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[Continued on next page]

(54) Title: ELONGATED BIODEGRADABLE DEPOT FOR SUSTAINED DRUG RELEASE TO TREAT CHRONIC PELVIC PAIN

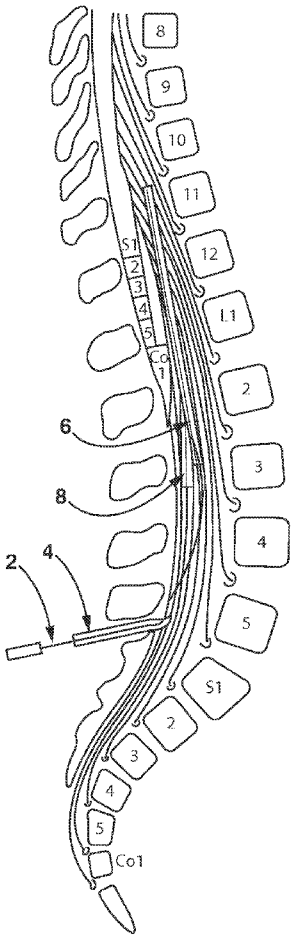

FIG. 1

(57) Abstract: The invention describes a device for administering a therapeutic agent to a subject at a sustained rate over a period of time, the device being shaped, sized and adapted for administering the therapeutic agent into the region of the spinal column of the subject, the device comprising: an elongated first polymeric substrate having a proximal end, a distal end and diameter or width of about 1 mm to about 10 mm and a length of about 4 cm to about 35 cm; optionally, an elongated second polymeric substrate positioned within the first polymeric substrate; and at least one therapeutic agent, loaded into or onto the first polymeric substrate or second polymeric substrate or both, wherein the therapeutic agent is available for diffusion into the region of the spinal column of the subject.

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ELONGATED BIODEGRADABLE DEPOT FOR SUSTAINED DRUG RELEASE TO TREAT CHRONIC PELVIC PAIN

FIELD OF THE INVENTION

he invention relates generally to a drug delivery device having an elongated first polymeric substrate having a proximal end, a distal end and diameter or width of about 1 mm to about 10 mm and a length of about 4 cm to about 35 cm. Optionally, an elongated second polymeric substrate can be positioned within the first polymeric substrate. The device includes at least one therapeutic agent, loaded into or onto the first polymeric substrate or second polymeric substrate or both, wherein the therapeutic agent is available for diffusion into the region of the spinal canal of the subject.

BACKGROUND OF THE INVENTION

Constant or chronic pain is a significant medical problem for many members of the general population. Suitable drugs, such as the opioid class of analgesics, used to treat severe chronic pain act on receptors found in the neuraxis. By "neuraxis" as used herein is meant any region of tissue that comprises the spinal cord, brain or central nervous system.

In addition, pain-relieving drugs when administered intraspinally (i.e., into the spinal canal via the epidural or intrathecal routes of administration) may also act on the spinal nerve roots or dorsal root ganglia that are within or in close proximity to the spinal canal.

For example, chronic pelvic pain may occur in both men and women of all ages and results from a variety of injuries and disorders. It is a common and debilitating problem that can significantly impair the quality of life of the patient suffering from it. Chronic pelvic pain occurs in the pelvic or abdominal region and can last for up to six months or longer. It often has a relapsing-remitting disease course with painful flare ups often times associated with physical or emotional stress.

In men, chronic pelvic pain may result from chronic idiopathic prostatitis (also referred to as nonbacterial prostatitis or chronic pelvic pain syndrome), chronic bacterial prostatitis or interstitial cystitis where the symptoms of both typically include in addition

to pelvic pain, urinary urgency and frequency, sexual dysfunction and in most cases patients have a nonrelaxing pelvic floor upon physical examination. It is thought that the pelvic floor dysfunction and hypertonicity which occurs in the vast majority of patients with chronic prostatitis and painful bladder syndrome plays a critical role in the symptoms of the patient including pain, urinary urge and voiding frequency. Baclofen and benzodiazepines are sometimes used orally to treat pelvic pain syndromes but efficacy is limited because of dose-limiting side effects.

Other types of chronic pelvic pain experienced by men include chronic testicular pain (CTP), post vasectomy pain, genitofemoral neuralgia and other pain originating from the testicles, groin, or abdomen. The incidence of patients with CTP, also referred to as orchialgia, orchidynia, or chronic scrotal pain, is large and may be caused by on-going inflammation of the testicle (orchitis) or epididymis (epdidymitis), trauma, tumors, hernia, torsion (twisting of the testicle), varicocele, hydrocele, spermatocele polyarteritis nodosa, and previous surgical interventions such as vasectomy and hernia surgery.

Typically, testicle removal and spermatic cord denervation procedures are used to treat CTP. In spermatic cord denervation procedures, nerves in or adjacent to the spermatic cord, i.e., the genitofemoral nerve or sympathetic nerves, are severed or permanently removed. Such procedures may result in permanent and substantial pain relief regardless of the origin of pain. However, severing or removing these nerves may result in loss of sensation in the testicle and/or scrotum, loss of the cremasteric reflex which may cause fertility issues, and even loss of blood flow causing the testicle to die. Therapeutic nerve blocks may also be used to treat CTP, but generally only relieve pain temporarily.

Chronic pelvic pain is also a common medical problem affecting women today. Sources of pain may include injury to nerves resulting from surgical procedures, non-surgical conditions, vulvodynia which can be very debilitating but has no obvious source, and interstitial cystitis (painful bladder syndrome). Surgical procedures that may injure nerves in the pelvic region resulting in pelvic pain may include urological operations in the pelvic area, gynecological surgery, and hysterectomy. Non-surgical conditions which cause pain in women include adhesions, endometriosis, and pelvic congestion.

The current regimen for treatment of these patients is systemic administration of relatively high doses of analgesics by for example oral, subcutaneous, intramuscular,

intravenous and related routes on a daily or continuous basis. Oral administration of an analgesic is problematic because the patient experiences high systemic concentration of drug at the time of ingestion followed by a gradual decrease in systemic concentration of the drug until the next dose is ingested. Other methods of systemic administration are problematic because they may be invasive, for example placement of an intravenous catheter for continuous administration of the analgesic. In either case, however, the analgesic is distributed equally throughout the body after being administered systemically and diffuses across the blood-brain barrier into the neuraxis to its central site of action, blocking pain messages to the brain. The cost for treating these patients is high from a hospital care as well as from a pharmaceutical standpoint since many patients must be maintained in the hospital to continue their pain treatment regimen of high doses of the analgesic. Furthermore, side effects related to the systemic administration of high doses of, for example, opioids include sedation, respiratory depression, nausea, constipation and vomiting. These side effects are well documented in product labeling and the literature and detract greatly from the already compromised quality of life of these patients.

BRIEF SUMMARY OF THE INVENTION

Therefore, a need exists for a method and system that overcomes one or more of the current disadvantages noted above.

The present invention provides an alternative means for achieving continuous central nervous system administration of a therapeutic agent into the neuraxis via epidural, intrathecal and related routes for those suffering chronic pevlic pain and is directed to solving one or more of the problems noted above. The invention comprises a therapeutic-agent-carrying device and its method of use, including implantation, which releases the therapeutic agent in a continuous and sustained-release manner. The device consists of a biocompatible polymer matrix body loaded with a therapeutic agent such that a slow, constant release of the therapeutic agent is provided. The polymer matrix substrate can be constructed of any of a number of biodegradable or non-biodegradable polymers that act as the carrier matrix for the therapeutic agent. Ideally, therapeutic levels of the therapeutic agent will be delivered over the long term, for example, from about one month to about

one year. Suitable analgesics include, for example, bupivacaine, baclofen or midazolam. Preferably the method of the invention administers the therapeutic agent intrathecally, epidurally, or by other related routes to the neuraxis.

The device can have any shape suitable for implantation into the epidural, intrathecal or related space, but in particular can be in the shape of a rod, rectangle or tube that is solid or hollow. When a lumen is present, one or both ends of the tube can be sealed. The device dimensions are generally from about 1 mm to about 10 mm in diameter (or width) and from about 4 cm to about 35 cm in length. The device can be positioned by various methods known in the art into the intrathecal or epidural space, such as by use of a large gauge needle, trocar or catheter. The device is dimensioned such that it remains in position throughout the treatment period with sustained release of the therapeutic agent. In one aspect the device is formed from a shape memory polymer. This provides an added feature such that the device is shaped to mirror the shape of desired treatment site, e.g., the lumbar region. In certain embodiments, the device has a first shape optimized for implantation, and changes to a second shape optimized for fixation and retention in the desired space after implantation. This may also serve to increase the surface area of delivery and total drug load by going from a linear to a preformed shape.

While multiple embodiments are disclosed, still other embodiments of the present invention will become apparent to those skilled in the art from the following detailed description. As will be apparent, the invention is capable of modifications in various obvious aspects, all without departing from the spirit and scope of the present invention. Accordingly, the detailed descriptions are to be regarded as illustrative in nature and not restrictive.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 provides a general depiction of one aspect of an elongated delivery device of the invention.

DETAILED DESCRIPTION

In the specification and in the claims, the terms "including" and "comprising" are open-ended terms and should be interpreted to mean "including, but not limited to. . . . "

These terms encompass the more restrictive terms “consisting essentially of” and “consisting of.”

It must be noted that as used herein and in the appended claims, the singular forms "a", "an" and "the" include plural reference unless the context clearly dictates otherwise. As well, the terms "a" (or "an"), "one or more" and "at least one" can be used interchangeably herein. It is also to be noted that the terms "comprising", "including", “characterized by” and "having" can be used interchangeably.

The present invention relates to methods and devices for decreasing, eliminating, or managing chronic pelvic pain by providing direct and controlled administration of a therapeutically effective dose of a pelvic pain-alleviating drug to a patient intrathecally, peridurally, or epidurally

In one aspect, the present invention pertains to a device for administering a therapeutic agent to a subject at a sustained rate over a period of time. The device is shaped, sized and adapted for administering the therapeutic agent into the region of the spinal column of the subject. The device includes an elongated first polymeric substrate having a proximal end, a distal end and a diameter or width of about 1 mm to about 10 mm and a length of about 4 cm to about 35 cm and, optionally, one or more additional polymeric substrates positioned within the first polymeric substrate. The therapeutic agent is loaded into the first polymeric substrate or additional polymeric substrate(s) or both, wherein the therapeutic agent is available for delivery into the region of the spinal column of the subject.

In one aspect, the device can be configured as a solid but flexible rod having at least one polymeric substrate. Alternatively, the device can be configured as a rod wherein a first polymeric substrate encircles a second rod or tube of a second polymeric substrate. In one aspect, a portion of the rod can be a first polymer with a first agent and a second portion or the rod can be a second or additional polymer with one or more additional agents. For example, a 180 degree segment of a rod can be a first polymer and the second 180 degree segment of the rod can be a second polymer. Likewise, a 60 degree segment can be a first polymer, a second 60 degree segment can be a second polymer, etc.

As should be understood, the device is not limited to only two polymeric substrate layers and can include three or more polymeric substrate layers. Each layer can include

one or more therapeutic agents. It is also possible to have the different polymer in a series such that one polymer releases a different drug that the other and thereby targets different structures with the spinal canal, e.g., bupivacaine in the sacrum to block spinal nerves, baclofen in lumbar spine to affect the spinal cord. Polymers can also have different release rates of the same or different drugs. Through careful selection of each polymeric layer, one can therefore deliver therapeutic agents at different rates and different times, depending on measurable properties such as solubility and diffusivity for biodegradable and non-degradable polymers, and degradation rates for biodegradable polymers.

In another aspect, the device can be configured as a tube having a hollow interior. The hollow interior or lumen can be used to deliver the device via a stylet or guidewire as is known in the art. Again, the tube can include one or more polymeric substrates and can include one or more therapeutic agents.

In those instances where the device is a tube, a therapeutic agent can be placed into the hollow cavity. The form of the therapeutic agent is not limited and can be a solid, a gel, a paste, or a liquid. Where the therapeutic agent is contained in a carrier, it is advantageous to "cap" the ends of the hollow tube to contain the therapeutic within the device. In this embodiment the drug can be delivered by simple diffusion through the tube wall or end or by an active force, such as osmotic pressure.

From an end view, the rod or tube can be a ribbon, round, square, rectangular, octagonal, triangular, etc. The configuration and dimensions of the device are such that once the device is positioned within the neuraxis, it remains without substantial movement from the site of implantation. In one aspect, the device can be anchored via a suture or tether secured to the surrounding tissue.

Typically the diameter (or width) of the device is from about 1 mm to about 10 mm, more particularly from about 2 mm to about 4 mm and more particularly from about 2 mm to about 3 mm.

The length of the device is from about 4 cm to about 35 cm, more particularly from about 6 cm to about 14 cm and more particularly from about 8 cm to about 12 cm. Since the device is not particulate in form or a flowable gel, it has the advantage of remaining at the implantation site and not dislodging from the implantation/treatment site.

The design of the device provides another advantage in that the therapeutic agent is

provided to the treatment site over a period of time without concern that the delivery system may not remain at the implantation site due to physical movement. The design further provides more consistent, uniform and sustained coverage of the targeted structures (spinal cord, nerve roots, dorsal root, ganglia). In the event of an adverse patient reaction, the device can be removed, which is more difficult or impossible with a gel or microparticle formulation.

The therapeutic agent can be included the first polymeric substrate, the second polymeric substrate or both. In one embodiment, the therapeutic agent(s) can be released at different rates by selection of different polymers having different release profiles. Alternatively, when the device is a tube, the therapeutic agent can be contained within the hollow portion of the tube.

The device can comprise two or more segments. As such, the two or more segments can deliver different therapeutic agents or therapeutics to the treatment site(s). For example, bupivacaine can target the spinal nerve roots that travel in the spinal canal below L2 whereas baclofen can target the spinal cord from L2 to T10. Therefore, these two agents for example, can be located in two different segments of the device, or two different devices can be positioned adjacent to each other to achieve the same therapeutic effect.

The device can be made from polymers; biodegradable (also referred to as "resorbable" polymers) and/or non-biodegradable polymers can be used. Biodegradable polymers are useful because of their versatile degradation kinetics, safety, and biocompatibility profiles. The polymers can be manipulated to modify the pharmacokinetics of the least one therapeutic agent contained within the device, to shield the pharmaceutical agent from enzymatic attack, as well as degrade over time at the site of attachment such that the therapeutic agent is released over time.

Natural biodegradable polymers include, but are not limited to, proteins (e.g., collagen, albumin, elastin, silk, glycosaminoglycans, chondroitin sulfate, or gelatin); polysaccharides (e.g., cellulose, cellulose starch, starch, alginates, chitin, chitosan, cyclodextrins, polydextrose, dextrans, glucosamine, hyaluronic acid, or hyaluronic acid esters) or lipids.

Suitable examples of resorbable polymers include, but are not limited to, poly(alpha-hydroxy acids), poly(lactide-co-glycolide) (PLGA), polylactide (PLA), polyglycolide (PLG), polyethylene glycol (PEG), PEG conjugates of poly(alpha-hydroxy acids), polyorthoesters, polyaspirins, polyphosphazenes, vinylpyrrolidone, polyvinyl alcohol (PVA), PVA-g-PLGA, polyethylene glycol-terephthalate and polybutylene-terephthalate (PEGT-PBT) copolymer(polyactive), polyethylene oxides (as known as polyoxyethylene or PEO), polyethylene oxide/polyethylene terephthalate,poly-propylene oxide (also known as polyoxypropylene or PPO), poly(aspartic acid) (PAA), PEO-PPO-PEO (Pluronics®, BASF), PEO-PPO-PAA copolymers, PLGA-PEO-PLGA, polyphosphoesters, polyphosphonates, polyanhydrides, polyester-anhydrides, polyamino acids, polyurethane-esters, polyphosphazines, polycaprolactones, polytrimethylene carbonates, polydioxanones, polyamide-esters, polyketals, polyacetals, polyethylene-vinyl acetates, silicones, polyurethanes, polypropylene fumarates, polydesaminotyrosine carbonates, polydesaminotyrosine arylates, polydesaminotyrosine ester carbonates, polydesaminotyrosine ester arylates, polyorthocarbonates, polycarbonates, or copolymers or physical blends thereof or combinations thereof.

More examples of synthetic biodegradable polymers include, but are not limited to, various polyesters, copolymers of L-glutamic acid and gamma ethyl-L-glutamate (Sidman et al., 1983, Biopolymers 22:547-556), polyphosphagenes, various hydrogels (see, for example, Langer et al., 1981, J. Biomed. Mater. Res. 15:167-277; Langer, 1982, Chem. Tech. 12:98-105), and poly-D-(-)-3-hydroxybutyric acid (EP 133,988). Polylactide (PLA) and its copolymers with glycolide (PLGA) have been well known in the art since the commercialization of the Lupron Drug delivery device™, approved in 1989 as the first parenteral sustained-release formulation utilizing PLA polymers. Additional examples of products which utilize PLA and PLGA as excipients to achieve sustained-release of the active ingredient include Atridox (PLA; periodontal disease), Nutropin Drug delivery device (PLGA; with hGH), and the Trelstar Drug delivery device (PLGA; prostate cancer).

In various embodiments, the device comprises poly(lactide-co-glycolide) (PLGA), polylactide (PLA), polyglycolide (PGA), D-lactide, D,L-lactide, L-lactide, D,L-lactide-

epsilon-caprolactone, D,L-lactide-glycolide-epsilon-caprolactone, polyepsilon-caprolactone, glycolide-caprolactone or combinations thereof.

Examples of non-biodegradable polymers include, but are not limited to, various cellulose derivatives (carboxymethyl cellulose, cellulose acetate, cellulose acetate propionate, ethyl cellulose, hydroxypropyl methyl cellulose, hydroxyalkyl methyl celluloses, and alkyl celluloses), silicon and silicon-based polymers (such as polydimethylsiloxane), polyethylene-co-(vinyl acetate), poloxamer, polyvinylpyrrolidone, poloxamine, polypropylene, polyamide, polyacetal, polyester, poly ethylene-chlorotrifluoroethylene, polytetrafluoroethylene (PTFE or "Teflon™"), styrene butadiene rubber, polyethylene, polypropylene, polyphenylene oxide-polystyrene, poly-alpha-chloro-p-xylene, polymethylpentene, polysulfone, non-degradable ethylene-vinyl acetate (e.g., ethylene vinyl acetate disks and poly(ethylene-co-vinyl acetate)), methacrylates, poly(N-isopropylacrylamide), and other related polymers.

Non-resorbable polymers can also include, but are not limited to, delrin, polyurethane, copolymers of silicone and polyurethane, polyolefins (such as polyisobutylene and polyisoprene), acrylamides (such as polyacrylic acid and poly(acrylonitrile-acrylic acid)), neoprene, nitrile, acrylates (such as polyacrylates, poly(2-hydroxy ethyl methacrylate), methacrylates, methyl methacrylate, 2-hydroxyethyl methacrylate, and copolymers of acrylates with N-vinyl pyrrolidone), N-vinyl lactams, polyacrylonitrile, glucomannan gel, vulcanized rubber, poly(3-hydroxybutyrate) and combinations thereof. Examples of polyurethanes include thermoplastic polyurethanes, aliphatic polyurethanes, segmented polyurethanes, hydrophilic polyurethanes, polyether-urethane, polycarbonate-urethane and silicone polyether-urethane. The vulcanized rubber described herein may be produced, for example, by a vulcanization process utilizing a copolymer produced as described, for example, in U.S. Pat. No. 5,245,098 to Summers et al. from 1-hexene and 5-methyl-1,4-hexadiene.

Other suitable non-resorbable material include, but are not limited to, lightly or highly cross-linked biocompatible homopolymers and copolymers of hydrophilic monomers such as 2-hydroxyalkyl acrylates and methacrylates, N-vinyl monomers, and ethylenically unsaturated acids and bases; polycyanoacrylate, polyethylene oxide-polypropylene glycol block copolymers, polygalacturonic acid, polyvinyl pyrrolidone,

polyvinyl acetate, polyalkylene glycols, polyethylene oxide, collagen, sulfonated polymers, vinyl ether monomers or polymers, alginate, polyvinyl amines, polyvinyl pyridine, and polyvinyl imidazole. Depending on the amount of crosslinking within the bioresorbable polymers, the degradation time of the polymer can be reduced, thus making the polymer, for the purpose of this invention, appear to be non-resorbable over the time frame of the use of the material for this invention.

The device can also contain shape memory polymers so that the device can be compressed or folded prior to and during insertion into the neuraxis and then be able to uncompress or unfold after the drug delivery device is within the neuraxis space. Shape memory polymers are a result of selecting suitable polymer segments within a block polymer having differing glass transition temperatures. Suitable shape memory polymers are known in the art and include, for example, styrene copolymers, such as those described in US Patent 6,759,481, polyester copolymers, such as those described in US Patent 7,498,385, copolymers such as those described in US Patents 6,388,043 and 6,720,402, polyester-urethane copolymers such as those described in US Patent 6,852,825 or any of the polymers described in “Shape-Memory Polymers”, Andreas Lendlein and Stefen Kelch, Angew. Chem. Int. Ed. 2002, 41, 2034-2057, the contents of which are incorporated herein in their entirety for all purposes.

For example, a multi-block copolymer of oligo(epsilon-caprolactone)diol and crystallisable oligo(rho-dioxanone)diol can be used to create a shape memory polymer. This shape memory polymer features two block-building segments, a hard segment and a “switching” segment, which are linked together in linear chains. The higher-temperature shape is the polymer's “permanent” form, which it assumes after heating. One component, oligo(epsilon-caprolactone)dimethacrylate, furnishes the crystallizable "switching" segment that determines both the temporary and permanent shape of the polymer. By varying the amount of the comonomer, n-butyl acrylate, in the polymer network, the cross-link density can be adjusted. In this way, the mechanical strength and transition temperature of the polymers can be tailored such that it can be used in the present invention. The shape memory polymers can be generated such that they return to their original shape with the application of an external stimulus. The external stimulus can be temperature, an electric or magnetic field, light, or a change in pH.

The device can include radiographic markers to aid in visualization. The expanded device will lodge at or near the target tissue and will be held in place by the expansion. This design allows the device to be folded and allows the device to expand after the device is deployed (e.g., catheter, large gauge needle, trocar, etc.).

The device can further include a "tether". The tether can be attached to the device by any suitable means of connection such as adhesive or fusion. The tether has such a length as to allow for retrieval of the device at any time following implantation thereof into the neuraxis region of the subject. The tether ideally is a filament contained along the length of the inner core of the device and has a portion that extends into the subcutaneous space of the patient. The subcutaneous portion of the filament can contain a bead or similar small but palpable structure that allows the physician to readily locate the device for removal if desired. The tether can be of any known biocompatible material such as nylon as is generally used in surgery. The tether can also be biodegradable but at a much slower rate than the drug-containing polymer. This will ensure that the device can be withdrawn as long as any drug-containing material remains in the body but that the entire device including the filament will eventually resorb.

For example, the tether extends away from the body and terminates under the skin so that it is easily accessible when retrieval is desired. To retrieve the device, a catheter is simply inserted over the tether and positioned at the device. The tether is then used to draw the device into the catheter and the device is removed with the catheter. Alternatively, a physician could surgically expose the entry site, e.g., an epidural site, and remove the tether.

As noted above, in various embodiments, radiopaque material or markers can be positioned in or on or coated on the device to assist in determining the position of the drug delivery device relative to the tissue being treated. Examples of radiopaque material include, but are not limited to, barium sulfate, calcium phosphate, iopamidol, iodixanol, gadodiamide, Hypaque® sodium (diatrizoate sodium, Amersham Health, Inc., Princeton, N.J.), Hypaque®-76 (diatrizoate meglumine and diatrizoate sodium, Amersham Health, Inc., Princeton, N.J.), and Hypaque® Meglumine (combination of diatrizoic acid dehydrate, water and meglumine, Amersham Health, Inc., Princeton, N.J.).

Other types of radiopaque material include radioisotopes that can be linked to the drug delivery device. Examples of radioisotopes include, ^{18}F, ^{3}H, ^{124}I, ^{125}I, ^{131}I, ^{35}S, ^{14}C, and ^{11}C. Radioisotopes may be attached using a chelating agent such as EDTA or DTPA, and can be detected by gamma counter, scintillation counter, PET scanning, or autoradiography.

The term "subject" is intended to include those mammals that have a spine. Such mammals include humans, pigs, dogs, cats, equine and the like.

As used herein the term "therapeutically effective amount" means an amount of a drug which is effective to achieve a desired therapeutic effect, e.g., alleviation of chronic pelvic pain. The precise desired therapeutic effect (e.g., the degree of pain relief, the cause of the pain relief, etc.) will vary according to the condition to be treated and a variety of other factors that are known by those of ordinary skill in the art.

The phrase "therapeutic agent" is intended to include anesthetics, analgesics, anti-inflammatories, muscle relaxants and the like.

Anti-inflammatory agents can include cytokines, steroids, non-steroidal anti-inflammatories, and agents that inhibit inflammatory cytokines. Of course, these groups can overlap. Examples of agents that inhibit inflammatory cytokines include, but are not limited to, tumor necrosis factor alpha (TNF-alpha) inhibitors (for example, onercept, adalimumab, infliximab, etanercept, pegsunercept (PEG sTNF-R1), sTNF-R1, CDP-870, CDP-571, CNI-1493, RDP58, ISIS 104838, 1→ 3-beta-D-glucans, lenercept, PEG-sTNFR11 Fc mutein, D2E7, afelimomab and antibodies or antibody fragments that bind to TNF-alpha or that bind to its receptor), inhibitors of TNF-alpha production or release (for example, thalidomide, tenidap, and phosphodiesterase inhibitors, such as, but not limited to, pentoxifylline and rolipram, and TNF-alpha converting enzyme inhibitors (TACE)), inhibitors of interleukin-1 (IL-1) (for example, anakinra, a recombinant, non-glycosylated form of the human interleukin-1 receptor antagonist (IL-1Ra); Orthokine® (IL-1Ra obtained from human serum), AMG 108 (a monoclonal antibody that blocks IL-1 activity), and any other antibody or antibody fragment that binds to IL-1 or its receptors), inhibitors of IL-6 (for example, tocilizumab (a humanized anti-IL-6 mAb produced by Chugai Pharma USA, LLC, Bedminster, N.J.) or any other antibody or fragment that binds to IL-6 or its receptor), inhibitors of IL-8 (for example, any antibody or antibody fragment

that binds to IL-8 or its receptor), and inhibitors of classical or non-classical nuclear factor kappa B (NFκB) pathways (for example, ureido-thiophenecarboxamide derivatives, diferuloylmethane, IKK-1 and IKK-2 inhibitors, proteosomal inhibitors such as Bortezomib, sulindac, dexamethasone, fluocinolone, dithiocarbamate, and sulfasalazine), or clonidine.

Cytokines that have anti-inflammatory activity include but are not limited to interleukin-4 (IL-4) IL-10, IL-11, and IL-13.

Examples of steroidal anti-inflammatory agents include but are not limited to hydrocortisone, cortisol, hydroxyltriamcinolone, alpha-methyl dexamethasone, dexamethasone-phosphate, clobetasol valerate, desonide, desoxymethasone, desoxycorticosterone acetate, dexamethasone, dichlorisone, diflorasone diacetate, diflucortolone valerate, fluadrenolone, fluclorolone acetonide, fludrocortisone, flumethasone pivalate, fluocinolone acetonide, fluocinonide, flucortine butylesters, fluocortolone, fluprednidene(fluprednylidene)acetate, flurandrenolone, halcinonide, hydrocortisone acetate, hydrocortisone butyrate, methylprednisolone, triamcinolone acetonide, cortisone, cortodoxone, flucetonide, fludrocortisone, difluorosone diacetate, fluradrenolone, fludrocortisone, diflurosone diacetate, fluocinolone, fluradrenolone acetonide, medrysone, amcinafel, amcinafide, betamethasone and the balance of its esters, chloroprednisone, chlorprednisone acetate, clocortelone, clescinolone, dichlorisone, diflurprednate, flucloronide, flunisolide, fluoromethalone, fluperolone, fluprednisolone, hydrocortisone valerate, hydrocortisone cyclopentylpropionate, hydrocortamate, meprednisone, paramethasone, prednisolone, prednisone, beclomethasone dipropionate, and triamcinolone.

Non-limiting examples of non-steroidal anti-inflammatory compounds include acetaminophen, paracetamol, nabumetone, celecoxib, etodolac, nimesulide, apasone, gold, oxicams, such as piroxicam, isoxicam, meloxicam, tenoxicam, sudoxicam, and CP-14,304; the salicylates, such as aspirin, disalcid, benorylate, trilisate, safapryn, solprin, diflunisal, and fendosal; the acetic acid derivatives, such as diclofenac, fenclofenac, indomethacin, sulindac, tolmetin, isoxepac, furofenac, tiopinac, zidometacin, acematacin, fentiazac, zomepirac, clindanac, oxepinac, felbinac, and ketorolac; the fenamates, such as mefenamic, meclofenamic, flufenamic, niflumic, and tolfenamic acids; the propionic acid

derivatives, such as ibuprofen, naproxen, benoxaprofen, flurbiprofen, ketoprofen, fenoprofen, fenbufen, ketorolac, sulfasalazine, indopropfen, pirprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tioxaprofen, suprofen, alminoprofen, and tiaprofenic; and the pyrazoles, such as phenylbutazone, oxyphenbutazone, feprazone, azapropazone, and trimethazone.

Suitable analgesics include, without limitation, non-steroid anti-inflammatory drugs, non-limiting examples of which have been recited above. Analgesics also include other types of compounds, such as, for example, opioids (such as, for example, morphine naloxone, codeine, oxycodone, hydrocodone, diamorphine, pethidine, tramadol, tapentadol, or buprenorphine), local anaesthetics (such as, for example, bupivacaine, ropivacaine, mupivacaine, lidocaine and capsaicin), glutamate receptor antagonists, alpha-adrenoreceptor agonists (for example, clonidine), beta one receptor antagonists (e.g., HOE-140), adenosine, sodium or calcium channel blockers, neurotoxins (BoNT/A Botulinum toxin), TrkA receptor antagonists, canabinoids, cholinergic and GABA receptors agonists, and different neuropeptides.

The therapeutic agent can be loaded into the polymeric substrate by a number of techniques. The choice of loading technique for a particular analgesic/polymer matrix/device geometry will be dependent on a number of factors including drug/polymer/solvent compatibility, desired final concentration of therapeutic agent in the polymer matrix, simplicity of the process, desired final geometry of the device and preferred elution characteristics of the completed device. As examples, a few loading technique options are listed as follows. The list is not intended to be complete or limiting, but rather to serve as examples well understood by anyone skilled in the art.

The therapeutic agent can be loaded into the polymeric substrate by means of dispersion loading. Dispersion loading is the technique of loading a powdered substance into a polymer by stir-mixing it into the polymer per se, either during the polymerization reaction or as a polymer melt, or solution to make a dispersion of the two materials. The powder is not dissolved by the polymer solution in dispersion loading. The polymer is solidified by cooling, curing or solvent evaporation and a homogeneous blend of therapeutic agent in the polymer is achieved. The therapeutic agent has not reacted with the polymer, but rather is dispersed within the interstitial spaces of the cured polymer. The

concentration of therapeutic agent that can be loaded into the polymer is limited only by the physical integrity of the resulting polymer matrix. Dispersion mixing is a standard technique for loading dexamethasone into polymeric lead tips to create steroid eluting leads.

The dispersion loading method is a preferred method of combining the therapeutic agent with the polymeric substrate because the method allows for a fairly high percentage of therapeutic agent to be added to the polymer to form the device. The percentage of therapeutic agent added to the polymer to form the device is preferably from about 1% to about 80% by weight, e.g., from 5% to about 50%, more particularly from about 10% to about 40% by weight. This percentage has been found to maintain the integrity of the polymer substrate in a device.

The dispersion loading method also allows the device to be formed into optimal geometries prior to cure of the polymer or to be extruded as a tube or other geometry. Finally, solvent compatibility between the polymeric substrate and the therapeutic agent is not a factor.

Alternatively, solvent swelling can be used to combine the therapeutic agent with the polymeric substrate(s) of the device. This method is particularly useful where a preformed polymer polymeric device is introduced into a solution of the therapeutic agent in a solvent that acts as a swelling agent for the polymeric substrate. The polymeric substrate/device, while swelling, absorbs the solvent along with the dissolved therapeutic agent until a steady state is achieved. The polymeric device is then allowed to dry with the solvent evaporating from the sample and the therapeutic agent left behind in the polymeric body of the device. As the device dries, it returns from its swelled state to its original geometry and size. Solubility of the therapeutic agent in the solution limits the possible concentration of drug that can be introduced by this technique. Even so, the technique is well known and has been used successfully to load antimicrobials into polymer matrices. (See, for example, U.S. Pat. No. 4,917,686).

Solution loading is similar to dispersion loading except that the therapeutic agent must be soluble in the polymer-swelling solvent. The cured polymer device then includes the dissolved therapeutic agent in its matrix.

Finally, the method of reservoir loading may be used to combine the therapeutic agent with the device when the device is configured as a tube. This method comprises loading the therapeutic agent inside the hollow tube of the device and sealing the ends of the tube. The therapeutic agent then diffuses through the polymeric tubing wall of the device or is actively transported from the tube using osmotic or pneumatic pressure. A carrier can be used with the therapeutic agent. Suitable carriers are pharmaceutically acceptable solvents, aqueous solutions, gels, pastes and the like.

Alternatively, the therapeutic agent can be coated on the surface(s) of the device. It should be understood that the coating process can be by dip coating, spray coating, and other conventional methods known in the art. Additionally, multiple coatings can be effected with different carrier/polymeric systems to provide different rates of dissolution. For example, a first polymeric substrate of the device can be coated with a therapeutic agent dissolved with PLGA, coated, and dried. A subsequent layer can then be applied with either the same therapeutic or a different therapeutic and a different polymer, such as PLA. This can be repeated as desired with the various configurations of the device as described herein, e.g., tubular, or as a solid rod.

It will be understood that the amount of chronic pelvic pain-alleviating drug delivered and the target site of the delivery may be altered based upon the response of a patient to the drug. Any measure of pelvic pain improvement or worsening may be used to evaluate whether a therapy modification may be appropriate. Such determinations can be readily made by, for example, a physician attending to the subject's care. In an embodiment, a Visual Analog Scale (VAS) can be used to assess pain. The VAS is typically either a horizontal or vertical straight line; usually 10 cm in length with the descriptors of "least possible pain" or "no pain" on one end and "worst possible pain" on the other. The patient marks on the line where their pain level is at the present moment.

The distance from the patient's mark to the end of the line is the measure of severity of the pain. The measurement is reproducible, as shown in the correlation coefficients between successive measurements. It is one of the most sensitive measurements of pain. The VAS is easy to administer and understand. It has been administered to children as young as 5 and they were able to use the scale. Alternatively, other quality of life instruments can be used to measure impact (i.e., SF-36). The condition

of the pelvic floor musculature may also be assessed by physical exam and urodynamic testing.

In an embodiment of the invention, the effective amount to treat chronic pelvic pain, for example, will be the amount of drug required to alleviate chronic pelvic pain by an amount of at least about 25% based upon a pain assessment such as VAS and desirably by an amount of at least about 50% without the subject experiencing side effects that significantly diminish the subject's quality of life. In yet another aspect, this invention may allow the subject to decrease or eliminate oral medications that may have severe side effects. Examples include narcotics that may limit living a normal life (i.e., cognitive capability may be diminished which may impact driving, intellectual or high motor jobs). Further, it may allow a level of pain relief unachievable via oral or alternative medication or medical procedures.

The amount of the chronic pelvic pain-alleviating drug and target site of its delivery may be adjusted based upon the presentation and severity of side effects in a patient. Side effects may be recognizable by the patient, a physician attending to the care of the patient, other health care professionals, and the like. A physician or other health care professional may adjust therapy parameters based on side effects. Side effects which may be associated with some chronic pelvic pain-alleviating drugs useful with the method of the invention include: dizziness, insomnia, lightheadedness, changes in blood pressure, gastrointestinal disturbances, sexual dysfunction in males, nausea and/or vomiting.

Certain classes of drugs that may be useful chronic pelvic pain-alleviating drugs, such as opioid compositions may have particular side effects to consider. Opioid compositions may cause significant respiratory depression and may cause respiratory arrest if given too much too rapidly.

Effective dosages for use in methods as described herein can be determined by those of skill in the art, particularly when effective systemic dosages are known for a particular therapeutic agent. Dosages may typically be decreased by at least 90% of the usual systemic dose if the therapeutic agent is provided in a targeted fashion. In other embodiments, the dosage is at least 75%, at least 80% or at least 85% of the usual system dose for a given condition and patient population. Dosage is usually calculated to deliver a minimum amount of one or more therapeutic agent per day, although daily

administration is not required. If more than one pharmaceutical composition is administered, the interaction between the same is considered and the dosages calculated. Intrathecal dosage, for example, can comprise approximately ten percent of the standard oral dosage. Alternatively, an intrathecal dosage is in the range of about 10% to about 25% of the standard oral dosage.

"Target site" as used herein is used to refer to an area of the body to which the drug is administered. Target sites desirably used with the methods of this invention include specific regions within the spinal canal. As used herein, the term "spinal region" includes the spinal canal (including the spinal cord, intrathecal space, dura, epidural space, etc.), vertebrae, spinal discs, nerve roots, and the ligaments, tendons and muscles in between and surrounding the vertebrae. In one embodiment of the invention, the target site is intrathecal. In other embodiments the target site is in the epidural or peridural spaces of the spinal region. The target sites for the administration of a drug to alleviate pelvic pain in subjects also experiencing bladder or pelvic floor disorders is desirably in the epidural, peridural or intrathecal spaces in the spinal region desirably between Co1 and L1, between S5 and S1, between S2 and L1, or between T10 and S5. In one embodiment, the target site is the spinal region that may be accessed through the sacral hiatus or a sacral foramen.

The device provides that an optimum geometry and therapeutic loading may be prepared to allow for nearly zero order release kinetics (constant rate) of therapeutic amounts of an agent over a period of time, for example one month to one year. More particularly, the therapeutic agent can be released at a sustained rate over a period of time of from about 1 week to about 6 months, more particularly from about 2 month to 4 months and most particularly from about 3 months to about 6 months. Alternatively, if desired, the device can provide and initial burst of drug followed by slower, continuous release of the active agent(s).

In one embodiment, a catheter is inserted into the spinal region at a level below the end of the spinal cord then threaded up to the desired level. Many catheters are very limp, making it difficult or impossible to steer the catheter into a desired specific area of the spinal region. Therefore, a guidewire and/or stylet can be used to stiffen and advance the catheter during placement. The guidewire and/or stylet is then typically removed before the catheter is used to administer the device of the invention. Alternatively the device

itself (with a guiding catheter) has the appropriate mechanical properties such that it can be directly placed over the preplaced guide wire or with a stylet placed in a central lumen of the device. The guide wires or stylets may be curved to various degrees in so that the device can be steered by rotating the stylet or guidewire.

Subsequent to the insertion of the catheter, the device of the invention can be positioned into place via a guidewire or a stylet as are known in the art. For example, when the device is tubular, the device can be fitted over the guidewire or stylet and positioned by sliding along the guidewire or stylet. Release of the device and removal of the guidewire or stylet and catheter provides proper placement of the device at the desired location.

Alternatively, when the device is a rod or ribbon, the device can be "pushed" to the desired location by a stylet or guidewire within the catheter. Again, removal of the apparatus provides for placement of the device at the desired location.

In one embodiment, the device is delivered to the spinal region below the sacrum. As described above, the delivery can be via a catheter. The techniques for such delivery method (caudal anesthetic block) are well known in the art. In one embodiment, the Seldinger technique is used and an introducer having a lumen is used to enter the spinal space through one of the sacral hiatus or a sacral foramen, a guidewire is passed through the introducer, the introducer is removed and the catheter is advanced over the wire until it is in position for drug delivery. The tubular device of the invention can be passed over the guidewire for appropriate placement.

In one particular aspect, implantation of the device will occur in the intrathecal space as opposed to the epidural space. This is because less analgesic is generally required for effective control of chronic pain when the device is introduced to the intrathecal space as compared to the epidural space.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. All publications and patents specifically mentioned herein are incorporated by reference in their entirety for all purposes including describing and disclosing the chemicals, instruments, statistical analyses and methodologies which are

reported in the publications which might be used in connection with the invention. All references cited in this specification are to be taken as indicative of the level of skill in the art. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

The following paragraphs enumerated consecutively from 1 through 21 provide for various aspects of the present invention. In one embodiment, in a first paragraph (1), the present invention provides a device for administering a therapeutic agent to a subject at a sustained rate over a period of time, the device being shaped, sized and adapted for administering the therapeutic agent into the region of the spinal column of the subject, the device comprising:

1. an elongated first polymeric substrate having a proximal end, a distal end and diameter or width of about 1 mm to about 10 mm and a length of about 4 cm to about 35 cm;

   optionally, an elongated second polymeric substrate positioned within the first polymeric substrate; and

   at least one therapeutic agent, loaded into or onto the first polymeric substrate or second polymeric substrate or both, wherein the therapeutic agent is available for diffusion into the region of the spinal column of the subject.

2. The device of paragraph 1, wherein the first polymeric substrate is in the form of a rod, a tube, a ribbon or rectangle.

3. The device of either of paragraphs 1 or 2, wherein the second polymeric substrate is in the form of a rod, a tube, a ribbon, a rectangle or string.

4. The device of any of paragraphs 1 through 3, wherein the polymers of the first and second polymeric substrate are silicone, polyurethane, polyether urethane, polyether urethane urea, polyamide, polyacetal, polyester, poly(ethylene-chlorotrifluoroethylene), poly tetrafluoroethylene (Teflon), styrene butadiene rubber, polyethylene, polypropylene, polyphenylene oxide-polystyrene, poly-a-chloro-p-xylene, polymethylpentene, polysulfone poly(alpha-hydroxy acids), poly(lactide-co-glycolide) (PLGA), polylactide (PLA), polyglycolide (PLG), polyethylene glycol (PEG), PEG conjugates of poly(alpha-hydroxy acids), polyorthoesters, polyaspirins, polyphosphazenes, vinylpyrrolidone,

polyvinyl alcohol (PVA), PVA-g-PLGA, polyethylene glycol-terephthalate and polybutylene-terephthalate (PEGT-PBT) copolymer(polyactive), methacrylates, poly(N-isopropylacrylamide), polyethylene oxides (as known as polyoxyethylene or PEO), poly-propylene oxide (also known as polyoxypropylene or PPO), poly(aspartic acid) (PAA), PEO-PPO-PEO (Pluronics®, BASF), PEO-PPO-PAA copolymers, PLGA-PEO-PLGA, or mixtures thereof.

5. The device of any of paragraphs 1 through 3, wherein the at least one of the polymers of the first and second polymeric substrate is a shape memory polymer.

6. The device of paragraph 5, wherein the shape memory polymer is oligo(ε-caprolactone)diol and crystallisable oligo(ρ-dioxanone)diol.

7. The device of any of paragraphs 1 through 6, wherein the therapeutic agent is an analgesic.

8. The device of paragraph 7, wherein the analgesic is morphine naloxone, codeine, oxycodone, hydrocodone, diamorphine, pethidine, tramadol, tapentadol, buprenorphine, bupivacaine, bupivacaine (L-isomer), ropivacaine, mupivacaine, lidocaine, capsaicin, clonidine, or mixtures thereof.

9. The device of any of paragraphs 1 through 6, wherein the therapeutic agent is a muscle relaxant.

10. The device of paragraph 9, wherein the muscle relaxant is baclofen, baclofen (L-isomer), midazolam, tizanidine or mixtures thereof.

11. The device of any of paragraphs 1 through 6, wherein the therapeutic agent is an anti-inflammatory.

12. The device of paragraph 11, wherein the anti-inflammatory is hydrocortisone, cortisol, hydroxyltriamcinolone, dexamethasone, dichlorisone, diflorasone diacetate, diflucortolone valerate, fluadrenolone, fluclorolone acetonide, fludrocortisone, flumethasone pivalate, fluocinolone acetonide, fluocinonide, flucortine butylesters, fluocortolone, fluprednidene(fluprednylidene)acetate, flurandrenolone, halcinonide, hydrocortisone acetate, hydrocortisone butyrate, methylprednisolone, triamcinolone acetonide, cortisone, cortodoxone, flucetonide, fludrocortisone, difluorosone diacetate, fluradrenolone, fludrocortisone, diflurosone diacetate, fluocinolone, fluradrenolone acetonide, medrysone, amcinafel, amcinafide, betamethasone and the balance of its esters,

chloroprednisone, chlorprednisone acetate, clocortelone, clescinolone, dichlorisone, diflurprednate, flucloronide, flunisolide, fluoromethalone, fluperolone, fluprednisolone, hydrocortisone valerate, hydrocortisone cyclopentylpropionate, hydrocortamate, meprednisone, paramethasone, prednisolone, prednisone, beclomethasone dipropionate, triamcinolone, acetaminophen, paracetamol, nabumetone, celecoxib, etodolac, nimesulide, apasone, gold, piroxicam, isoxicam, meloxicam, tenoxicam, sudoxicam, aspirin, disalcid, benorylate, trilisate, safapryn, solprin, diflunisal, and fendosal, diclofenac, fenclofenac, indomethacin, sulindac, tolmetin, isoxepac, furofenac, tiopinac, zidometacin, acematacin, fentiazac, zomepirac, clindanac, oxepinac, felbinac, ketorolac, mefenamic, meclofenamic, flufenamic, niflumic, ibuprofen, naproxen, benoxaprofen, flurbiprofen, ketoprofen, fenoprofen, fenbufen, ketorolac, sulfasalazine, indopropfen, pirprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tioxaprofen, suprofen, alminoprofen, tiaprofenic, phenylbutazone, oxyphenbutazone, feprazone, azapropazone, trimethazone or mixtures thereof.

13. The device of any of paragraphs 1 through 12, wherein the therapeutic agent is in or on the first polymeric substrate.

14. The device of any of paragraphs 1 through 12, wherein the therapeutic agent is in or on the second polymeric substrate.

15. The device of any of paragraphs 1 through 12, wherein the device configuration is a tube and the therapeutic agent is contained within a hollow portion of the first polymeric substrate.

16. The device of paragraph 15, wherein the therapeutic agent is in the form of a solid, liquid, paste or gel.

17. The device of paragraph 15, further including end portions to seal the proximal and/or distal ends of the device.

18. A method for administering a therapeutic agent to a subject comprising the steps of:

implanting in the spinal column region of the subject the device of any of paragraphs 1 through 17; and

releasing an effective amount of the therapeutic agent over time from one of the polymeric substrates to the subject.

19. The method of paragraph 18, wherein the device is delivered to the subject's spinal region via an epidural, peridural or intrathecal route.

20. The method of paragraph 18, wherein the target site is within the subject's spinal region between Co1 and L1.

21. The method of paragraph 18, wherein the target site is within the subject's spinal region between S5 and L1.

22. The method of paragraph 18, wherein the target site is within the subject's spinal region between S5 and T10.

21. The method of paragraph 16, wherein the target site is the spinal region accessible through the sacral hiatus or one of the sacral foramina.

The invention will be further described with reference to the following non-limiting Examples. It will be apparent to those skilled in the art that many changes can be made in the embodiments described without departing from the scope of the present invention. Thus the scope of the present invention should not be limited to the embodiments described in this application, but only by embodiments described by the language of the claims and the equivalents of those embodiments. Unless otherwise indicated, all percentages are by weight.

Figure 1 provides a method of delivery of one embodiment of the invention. First an epidural needle 4 is placed appropriately using standard clinical procedure. Then a stylet 2 (of appropriate stiffness, straight or curved) is introduced into the central lumen of the device 6. The stylet-device tandem is then advanced through the epidural needle 4 in a cephalad direction. Since the stylet 2 is longer than the device 6, it can be used to advance the device 6 to a desired location. Once final positioning is achieved and verified via fluoroscopy (via the metal stylet), the stylet 2 can be withdrawn without affecting the position of the implant 6. Finally the epidural needle 4 is removed.

As shown in Figure 1, the procedure can be repeated as necessary to deliver multiple devices to target site(s). (Figure 1 shows a second device 8 already implanted via a prior procedure.)

Although the present invention has been described with reference to preferred embodiments, persons skilled in the art will recognize that changes may be made in form and detail without departing from the spirit and scope of the invention. All references cited throughout the specification, including those in the background, are incorporated herein in their entirety. Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to specific embodiments of the invention described specifically herein. Such equivalents are intended to be encompassed in the scope of the following claims.

CLAIMS

What is claimed is:

1. A device for administering a therapeutic agent to a subject at a sustained rate over a period of time, the device being shaped, sized and adapted for administering the therapeutic agent into the region of the spinal column of the subject, the device comprising:
an elongated first polymeric substrate having a proximal end, a distal end and diameter or width of about 1 mm to about 10 mm and a length of about 4 cm to about 35 cm;
optionally, an elongated second polymeric substrate positioned within the first polymeric substrate; and
at least one therapeutic agent, loaded into or onto the first polymeric substrate or second polymeric substrate or both, wherein the therapeutic agent is available for diffusion into the region of the spinal column of the subject.

2. The device of claim 1, wherein the first polymeric substrate is in the form of a rod, a tube, a ribbon or rectangle.

3. The device of either of claims 1 or 2, wherein the second polymeric substrate is in the form of a rod, a tube, a ribbon, a rectangle or string.

4. The device of any of claims 1 through 3, wherein the polymers of the first and second polymeric substrate are silicone, polyurethane, polyether urethane, polyether urethane urea, polyamide, polyacetal, polyester, poly(ethylene-chlorotrifluoroethylene), poly tetrafluoroethylene (Teflon), styrene butadiene rubber, polyethylene, polypropylene, polyphenylene oxide-polystyrene, poly-a-chloro-p-xylene, polymethylpentene, polysulfone poly(alpha-hydroxy acids), poly(lactide-co-glycolide) (PLGA), polylactide (PLA), polyglycolide (PLG), polyethylene glycol (PEG), PEG conjugates of poly(alpha-hydroxy acids), polyorthoesters, polyaspirins, polyphosphazenes, vinylpyrrolidone, polyvinyl

alcohol (PVA), PVA-g-PLGA, polyethylene glycol-terephthalate and polybutylene-terephthalate (PEGT-PBT) copolymer(polyactive), methacrylates, poly(N-isopropylacrylamide), polyethylene oxides (as known as polyoxyethylene or PEO), poly-propylene oxide (also known as polyoxypropylene or PPO), poly(aspartic acid) (PAA), PEO-PPO-PEO (Pluronics®, BASF), PEO-PPO-PAA copolymers, PLGA-PEO-PLGA, or mixtures thereof.

5. The device of any of claims 1 through 3, wherein the at least one of the polymers of the first and second polymeric substrate is a shape memory polymer.

6. The device of claim 5, wherein the shape memory polymer is oligo(ε-caprolactone)diol and crystallisable oligo(ρ-dioxanone)diol.

7. The device of any of claims 1 through 6, wherein the therapeutic agent is an analgesic.

8. The device of claim 7, wherein the analgesic is morphine naloxone, codeine, oxycodone, hydrocodone, diamorphine, pethidine, tramadol, tapentadol, buprenorphine, bupivacaine, bupivacaine (L-isomer), ropivacaine, mupivacaine, lidocaine, capsaicin, clonidine, or mixtures thereof.

9. The device of any of claims 1 through 6, wherein the therapeutic agent is a muscle relaxant.

10. The device of claim 9, wherein the muscle relaxant is baclofen, baclofen (L-isomer), midazolam, tizanidine or mixtures thereof.

11. The device of any of claims 1 through 6, wherein the therapeutic agent is an anti-inflammatory.

12. The device of claim 11, wherein the anti-inflammatory is hydrocortisone, cortisol, hydroxyltriamcinolone, dexamethasone, dichlorisone, diflorasone diacetate, diflucortolone valerate, fluadrenolone, fluclorolone acetonide, fludrocortisone, flumethasone pivalate, fluocinolone acetonide, fluocinonide, flucortine butylesters, fluocortolone, fluprednidene(fluprednylidene)acetate, flurandrenolone, halcinonide, hydrocortisone acetate, hydrocortisone butyrate, methylprednisolone, triamcinolone acetonide, cortisone, cortodoxone, flucetonide, fludrocortisone, difluorosone diacetate, fluradrenolone, fludrocortisone, diflurosone diacetate, fluocinolone, fluradrenolone acetonide, medrysone, amcinafel, amcinafide, betamethasone and the balance of its esters, chloroprednisone, chlorprednisone acetate, clocortelone, clescinolone, dichlorisone, diflurprednate, flucloronide, flunisolide, fluoromethalone, fluperolone, fluprednisolone, hydrocortisone valerate, hydrocortisone cyclopentylpropionate, hydrocortamate, meprednisone, paramethasone, prednisolone, prednisone, beclomethasone dipropionate, triamcinolone, acetaminophen, paracetamol, nabumetone, celecoxib, etodolac, nimesulide, apasone, gold, piroxicam, isoxicam, meloxicam, tenoxicam, sudoxicam, aspirin, disalcid, benorylate, trilisate, safapryn, solprin, diflunisal, and fendosal, diclofenac, fenclofenac, indomethacin, sulindac, tolmetin, isoxepac, furofenac, tiopinac, zidometacin, acematacin, fentiazac, zomepirac, clindanac, oxepinac, felbinac, ketorolac, mefenamic, meclofenamic, flufenamic, niflumic, ibuprofen, naproxen, benoxaprofen, flurbiprofen, ketoprofen, fenoprofen, fenbufen, ketorolac, sulfasalazine, indopropfen, pirprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tioxaprofen, suprofen, alminoprofen, tiaprofenic, phenylbutazone, oxyphenbutazone, feprazone, azapropazone, trimethazone or mixtures thereof.

13. The device of any of claims 1 through 12, wherein the therapeutic agent is in or on the first polymeric substrate.

14. The device of any of claims 1 through 12, wherein the therapeutic agent is in or on the second polymeric substrate.

15. The device of any of claims 1 through 12, wherein the device configuration is a tube and the therapeutic agent is contained within a hollow portion of the first polymeric substrate.

16. The device of claim 15, wherein the therapeutic agent is in the form of a solid, liquid, paste or gel.

17. The device of claim 15, further including end portions to seal the proximal and/or distal ends of the device.

18. A method for administering a therapeutic agent to a subject comprising the steps of:

implanting in the spinal column region of the subject the device of any of claims 1 through 17; and

releasing an effective amount of the therapeutic agent over time from one of the polymeric substrates to the subject.

19. The method of claim 18, wherein the device is delivered to the subject's spinal region via an epidural, peridural or intrathecal route.

20. The method of claim 18, wherein the target site is within the subject's spinal region between Co1 and L1.

21. The method of claim 18, wherein the target site is within the subject's spinal region between S5 and L1.

22. The method of claim 18, wherein the target site is within the subject's spinal region between S5 and T10.

23. The method of claim 16, wherein the target site is the spinal region accessible through the sacral hiatus or one of the sacral foramina.

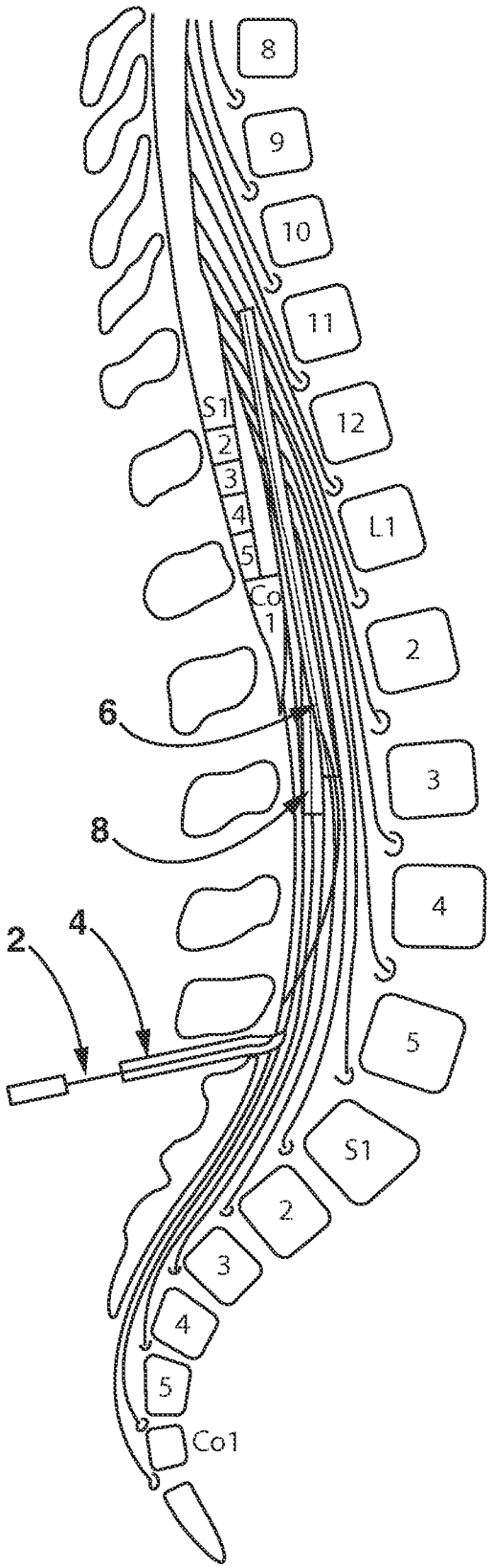

FIG. 1