamma-butyrolactone, epsilon-decalactone, hydroxybutyrate, hydroxyvalerate, 1,4-dioxepan-2-one (including its dimer 1,5,8,12-tetraoxacyclotetradecane-7,14-dione), 1,5-dioxepan-2-one, 6,6-dimethyl-1,4-dioxan-2-one 2,5-diketomorpholine, pivalolactone, alpha-diethylpropiolactone, ethylene carbonate, ethylene oxalate, 3-methyl-1,4-dioxane-2,5-dione, 3,3-diethyl-1,4-dioxan-2,5-dione, 6,8-dioxabicycloctane-7-one or polymer blends thereof.

[00116] In some embodiments, the fibers may be of different sizes depending on the procedure being performed and the implant site. Fibers (e.g., sutures) can range in size from #000000 (#6-0 or #6/0), #00 (#2-0 or #2/0), #0, #1, #2, #3, #4, #5, #6, with #000000 being the smallest.

[00117] In some embodiments, the fiber may be made by injection molding, compression molding, blow molding, thermoforming, die pressing, slip casting, electrochemical machining, laser cutting, water-jet machining, electrophoretic deposition, powder injection molding, sand casting, shell mold casting, lost tissue scaffold casting, plaster-mold casting, ceramic-mold casting, investment casting, vacuum casting, permanent-mold casting, slush casting, pressure casting, die casting, centrifugal casting, squeeze casting, rolling, forging, swaging, extrusion, shearing, spinning, powder metallurgy compaction or combinations thereof.

[00118] In some embodiments, a therapeutic agent (including one or more clonidine compounds) may be disposed on or in the fiber by hand by soaking, electrospraying, ionization spraying or impregnating, vibratory dispersion (including sonication), nozzle spraying, compressed-air-assisted spraying, brushing and/or pouring.

[00119] In some embodiments, the fiber may comprise sterile and/or preservative free material. The fiber can be implanted by hand or machine in procedures such as for example, laparoscopic, arthroscopic, neuroendoscopic, endoscopic, rectoscopic procedures or the like. In some embodiments, the fiber can be made from a collagen sponge material that can be spray coated or embedded with the clonidine, and as the sponge material degrades, the clonidine is released.

[00120] In some embodiments, the initial burst surfaces can be disposed on the edges of the fiber so that upon contact with the target tissue site, the edges will begin to release the clonidine. In some embodiments, the body of the fiber can comprise dense, entangled polymers and have the clonidine to provide slower release of the clonidine.

[00121] Alternatively, the clonidine can be disposed homogenously throughout the fiber to provide continuous extended release of the clonidine. In some embodiments, the clonidine can be layered in the fiber with some portions having different concentrations to provide burst

release and then slower release of the clonidine in areas that have dense crosslinked polymers, such as for example, in the core of the fiber.

[00122] FIG. 1 depicts a fiber 10 configured to be attached to a target tissue site, such as, for example, the center 18 of a ligament 20 located beneath the skin. The fiber 10 is made of biodegradable memory shaped fiber 16 and wraps around the ligament 20 starting at first end 14. The surgeon will wrap the memory shaped fiber around the ligament. As bodily fluid contacts the fiber, the fiber will degrade and release the therapeutic agent.

[00123] FIG. 2 depicts a fiber 21 that includes a first end 22 configured to be sutured to a target tissue site and a second end 24 configured to be sutured at or near a target tissue site. This can be accomplished, by for example, looping the fiber through a needle and then passing the needle through the target tissue site. The surgeon can then tie one or both ends of the fiber to the target tissue site and cut the fiber. In this way, the fiber can be anchored to the target tissue site. In this embodiment, the fiber comprises memory shaped polymers 26 that allow the fiber to conform to the surface of the tissue that it is attached to. The fiber comprises a burst release surface 30. The burst release surface can immediately release the therapeutic agent (e.g., clonidine, other analgesic, anti-inflammatory agent, statin, etc.). Therefore, on implantation, the fiber will immediately release the clonidine to provide its therapeutic effect locally at the target tissue site. This is particularly beneficial to reduce or treat postoperative pain. Alternatively, the clonidine can be disposed in the core of the fiber which may contain entangled polymers to slow the release of the clonidine. In some embodiments, the therapeutic agent is uniformly distributed on the surface of the fiber. In some embodiments, the therapeutic agent is uniformly distributed throughout the fiber.

[00124] While FIGS. 1 and 2 depict a fiber in a cylindrical form, alternate shapes and configurations may be contemplated. In further exemplary embodiments, the fiber may be a narrow tube for delivery through a catheter. For example, the fiber may be delivered percutaneously using a catheter through which it is inserted. Thus, the fiber may have dimensions suitable for receipt in the catheter. Optionally, the fiber may be stiffened to facilitate insertion into the catheter. Such stiffening may be achieved through choice of material for the fiber, by treating the material of the fiber, or other. In some embodiments, the fiber may be coated with a material to facilitate sliding engagement with the catheter.

[00125] In certain embodiments, the length of the fiber will range from about 1 cm to about 15 cm, the width will range from about 1 cm to about 5 cm, and the thickness will range from about 0.5 cm to about 5 cm. The length may range from about 2.5 to about 8 cm, the width may range from about 1 to about 3 cm, and the thickness may range from about 1 to about 3 cm.

[00126] As to volume, advantageous fibers can have a total volume of at least about 2 cubic centimeters (cc), e.g. in the range of about 2 cc to about 100 cc, and more typically in the range of about 10 cc to about 50 cc, although both smaller and larger overall volumes may also be used.

[00127] In some embodiments, fiber 10 of FIG. 1 has a modulus of elasticity in the range of about 1 x 10^2 to about 6 x 10^5 dynes/cm^2, or 2 x 10^4 to about 5 x 10^5 dynes/cm^2, or 5 x 10^4 dynes/cm^2 to about 5 x 10^5 dynes/cm^2.

[00128] In some embodiments, the semi-solid or solid fiber 10 may comprise a polymer having 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 0.55 dL/g, about 0.50 to about 0.70 dL/g, about 0.55 to about 0.6 dL/g, about 0.60 to about 0.80 dL/g, about 0.70 to about 0.90 dL/g, about 0.80 to about 1.00 dL/g, about 0.90 to about 1.10 dL/g, about 1.0 to about 1.2 dL/g, about 1.1 to about 1.3 dL/g, about 1.2 to about 1.4 dL/g, about 1.3 to about 1.5 dL/g, about 1.4 to about 1.6 dL/g, about 1.5 to about 1.7 dL/g, about 1.6 to about 1.8 dL/g, about 1.7 to about 1.9 dL/g, or about 1.8 to about 2.1 dL/g.

[00129] In some embodiments, the drug depot shown as a fiber may have a burst release surface that releases about 10%, 15%, 20%, 25%, 30%, 35%, 45%, to about 50% of the clonidine over 24 or 48 hours.

[00130] In some embodiments, the fiber comprises a polymer having an average molecular weight of the polymer can be from about 1000 to about 10,000,000 Da; or about 1,000 to about 1,000,000 Da; or about 5,000 Da to about 500,000 Da; or about 10,000 Da to about 100,000 Da; or about 20,000 Da to 50,000 Da.

[00131] In some embodiments, when the polymer materials have different chemistries (e.g., high MW DLG 5050 and low MW DL), the high MW polymer may degrade faster than the low MW polymer.

[00132] In some embodiments, the fiber may comprise a viscosity enhancing agent such as, for example, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl methylcellulose, carboxymethylcellulose and salts thereof, Carbopol, poly-(hydroxyethyl-methacrylate), poly-(methoxyethylmethacrylate), poly(methoxyethoxyethylmethacrylate), polymethyl-methacrylate (PMMA), methylmethacrylate (MMA), gelatin, polyvinyl alcohols, propylene glycol, mPEG, PEG 200, PEG 300, PEG 400, PEG 500, PEG 600, PEG 700, PEG

800, PEG 900, PEG 1000, PEG 1450, PEG 3350, PEG 4500, PEG 8000 or combinations thereof.

[00133] In some embodiments, the fiber may comprise 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. In some embodiments, the fiber may comprise 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 pyrolidone, N-vinyl lactams, polyacrylonitrile or combinations thereof.

[00134] In various embodiments, rather than directly admixing the therapeutic agent into the fiber, microspheres may be dispersed within the fiber, the microspheres being loaded with clonidine. In one embodiment, the microspheres provide for a sustained release of the clonidine.

[00135] Microspheres, much like a fluid, may disperse relatively quickly, depending upon the surrounding tissue type, and hence disperse the clonidine. In some situations, this may be desirable; in others, it may be more desirable to keep the clonidine tightly constrained to a well-defined target site. The present invention also contemplates the use of adherent gel or adhesive to so constrain the fiber close to the target tissue site. In this embodiment, an adherent gel or adhesive is used to anchor the fiber to the target tissue site. The adherent gel or adhesive can, like the fiber, also have the therapeutic agent disposed within it. In this way, the fiber and the adhesive release the therapeutic agent (e.g., clonidine, statin, etc.) at or near the target tissue site.

Fiber Delivery

[00136] It will be appreciated by those with skill in the art that the depot (e.g., fiber) 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 fiber device is designed to cause minimal physical and psychological trauma to the patient.

[00137] In some embodiments, the fiber can be sutured to a target tissue site using a suturing needle. The dimensions of the needle, among other things, will depend on the site for implantation. For example, the width of the muscle planes in different surgical procedures can vary from 1-40 cm. Thus, the needle, in various embodiments, can be designed for these specific areas.

[00138] Needles may have different shapes such as for example half curved or ski shaped, 1/4 circle, 3/8 circle, 1/2 circle, 5/8 circle, compound curve or the like. The thickness of the 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 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 25 gauge. In various embodiments the gauge of the needle or cannula is about 18 to about 22 gauge.

[00139] Suturing needles for applying the fiber, by hand or via an automated device, such as for example in arthroscopic surgeries can be used in the present application. Suturing needles are usually made from a cut blank of material, 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 needle may optionally include one or more tapered regions. In various embodiments, the needle generally includes a shaft, a rear end portion with an aperture or channel to secure a suture thread and a needle head at a front end portion for puncturing skin and passing through tissue. The needle head typically incorporates a sharpened needle tip at its distal end and cutting edges. Alternatively, the needle tip may be of a tapered configuration. Straight and curved needles including multiple curved configurations are also known in the art.

[00140] Suture needles typically incorporate a sharpened needle end. Sharper needles require less force to penetrate tissue and thus cause less tissue trauma. In addition, a sharper needle reduces fatigue on the needle itself, making it less likely to bend or break during suturing. Needle sharpness is typically defined in terms of "penetration force"--the force necessary for a needle to puncture, or penetrate, the tissue. The penetration force is primarily determined by the design and sharpness of the needle point and the cutting edges formed on the needle head. Needle sharpness is also affected by drag force on the needle as it travels through the tissue. The drag force also depends upon the design and sharpness of the needle, and the presence of a lubricating coating. The choice of materials of surgical needle is made to optimize strength, ductility and resistance to bending or breaking of the needle. However, the cross-sectional shape and dimensions of the needle contributes significantly to the physical characteristics of the needle. In various embodiments, the needle includes stainless steel such as series "300" stainless steels, which typically have tensile strengths of between 325,000-350,000 lbs/in^2. When the suture needle is metal such as, for example, stainless steal, the needle cam be manufactured through conventional cutting, coining, grinding and/or swaging processes, and

may be heat treated to further enhance its strength and resistance to bending. A lubricious coating such as silicon may be applied to needle body to further enhance penetration and drag characteristics.

[00141] In various embodiments, like the fiber, 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 (e.g., fiber) 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, bismuth, tantalum, tungsten, iodine, calcium, and/or metal beads or particles.

[00142] 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.

[00143] The fiber may be sterilizable. In various embodiments, one or more components of the fiber 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.

[00144] 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.

[00145] 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 reproductive 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 fiber is included in a gel.

[00146] Other methods may also be used to sterilize the depot (e.g., fiber) 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.

[00147] In various embodiments, a kit is provided that may include additional parts along with the fiber combined together to be used to implant the fiber. The kit may include the fiber device in a first compartment. The second compartment may include a canister holding the fiber 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. A fifth compartment may include an agent for radiographic imaging. 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. In some embodiments, a kit is provided with instruction to use an injectable drug from another kit.

[00148] In various embodiments, a method for delivering a therapeutic agent into a site of a patient is provided, the method comprising inserting a needle at or near a target tissue site and suturing the fiber at the target site beneath the skin of the patient. In this way unwanted migration of the fiber away from the target site is reduced or eliminated.

[00149] In some embodiments, the fiber 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, connective tissue, fascia, subcutaneous space, or spinal canal.

[00150] In some embodiments, it is preferable to co-administer clonidine with an antagonist to counteract undesirable effects, for example the blood pressure decrease that can be caused by clonidine. 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. These compounds may prevent or reduce glial and fibroblastic scar formation associated with some types of surgeries.

[00151] Another embodiment is directed to a method for treating a mammal suffering from pain, said method comprising administering a therapeutically effective amount of clonidine at a target site beneath the skin. The clonidine (or pharmaceutically acceptable salt) may for example be administered locally to the target tissue site disposed within or on a fiber.

[00152] In some embodiments, the clonidine is encapsulated in a plurality of matrices comprising microparticles, microspheres, microcapsules, and/or microfibers and then put into a fiber.

[00153] In some embodiments there is a method for making an implantable fiber. The method may comprise combining a biocompatible polymer and a therapeutically effective amount of clonidine or a pharmaceutically acceptable salt thereof and forming the implantable fiber from the combination.

Method of Making the Fiber

[00154] In various embodiments, the fiber comprising the clonidine can be made by combining a biocompatible polymer and a therapeutically effective amount of clonidine or pharmaceutically acceptable salt thereof and forming the implantable fiber from the combination.

[00155] Various techniques are available for forming at least a portion of a fiber 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.

[00156] 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 (e.g., fiber) to obtain the desired release rate and desired thickness.

[00157] 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: clonidine 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 fiber 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.

[00158] Thermoplastic processing techniques for forming the depot (e.g., fiber) 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.

[00159] 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: clonidine, optional additional therapeutic agent(s), radiographic agent(s), and so forth. The resulting mixture is then shaped into an implantable fiber. The mixing and shaping operations may be performed using any of the conventional devices known in the art for such purposes.

[00160] 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, clonidine may undergo substantial degradation under ordinary thermoplastic processing conditions. Hence, processing is preferably performed under modified conditions, which prevent the 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 therapeutic agent, and the technique by which the polymeric material and the therapeutic agent(s) are mixed.

[00161] Mixing or compounding 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 materials with additives.

[00162] 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.

[00163] 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).

[00164] For example, in various embodiments, a biocompatible polymer is precompounded 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 precompounded material is then mixed with therapeutic agent under conditions of lower temperature and mechanical shear, and the resulting mixture is shaped into the clonidine containing fiber. Conversely, in another embodiment, the biocompatible polymer can be precompounded with the therapeutic agent under conditions of reduced temperature and mechanical shear. This precompounded 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 fiber.

[00165] 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.

[00166] As an example, different biocompatible polymers will typically soften to facilitate mixing at different temperatures. For instance, where a depot (e.g., fiber) 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 (*e.g.,* clonidine), in various embodiments, the PGLA or PLA can be premixed with the radio-opacifying agent at temperatures of about, for example, 150°C to 170°C. 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°C), 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 clonidine 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 (e.g., fiber) is shaped into the desired form, also under conditions of reduced temperature and shear.

[00167] 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.

[00168] As another example, the therapeutic agent can be dissolved or dispersed in a solvent system, which is then applied to a pre-existing fiber (the pre-existing fiber 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 fiber. As above, the resulting solid material can then be granulated for further processing, if desired.

[00169] Typically, an extrusion process may be used to form the fiber 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 fiber comprising the same or different layers or regions (for example, a structure comprising one or more polymeric fiber layers or regions that have permeability to fluids to allow immediate and/or sustained drug release). Multi-region depots (e.g., fibers) can also be formed by other processing and shaping techniques such as co-injection or sequential injection molding technology.

[00170] In various embodiments, the depot (e.g., fiber) that may emerge from the thermoplastic processing (*e.g.,* pellet) 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 (e.g., fiber). However, where a water-soluble therapeutic agent such as clonidine is used, the immersion time should be held to a minimum to avoid unnecessary loss of therapeutic agent into the bath.

[00171] 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 (e.g., fiber) 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.

[00172] In various embodiments, the fiber can be prepared by mixing or spraying the drug with the polymer and then molding the depot (e.g., fiber) to the desired shape. In various embodiments, clonidine is used and mixed or sprayed with the PLGA or PEG550 polymer, and the resulting depot (e.g., fiber) may be formed by extrusion and dried.

[00173] In various embodiments, there is a pharmaceutical formulation comprising: clonidine, wherein the clonidine comprises from about 0.1 wt.% to about 40 wt.% of the formulation, and at least one biodegradable polymer. In some embodiments, the clonidine comprises from about 3 wt.% to about 20 wt.%, about 3 wt.% to about 18 wt.%, about 5 wt.% to about 15 wt.%, 0.1 wt% to about 10 wt%, about 0.1 wt% to about 3wt%, or about 7.5 wt.% to about 12.5 wt.% of the formulation. By way of example, when using a 5% - 15% clonidine composition, the mole ratio of clonidine to polymer would be from approximately 16 – 53 when using an approximately 80 kDalton polymer that has a 267 grams/mole ratio. By way of another example, when using a 5% - 15% clonidine base in the composition, the mole ratio of clonidine base to polymer would be from approximately 18 – 61 with a mole mass of 230g/mol.

[00174] In some embodiments, the clonidine can be in the formulation in an amount of about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, or 40% by weight based on the total weight of the formulation.

[00175] In some embodiments, the fiber comprises at least one biodegradable material in a wt% of about 99.5%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, , 89%, 88%, 87%, 86%, 85%, 84%, 83%, 82%, 81%, 80%, 79%, 78%, 76%, 75%, 74%, 73%, 72%, 71%, 70%, 65%, 60%, 55%, 50%, 45%, 35%, 25%, 20%, 15%, 10%, or 5% based on the total weight of the depot (e.g., fiber) and the remainder is active and/or inactive pharmaceutical ingredients.

[00176] In some embodiments, the at least one biodegradable polymer comprises poly(lactic-co-glycolide) (PLGA) or poly(orthoester) (POE) or a combination thereof. The poly(lactic-co-glycolide) may comprise a mixture of polyglycolide (PGA) and polylactide and in some embodiments, in the mixture, there is more polylactide than polyglycolide. In various embodiments there is 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; and 0% polylactide and 100% polyglycolide.

[00177] 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.

[00178] In various embodiments, the drug particle size (e.g., clonidine) is from about 5 to 30 micrometers, or about 2 microns to about 20 microns, or from 30 microns to 100 microns, however, in various embodiments ranges from about 1 micron to 250 microns may be used. In some embodiments, the biodegradable polymer comprises at least 50 wt.%, at least 60 wt.%, at least 70 wt.%, at least 80 wt.% of the formulation, at least 85 wt.% of the formulation, at least 90 wt.% of the formulation, at least 95 wt.% of the formulation or at least 97 wt.% of the formulation. In some embodiments, the at least one biodegradable polymer and the clonidine are the only components of the pharmaceutical formulation.

[00179] In some embodiments, at least 75% of the particles have a size from about 10 micrometer to about 200 micrometers. In some embodiments, at least 85% of the particles have a size from about 10 micrometer to about 200 micrometers. In some embodiments, at least 95% of the particles have a size from about 10 micrometer to about 200 micrometers. In some embodiments, all of the particles have a size from about 10 micrometer to about 200 micrometers.

[00180] In some embodiments, at least 75% of the particles have a size from about 20 micrometer to about 180 micrometers. In some embodiments, at least 85% of the particles have a size from about 20 micrometers to about 180 micrometers. In some embodiments, at least 95% of the particles have a size from about 20 micrometer to about 180 micrometers. In some embodiments, all of the particles have a size from about 20 micrometer to about 180 micrometers. In some embodiments, at least 80% of the particles have a size from 5 microns to about 100 microns on a volume basis.

[00181] In some embodiments, at least 75% of the particles have a size from about 0.5 micrometer to about 100 micrometers. In some embodiments, at least 85% of the particles have a size from about 0.5 micrometers to about 100 micrometers. In some embodiments, at least 95% of the particles have a size from about 0.5 micrometer to about 100 micrometers. In some embodiments, all of the particles have a size from about 0.5 micrometer to about 100

micrometers. In some embodiments, at least 80% of the particles have a size from 2 microns to about 50 microns on a volume basis.

[00182] In some embodiments, there is a pharmaceutical formulation comprising: clonidine, wherein the clonidine is in the form of a hydrochloride salt, and comprises from about 0.1 wt.% to about 30 wt.% of the formulation, and at least one biodegradable polymer, wherein the at least one biodegradable polymer comprises poly(lactide-co-glycolide) (or poly(lactic-co-glycolic acid)) or poly(orthoester) or a combination thereof, and said at least one biodegradable polymer comprises at least 70 wt.% of said formulation.

[00183] In some embodiments, the fiber comprises about 95 wt% poly(D,L-lactide) and 5 wt% clonidine HCl where the polymer has an ester end group and 50,000-70,000 Da MW and an IV 0.45-0.55 dL/g and has a burst release of under 10% of the amount of drug in the depot (e.g., fiber) within 24 hours (e.g., 5-10 wt%) or 2-40 mcg in 24 hours. This formulation has 50% of total cumulative dose remaining for at least 60 days. About 80% of the particles in this depot (e.g., fiber) including the clonidine are from about 5 to about 150 microns or 5-100 microns. The depot (e.g., fiber) releases about 0.5 mcg/day up to about 5 mcg/day of clonidine in 24 hours and then continues release for 70 days.

[00184] In some embodiments, the fiber comprises about 92 wt% poly(D,L-lactide) and 8 wt% clonidine HCl where the polymer has an ester end group and the polymer comprises 50,000-70,000 Da MW and an IV of about 0.45-0.55 dL/g and has a burst release of under 10% of the amount of drug in the depot (e.g., fiber) within 24 hours (e.g., 5-10%) or 5-6 mcg in 24 hours and then 1 to 20 mcg/day with a constant release for about 50 days, and then about 0.1 mcg to about 10mcg/day for 70 days. This formulation has 50% of total cumulative dose remaining for at least 30-42 days and less than 80% cumulative drug release by 70 days. About 80% of the particles in this depot (e.g., fiber) including the clonidine are from about 5 to about 150 microns or 5-100 microns.

[00185] In some embodiments, the fiber comprises about 85 wt% poly(D,L-lactide) and 15 wt% clonidine HCl where the polymer has an ester end group and the polymer comprises 50,000-70,000 Da MW and an IV of about 0.45-0.55 dL/g and has a burst release of under 10% of the amount of drug in the depot (e.g., fiber) within 24 hours (e.g., 5-10%) or 20-150 mcg in 24 hours and then 5 to 80 mcg/day with a constant release for about 30 days, and then about 0.1 mcg to about 5 mcg/day for 70 days. This formulation has about 80% of total cumulative dose released within 35 days and 20% over several months. About 80% of the particles in this depot (e.g., fiber) including the clonidine are from about 5 to about 150 microns or 5-100 microns.

[00186] In some embodiments, there is a pharmaceutical formulation comprising clonidine, wherein the clonidine is in a mixture of clonidine hydrochloride and clonidine base and the

mixture comprises from about 0.1 wt.% to about 30 wt.% of the formulation and a polymer comprises at least 70% of the formulation. In some embodiments, the polymer in this formulation is polyorthoester.

[00187] In some embodiments, the formulation comprises a fiber that comprises a biodegradable polyorthoester. The mechanism of the degradation process of the polyorthoester can be hydrolytical or enzymatical in nature, or both. In various embodiments, the degradation can occur either at the surface of the fiber (heterogeneous or surface erosion) or uniformly throughout the drug delivery system depot (e.g., fiber) (homogeneous or bulk erosion). Polyorthoester can be obtained from A.P. Pharma, Inc. (Redwood City, CA) or through the reaction of a bis(ketene acetal) such as 3,9-diethylidene-2,4,8,10-tetraoxospiro[5,5]undecane (DETOSU) with suitable combinations of diol(s) and/or polyol(s) such as 1,4-trans-cyclohexanedimethanol and 1,6-hexanediol or by any other chemical reaction that produces a polymer comprising orthoester moieties.

[00188] In some embodiments, there are methods for treating acute pain. These methods comprise: administering a pharmaceutical composition to an organism, wherein said pharmaceutical composition (e.g., clonidine) comprises from about 0.1 wt.% to about 30 wt.% of the formulation, and at least one biodegradable polymer. In some embodiments, the loading is from about 0.1 wt% to about 10 wt%, about 0.1 wt% to about 3wt%, 1 wt% to about 25 wt%, or about 5 wt.% to about 10 wt.%. In some embodiments, the loading is from about 10 wt.% to about 20 wt.%.

[00189] In some embodiment there is a higher loading of clonidine, *e.g.,* at least 20 wt.%, at least 30 wt.%, at least 40 wt.%, at least 50 wt.%, at least 60 wt.%, at least 70 wt.%, at least 80 wt.%, or at least 90 wt.%.

[00190] A strategy of triangulation may be effective when administering these pharmaceutical formulations. Thus, a plurality (at least two, at least three, at least four, at least five, at least six, at least seven, *etc.*) fibers comprising the pharmaceutical formulations may be placed around the target tissue site (also known as the pain generator or pain generation site) such that the target tissue site falls within a region that is either between the formulations when there are two, or within an area whose perimeter is defined by a set of plurality of formulations.

[00191] In some embodiments, the formulations are slightly rigid with varying length, widths, diameters, *etc.* For example, certain formulations may have a diameter of 0.50 mm and a length of 4 mm. It should be noted that particle size may be altered by techniques such as mort and pestle, jet-drying or jet milling.

[00192] In some embodiments, clonidine is released at a rate of 2-3 μg per day for a period of at least three days. In some embodiments, this release rate continues for, at least ten days, at

least fifteen days, at least twenty-five days, at least fifty days, at least ninety days, at least one hundred days, at least one-hundred and thirty-five days, at least one-hundred and fifty days, or at least one hundred and eighty days. For some embodiments, 300 –425 micrograms of clonidine as formulated with a biopolymer are implanted into a person at or near a target tissue site. If clonidine is implanted at multiple sites that triangulate the target site then in some embodiments, the total amount of clonidine at each site is a fraction of the total 300-425 micrograms. For example, one may implant a single dose of 324 micrograms at one site, or two separate doses of 162 micrograms at two sites, or three separate dose of 108 micrograms at three sites that triangulate the tissue site. It is important to limit the total dosage to an amount less than that which would be harmful to the organism. However, in some embodiments, although when there are a plurality of sites each site may contain less than the total dose that might have been administered in a single application, it is important to remember that each site will independent have a release profile, and the biopolymers' concentration and substance should be adjusted accordingly to ensure that the sustain release occurs over sufficient time.

[00193] In some embodiments, clonidine is released at a rate of 7-20 μg per day for a period of at least three days. In some embodiments, this release rate continues for, at least ten days, at least fifteen days, at least twenty-five days, at least fifty days, at least ninety days, at least one hundred days, at least one-hundred and thirty-five days, at least one-hundred and fifty days, or at least one hundred and eighty days. For some embodiments, 900-1050 micrograms of clonidine as formulated with a biopolymer are implanted into a person at or near a target tissue site. If clonidine is implanted at multiple sites that triangulate the target site then in some embodiments, the total amount of clonidine at each site is a fraction of the total 900-1050 micrograms. For example, one may implant a single dose of 975 micrograms at one site, or two separate doses of 650 micrograms at two sites, or three separate dose of 325 micrograms at three sites that triangulate the tissue site. It is important to limit the total dosage to an amount less than that which would be harmful to the organism. However, in some embodiments, although when there are a plurality of sites each site may contain less than the total dose that might have been administered in a single application, it is important to remember that each site will independent have a release profile, and the biopolymers' concentration and substance should be adjusted accordingly to ensure that the sustain release occurs over sufficient time.

[00194] The dosage of clonidine may be from approximately 0.0005 to approximately 960 μg/day. Additional dosages of clonidine include from approximately 0.0005 to approximately 900 μg/day; approximately 0.0005 to approximately 500 μg/day; approximately 0.0005 to approximately 250 μg/day; approximately 0.0005 to approximately 100 μg/day; approximately 0.0005 to approximately 75 μg/day; approximately 0.001 to approximately 70 μg/day;

approximately 0.001 to approximately 65 μg/day; approximately 0.001 to approximately 60 μg/day; approximately 0.001 to approximately 55 μg/day; approximately 0.001 to approximately 50 μg/day; approximately 0.001 to approximately 45 μg/day; approximately 0.001 to approximately 40 μg/day; approximately 0.001 to approximately 35 μg/day; approximately 0.0025 to approximately 30 μg/day; approximately 0.0025 to approximately 25 μg/day; approximately 0.0025 to approximately 20 μg/day; approximately 0.0025 to approximately 15 μg/day; approximately 0.0025 to approximately 10 μg/day; approximately 0.0025 to approximately 5 μg/day; and approximately 0.0025 to approximately 2.5 μg/day. In another embodiment, the dosage of clonidine is from approximately 0.005 to approximately 15 μg/day. In another embodiment, the dosage of clonidine is from approximately 0.005 to approximately 10 μg/day. In another embodiment, the dosage of clonidine is from approximately 0.005 to approximately 5 μg/day. In another embodiment, the dosage of clonidine is from approximately 0.005 to 2.5 μg/day. In some embodiments, the amount of clonidine is between 40 and 600 μg/day. In some embodiments, the amount of clonidine is between 200 and 400 μg/day.

[00195] In some embodiments, the therapeutically effective dosage amount (e.g., clonidine dose) and the release rate profile are sufficient to reduce inflammation and/or pain for a period of at least one day, for example, 1-90 days, 1-10 days, 1-3 days, 3-7 days, 3-12 days; 3-14 days, 7-10 days, 7-14 days, 7-21 days, 7-30 days, 7-50 days, 7-90 days, 7-140 days, 14-140 days, 3 days to 135 days, 3 days to 180 days, or 3 days to 6 months or 1 year or longer.

[00196] In some embodiments the clonidine in the fiber is designed for a bolus dose or burst dose within 1, 2, or 3 days after implantation to provide an immediate release of the clonidine for treatment of pain and/or inflammation.

[00197] In some embodiments, the clonidine fiber is administered parenterally, *e.g.,* by injection. 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. In other embodiments, the clonidine depot (e.g., fiber) is administered by placement into an open patient cavity during surgery.

[00198] In some embodiments, the fiber (i) comprises one or more immediate release layer(s) that is capable of releasing about 5% to about 20% of the clonidine or pharmaceutically acceptable salts thereof relative to a total amount of the clonidine or pharmaceutically acceptable salt thereof loaded in the drug depot (e.g., fiber) over a first period of up to 48 hours and (ii) one or more sustain release layer(s) that is capable of releasing about 21% to about 99% of the clonidine or pharmaceutically acceptable salt thereof relative to a total amount of the

clonidine or pharmaceutically acceptable salt thereof loaded in the drug depot (e.g., fiber) over a subsequent period of up to 3 days to 90 days, 150 days, 180 days, or 6 months to 1 year.

[00199] In some embodiments, there is a drug depot (e.g., fiber) comprising clonidine or clonidine hydrochloride and a polymer, wherein the polymer is one more of various embodiments, the drug depot (e.g., fiber) comprises poly(lactide-co-glycolide) (PLGA), polylactide (PLA), polyglycolide (PGA), D-lactide, D,L-lactide, L-lactide, D,L-lactide-co-ε-caprolactone, D,L-lactide-co-glycolide-co-ε-caprolactone or a combination thereof.

[00200] In some embodiments, the polymer fiber of present application enables one to provide efficacy of the active ingredient that is equivalent to subcutaneous injections that deliver more than 2.5 times as much drug.

[00201] In some embodiments, the fiber comprises a polymer having 65 mol. % poly L-lactide and 35 mol. % caprolactone, where the poly (L-lactide-co-caprolactone) has a MW of 30,000 to 40,000 Da and an IV of about 0.5-0.6 dL/g and has a burst release of under 35% of the amount of drug in the depot (e.g., fiber) within 24 hours (e.g., 5-15% within 4 hours). The fiber comprises clonidine in an amount of 3-8 wt.%. The fiber releases 400 mcg to about 1000 mcg for 7 days, which is about 40 mcg/day. This fiber contains 5-10 wt% mannitol as an excipient. The clonidine has a particle size of 25 microns or less and a 90% volume diameter less than 50 microns. The degradation time in the body is not more than 8 months and the fiber releases all of the clonidine within 2-4 weeks.

[00202] In some embodiments, the fiber comprises a polymer having 10 mol. % poly D-L-lactide and 90 mol. % caprolactone, where the poly (D,L-lactide-co-caprolactone) has a MW of 50,000 to 125,000 Da and an IV of about 0.6 dL/g and has a burst release of under 25% of the amount of drug in the fiber within 24 hours (e.g., 5-15% within 4 hours). The fiber comprises clonidine in an amount of 3-10 wt.%. The fiber releases 400 mcg to about 1000 mcg for 7 days, which is about 40 mcg/day. This fiber contains from about 1% to about 5% by weight of mannitol or trehalose as a pore forming agent or plasticizer. The clonidine has a particle size of 5 microns or less and a 90% volume diameter less than 20 microns. The degradation time in the body is not more than 12 months and the drug depot (e.g., fiber) releases all of the clonidine within 2-4 weeks. As you drop the drug load the drug released from the depot (e.g., fiber) is faster.

EXAMPLES

[00203] The examples below with respect to certain formulations comprising clonidine as the biologically active agent show certain particularly advantageous results.

[00204] The inherent viscosity (IV) designations for the polymers are mentioned in Table A below. In some embodiments, the polymers can have the following inherent viscosities.

[00205] **Table A**

IV Target Designator	*IV Range*
1	*0.05 - 0.15*
1.5	*0.10 - 0.20*
2	*0.15 - 0.25*
2.5	*0.20 - 0.30*
3	*0.25 - 0.35*
3.5	*0.30 - 0.40*
4	*0.35 - 0.45*
4.5	*0.40 - 0.50*
5	*0.45 - 0.55*
6	*0.50 - 0.70*
7	*0.60 - 0.80*
8	*0.70 - 0.90*
9	*0.80 - 1.0*
10	*1.0-1.2*

[00206] The final letter within the code of the polymer is the end group designator. For examples "E" refers to an ester end group, while "A" refers to an acid end group.

[00207] By way of example, 100 LCL 5A is a polymer that has an inherent viscosity of about 0.45 - 0.55 dL/g. It contains 100% poly(L-lactide-co-caprolactone), where the ratio of L-lactide to caprolactone is 60:40 and has an ester end group. It is available from Lakeshore Biomaterials, Birmingham, Alabama.

[00208] The fiber formulations tested are listed below in Table B.

[00209] **Fiber Formulations**

Table B

	Batch	Formulation	% Content	Diameter
1	397-121	8% loaded 60:40 LCL 5A	6.5	0.4 mm
2	397-122	8% loaded 60:40 LCL 5A	6.6	0.8 mm
3	307-123	16% loaded 60:40 LCL 5A	13.2	0.6 mm

[00210] Figure 3 illustrates the release of clonidine from the fibers tested in Table B. The fiber has an initial burst from about 10% to about 40% cumulative release of the clonidine within 1 day. This is for a clondine drug load of about 8 wt.% to about 16 wt. % as shown in Figure 3. The polymer used in the fiber comprises poly(L-lactide-co-caprolactone), where the ratio of L-lactide to caprolactone is 60:40. The fiber has a % cumulative release rate of 10% to

20% per day over at least 14 days. The release is linear after the initial burst. The high initial burst release is beneficial for treating, for example, post-operative pain. The fiber has a diameter of from about 0.4 mm to about 0.8 mm and a length of from about 25 mm to about 50 mm. The fibers that have a smaller diameter elute faster also the fibers with a higher drug load have a faster release. In some embodiments, the diameter of the fiber can be from about 0.25 mm to about 1 mm, which is suitable for implantation at or near a target tissue site. In some embodiments, the diameter of the fiber can be from about 0.5 mm to about 0.75 mm, which is suitable for implantation at or near a target tissue site. In some embodiments, the fiber can have a length from about 10 mm to about 100 mm.

[00211] Figure 4 illustrates the release of clonidine from the fibers of Table B in micrograms/day. The fiber has an initial burst of from about 100 to about 300 micrograms of the clonidine within 1 to 2 days. This is for a clondine drug load of about 8 wt.% to about 16 wt. % as shown in Figure 4. The polymer used in the fiber comprises poly(L-lactide-co-caprolactone), where the ratio of L-lactide to caprolactone is 60:40. The fiber has a release of about 1 micrograms to about 125 micrograms per day over at least 14 days. The release is relatively linear after about 48 hours. In some embodiments, the fiber may comprise from about 8% to about 16% clonidine drug load. For example, an 8% loaded 60:40 LCL 5A with a 6.5% content having a 0.4 mm diameter; an 8% loaded 60:40 LCL 5A with a 6.6% content having a 0.8 mm diameter; or a 16% loaded 60:40 LCL 5A with a 13.2% content having a 0.6 mm diameter. In some embodiments, the fiber comprises 10:90 poly(D,L-lactide-co-caprolactone) and has an inherent viscosity of 1.0-1.2 and has an acid end cap. In some embodiments, the fiber comprises 85:15 poly(D,L-lactide-co-caprolactone) and has an inherent viscosity of 0.6-0.8 and has an acid end cap and comprises a plasticizer (e.g., mannitol, trehalose, mPEG, hydroxypropylcellulose, ethylcellulose, dextran or the like). Other lengths, thicknesses, and diameters may be made.

[00212] 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.

[00213] 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 fiber for reducing or treating pain in a patient in need of such treatment, the implantable fiber comprising at least a portion configured to be attached to a target tissue site beneath the skin of the patient, the implantable fiber comprising clonidine in an amount from about 0.1 wt.% to about 40 wt.% of the implantable fiber, and at least one biodegradable polymer, wherein the implantable fiber is configured to release the clonidine over a period of at least three days.

2. An implantable fiber according to claim 1, wherein the implantable fiber comprises a first end and a second end, each end configured to be sutured to the target tissue site.

3. An implantable fiber according to claim 1, wherein the fiber comprises memory shape fiber to attach to the target tissue site.

4. An implantable fiber according to claim 1, wherein said at least one biodegradable polymer comprises at least 90 wt. % of the fiber.

5. An implantable fiber according to claim 1, wherein the at least one biodegradable polymer comprises one or more of poly(lactide-co-glycolide) (PLGA), polylactide (PLA), polyglycolide (PGA), D-lactide, D,L-lactide, L-lactide, D,L-lactide-co-ε-caprolactone, L-lactide-co-ε-caprolactone, D,L-lactide-co-glycolide-co-ε-caprolactone, poly(D,L-lactide-co-caprolactone), poly(L-lactide-co-caprolactone), poly(D-lactide-co-caprolactone), poly(D,L-lactide), poly(D-lactide), poly(L-lactide), poly(esteramide) or a combination thereof.

6. An implantable fiber according to claim 1, wherein at least one biodegradable polymer is soaked or sprayed with the clonidine.

7. An implantable fiber according to claim 5, wherein the at least one biodegradable polymer comprises polylactide and polyglycolide and the clonidine is an insoluble salt of clonidine comprising a fatty acid salt.

8. An implantable fiber according to claim 1, wherein the biodegradable polymer comprises poly(D,L-lactide-co-caprolactone), poly(L-lactide-co-caprolactone), poly(D-lactide-co-caprolactone), poly(D,L-lactide), poly(D-lactide), poly(L-lactide) or a combination thereof.

9. An implantable fiber according to claim 2, wherein the drug fiber releases: (i) a bolus dose of the clonidine at a site beneath the skin; and (ii) an effective amount of the clonidine over a period of at least five days.

10. An implantable fiber according to claim 2, wherein the drug fiber releases: (i) a bolus dose of the clonidine at a site beneath the skin; and (ii) an effective amount of the clonidine over a period of at least three to seven days.

11. An implantable fiber for reducing or treating pain in a patient in need of such treatment, the implantable fiber comprising clonidine hydrochloride in an amount of from about 0.1 wt.% to about 30 wt.% of the fiber and the implantable fiber comprising at least a portion configured to be attached to a target tissue beneath the skin of the patient, and the implantable fiber comprising at least one biodegradable polymer comprising poly(D,L-lactide-co-caprolactone), poly(L-lactide-co-caprolactone), poly(D-lactide-co-caprolactone), poly(D,L-lactide), poly(D-lactide), poly(L-lactide), collagen, poly(esteramide) or a combination thereof.

12. An implantable fiber according to claim 11, wherein the fiber is memory shaped fiber configured to be wrapped around the target tissue site.

13. A method for treating acute pain in a patient in need of such treatment, the method comprising attaching an implantable fiber to a target tissue site beneath the skin of the patient, the implantable fiber comprising at least a portion configured to be attached to a target tissue site beneath the skin of the patient, the implantable fiber comprising clonidine in an amount from about 0.1 wt.% to about 40 wt.% of the implantable fiber, and at least one biodegradable polymer, wherein the implantable fiber is configured to release the clonidine over a period of at least three days.

14. A method according to claim 13, wherein said clonidine comprises from about 5 wt.% to about 15 wt.% of the fiber.

15. A method according to claim 13, wherein the method comprises (i) suturing the fiber to the target tissue site; or (ii) attaching the fiber to the target tissue site by wrapping the fiber around the target tissue site, wherein the fiber is a memory shaped fiber.

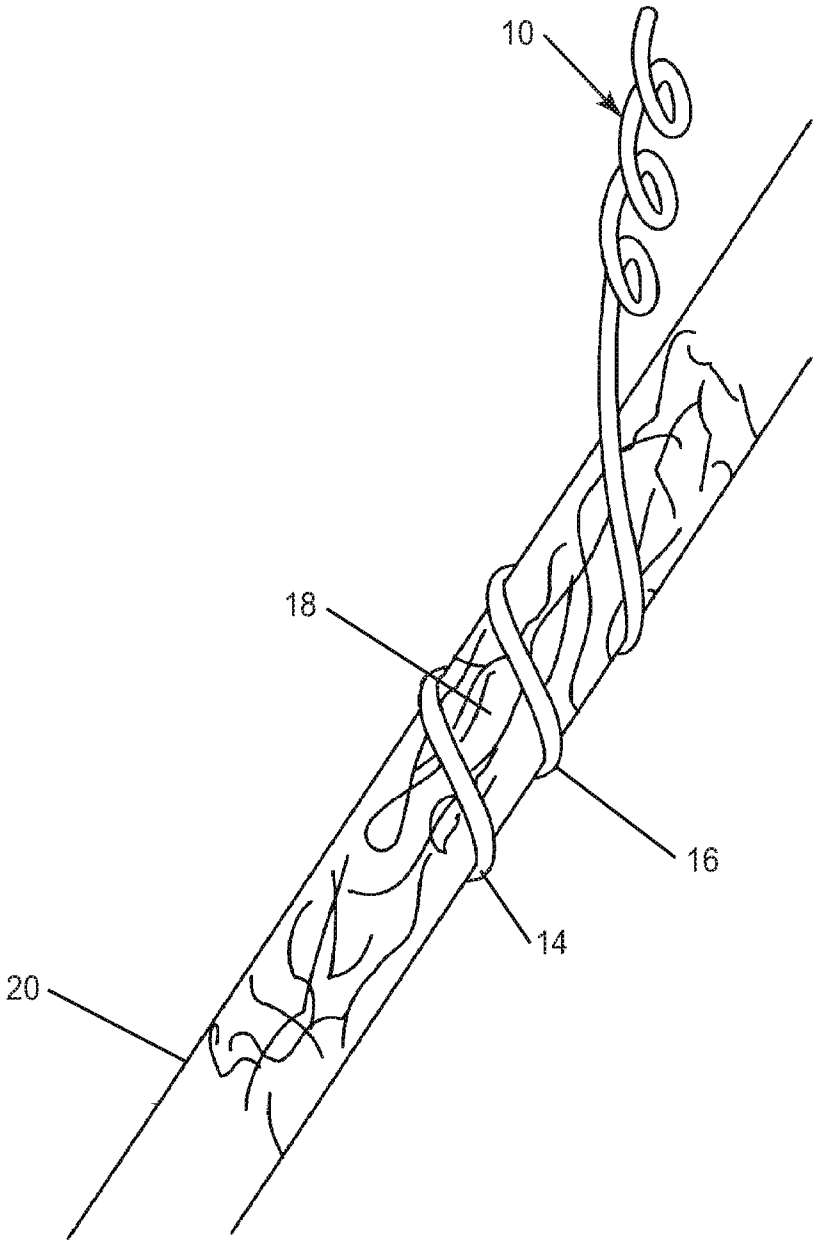


FIG. 1

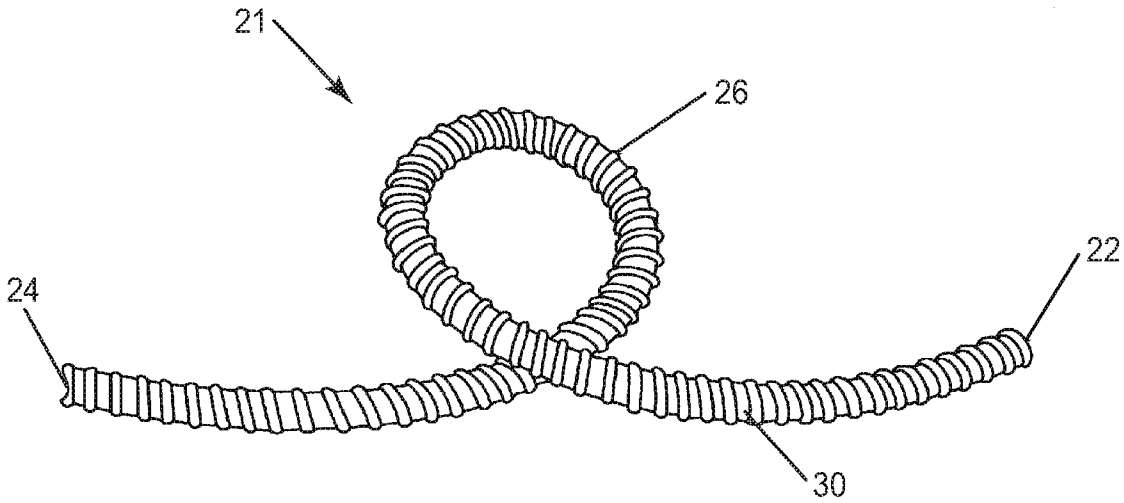


FIG. 2

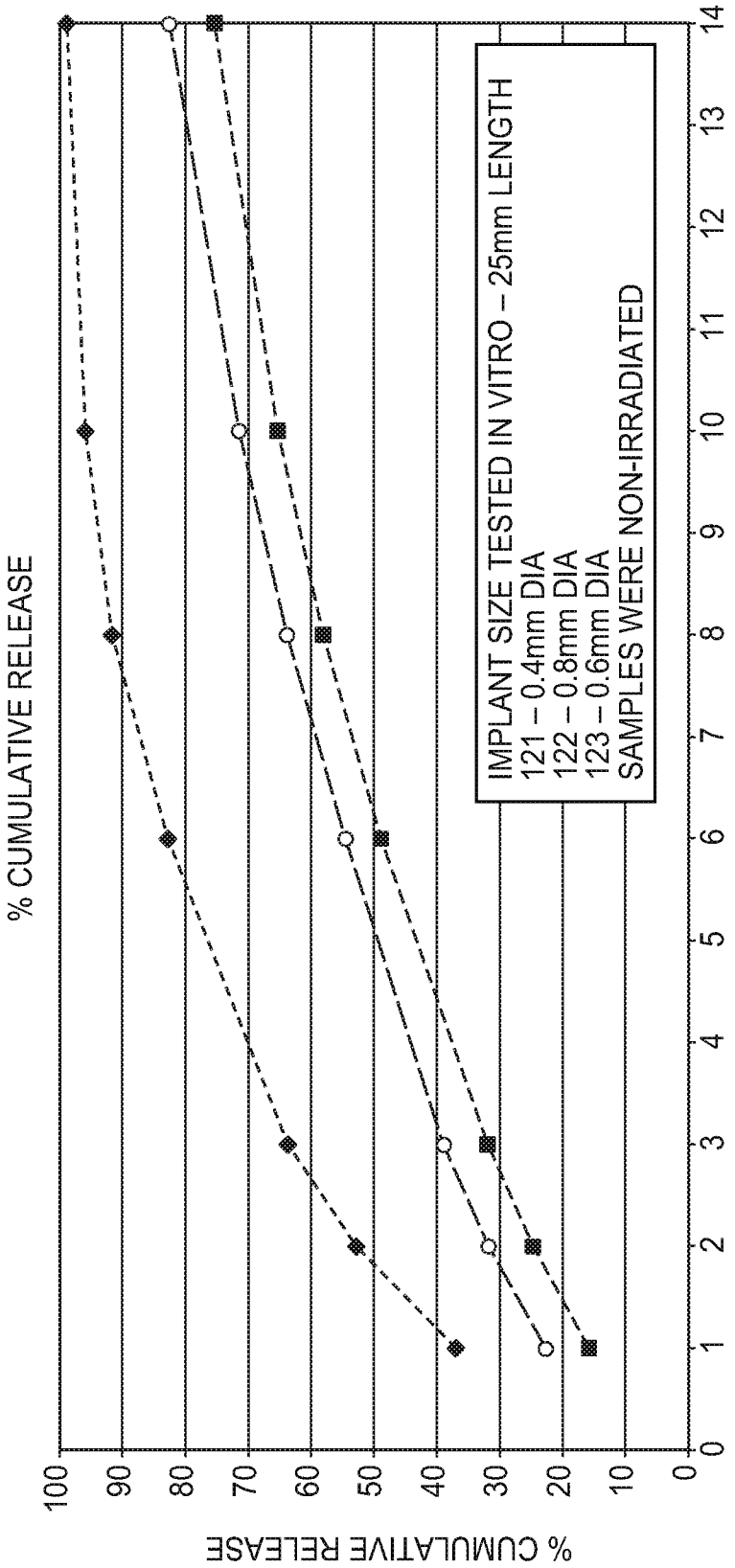

% CUMULATIVE RELEASE
% CUMULATIVE RELEASE
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
DAYS
IMPLANT SIZE TESTED IN VITRO – 25mm LENGTH
121 – 0.4mm DIA
122 – 0.8mm DIA
123 – 0.6mm DIA
SAMPLES WERE NON-IRRADIATED
397-121 8wt% CLONIDINE 60:40 LCL 5A
397-122 8wt% CLONIDINE 60:40 LCL 5A
397-123 16wt% CLONIDINE 60:40 LCL 5A

FIG. 3

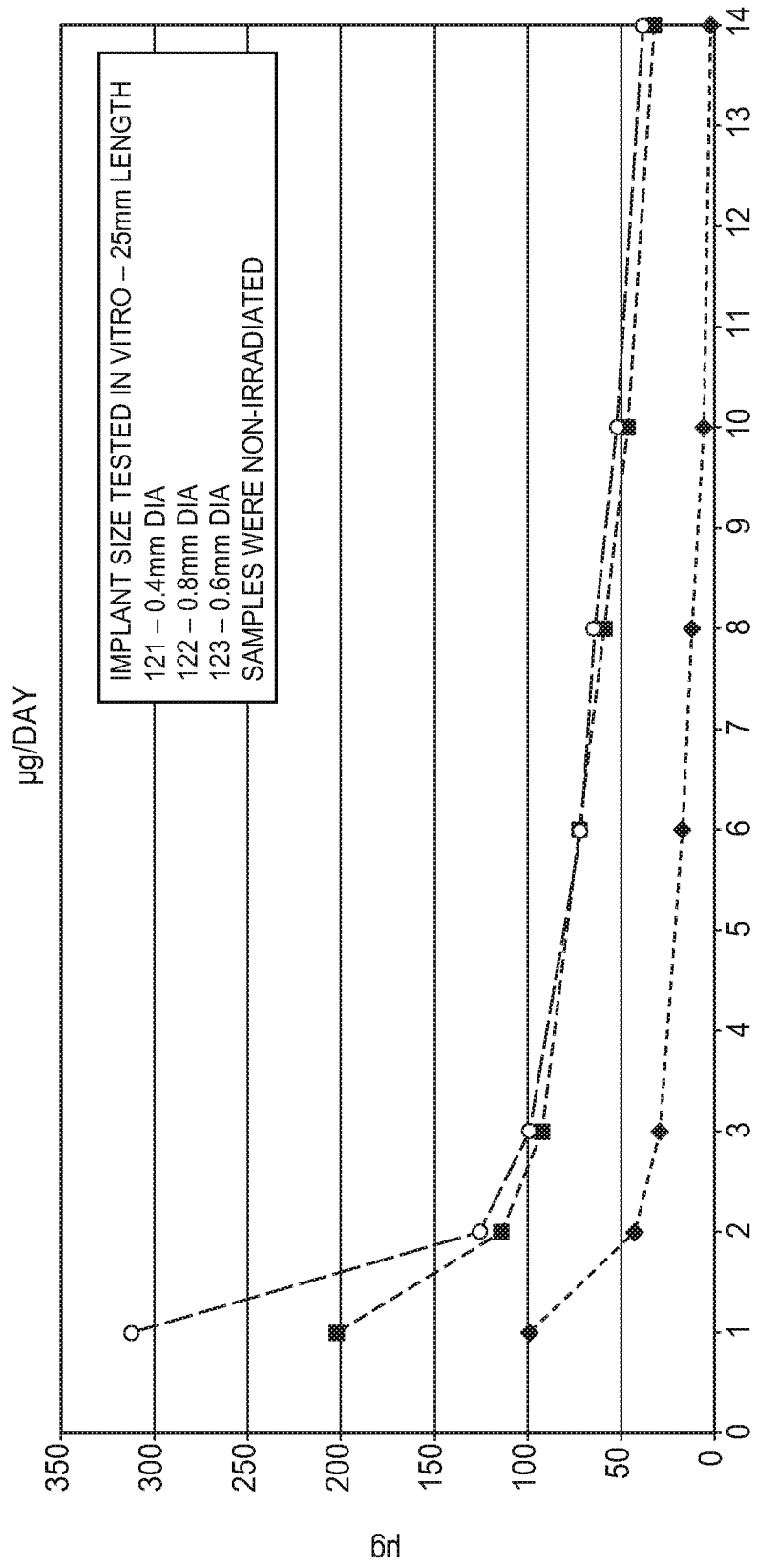

µg/DAY
IMPLANT SIZE TESTED IN VITRO – 25mm LENGTH
121 – 0.4mm DIA
122 – 0.8mm DIA
123 – 0.6mm DIA
SAMPLES WERE NON-IRRADIATED
350
300
250
200
150
100
50
0
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
DAYS
397-121 8wt% CLONIDINE 60:40 LCL 5A, 0.4mm DIA
397-122 8wt% CLONIDINE 60:40 LCL 5A, 0.8mm DIA
397-123 16wt% CLONIDINE 60:40 LCL 5A

FIG. 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/011192

A. CLASSIFICATION OF SUBJECT MATTER

A61F 2/10(2006.01)i, A61F 2/02(2006.01)i, A61L 27/14(2006.01)i, A61L 27/58(2006.01)i

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61F 2/10; A61K 31/4162; A61P 29/00; A61K 9/00; A61L 17/14; A61F 2/00; A61K 31/56; A61B 17/04; A61K 31/575; A61F 2/02; A61L 27/14; A61L 27/58

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: implantable fiber, clonidine, suture, memory-shaped

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009-129437 A2 (WARSAW ORTHOPEDIC, INC. and MEDTRONIC, INC.) 22 October 2009 See claims 1-20; paragraphs [0008]-[0021], [0064]-[0076], [0116]-[0127], [0161].	1-6,8-12
Y		7
Y	US 2012-0142649 A1 (GRAY, J. K. et al.) 07 June 2012 See abstract; claims 1-20; paragraph [0049].	7
A		1-6,8-12
A	WO 2012-061658 A2 (ANGIOTECH PHARMACEUTICALS, INC. and TISSUEGEN, INC.) 10 May 2012 See abstract; claims 1-21.	1-12
A	US 2010-0291182 A1 (PALASIS, M. et al.) 18 November 2010 See abstract; claims 1-29.	1-12
A	LIU, C. et al., `Review of progress in shape-memory polymers`, Journal of Materials Chemistry, 2007, Vol.17, No.16, pp.1543-1558 See the whole document.	1-12

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

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
07 May 2014 (07.05.2014)	**08 May 2014 (08.05.2014)**

Name and mailing address of the ISA/KR
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/011192

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

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

1. ☒ Claims Nos.: 13-15
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 13-15 pertain to methods for treatment of the human body by therapy or surgery, and thus relate to a subject-matter which this International Searching Authority is not required, under Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. ☐ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/US2014/011192

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2009-129437 A2	22/10/2009	AU 2009-236157 A1	22/10/2009
		EP 2209466 A2	28/07/2010
		JP 2011-518180 A	23/06/2011
		KR 10-1194894 B1	25/10/2012
		KR 10-2010-0055513 A	26/05/2010
		US 2009-0264491 A1	22/10/2009
		US 8629172 B2	14/01/2014
		WO 2009-129437 A3	18/02/2010
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		WO 2012-075447 A2	07/06/2012
		WO 2012-075447 A3	23/08/2012
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		CA 2816326 A1	10/05/2012
		EP 2635198 A2	11/09/2013
		KR 10-2013-0140762 A	24/12/2013
		US 2013-0317545 A1	28/11/2013
		WO 2012-061658 A3	19/07/2012
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		CA 2781108 A1	26/05/2011
		EP 2501369 A1	26/09/2012
		JP 2013-511527 A	04/04/2013
		US 2012-299223 A1	29/11/2012
		WO 2011-062974 A1	26/05/2011