

INJECTABLE MICROPARTICLES FOR HYPER-LOCALIZED RELEASE OF THERAPEUTIC AGENTS

CROSS REFERENCE TO RELATED APPLICATION

This application claims the benefit under 35 U.S.C. § 119(e) to
5 U.S. Provisional Application No. 62/052,959, filed September 19, 2014, which
application is hereby incorporated by reference in its entirety.

BACKGROUND

Technical Field

This disclosure relates to an injectable sustained release
10 composition comprising drug-loaded microparticles and a method of delivering
the same.

Description of the Related Art

Drug-loaded microparticles have been used for sustained release
of therapeutic agents. However, truly localized release is difficult to achieve
15 and burst release remains as one of the main factors to cause undesirable
systemic side effects. Accordingly, there is a medical need to not only extend
the local duration of action of the therapeutic agent, but to effectively reduce the
systemic side effects associated with that administration.

BRIEF SUMMARY

20 Described herein are pharmaceutical compositions, injectable
dosage forms and method of using the same for treating or managing pain,
infection, malignancy, in a body compartment, such as a joint space, an
epidural space, a vitreous body of an eye, a surgically created space, an
intracranial space or a space adjacent to an implant surgical site, or a solid
25 tumor.

The present disclosure provides a membrane based, diffusion-
driven release mechanism with drug particle sizing large enough to allow high
drug loading, but small enough to be injected.

As provided herein, a “drug” or “therapeutic agent” is coated with a semi-permeable polymeric shell and injected into a body compartment. Water then diffuses through the polymer and dissolves the drug core (D) creating a saturated solution inside the membrane (C) and essentially sink
5 conditions outside the particle (c). This concentration gradient drives a constant (zero order) release of drug from the drug particle as long as there is some drug core remaining to maintain a saturated solution. The period of release can be tuned by altering the permeability of the polymer coating.

The present disclosure further relates to using local anesthetics
10 (amides) for the purpose above focusing on subarachnoid block (primarily in palliative cancer pain); extradural blockade (palliative care); and nerve plexus blockade (i.e. Brachial Plexus) for analgesia, anesthesia, limb and digit grafting to improve blood flow, vascular procedures for same.

The present disclosure further relates to injection of therapeutic
15 agents (e.g., CNS modulators focused on GABA receptors) locally in the area of nerve damage, including intracranial injection and possibly also subcutaneous injection.

The present disclosure further relates to injection for systemic delivery (subcutaneously) and for local application (bonded to &/or applied with)
20 with implants (pacemakers, defibrillators, orthopedic implants, artificial hearts) of one or more antibiotics, and near or at a surgical site.

The present disclosure further relates to local delivery of powerful chemotherapeutic agents and hormones given for the treatment of malignancy.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

25 The following figures set forth embodiments in which like reference numerals denote like parts. Embodiments are illustrated by way of example and not by way of limitation in all of the accompanying figures wherein:

Figure 1 shows schematically a microparticle of core/shell morphology.

Figure 2 shows the *in vitro* release profiles of fluticasone propionate as uncoated powder, uncoated crystal and coated crystal.

Figure 3A shows the release profiles of fluticasone propionate microparticles having undergone heat-treatment at various temperatures.

5 Figure 3B shows the release half-lives of fluticasone propionate microparticles having undergone heat-treatment at various temperatures.

Figure 4A and 4B show the particle size distribution of the fluticasone propionate microparticles as compared to particle size distribution of triamcinolone hexacetonide (TA) (Kenalog™).

10 Figure 5 is a graph showing the relative amounts of fluticasone propionate and PVA in microparticles by ¹HNMR analysis.

Figure 6 is a graph showing dissolution profiles of triamcinolone hexacetonide (TA) as compared to sustained release (SR) formulations of fluticasone propionate (FP) according to embodiments of this disclosure.

15 Figure 7 is a graph showing plasma fluticasone (FP) levels, synovial fluid FP levels after injection of 20 mg formulation into knee joint of sheep as compared to intra-articular pharmacokinetics of triamcinolone hexacetonide (40mg) from human subjects.

20 Figures 8A, 8B and 8C demonstrate the results of a histological examination of the injected joints of sheep showing no abnormalities.

Figure 9 shows the local concentrations in tissue and synovial fluid of knee joints of dogs for a period of 60 days following a single injection of a low dose fluticasone propionate. The plasma concentrations were too low to detect.

25 Figure 10 shows the local concentrations in tissue and synovial fluid of knee joints of dogs, as well as the plasma concentrations, for a period of 60 days following a single injection of a high dose fluticasone propionate.

30 Figure 11 shows the plasma concentrations of fluticasone propionate following injections to the knee joints of sheep as compared to those of dogs. The microparticles for each injection had undergone different heat-treatments prior to being formulated into injectable compositions.

Figure 12 shows the plasma concentrations of fluticasone propionate in the knee joints of dogs over a period of 45 hours following a single injection. The pharmacokinetic (PK) curve indicates a lack of initial burst.

DETAILED DESCRIPTION

5 Described herein are pharmaceutical compositions, injectable dosage forms and method of using the same for treating or managing local inflammation, pain (including post-surgery pain), infection, malignancy, in a body compartment, such as a joint space, an epidural space, a vitreous body of an eye, a surgically created space, an intracranial space or a space adjacent to
10 an implant, a surgical site or a solid tumor.

The pharmaceutical composition includes a plurality of microparticles in core/shell morphology. In particular, the microparticle includes a crystalline drug core of a therapeutic agent and a polymeric shell encapsulating the crystalline drug core. As discussed in further detail herein,
15 the injectable microparticles are characterized with high drug-loading, narrow size distribution and a sustained release profile of pseudo zero-order release over a certain period within a body compartment, as defined herein, or subcutaneously. The release periods depend on the affliction or the corresponding therapeutic agent. Therapeutic agents for pain management
20 may be released during a period of 2-12 months, whereas antibiotics may be released during a period of 3-7 days.

The sustained release delivery mechanism is based on dissolution. While not wishing to be bound by any specific mechanism of action, it has been found that when the drug particles coated with semi-
25 permeable polymeric shells are injected into a body compartment, water from the body compartment diffuses through the polymeric shell and partially dissolves the crystal drug core. As a result, a saturated solution of the drug is formed inside the polymeric shell. Since there are essentially sink conditions in the fluid (e.g., synovia when the body compartment is a joint) in which the
30 microparticles are injected and reside, a concentration gradient is created which continuously drives the drug out of the microparticles and into the surrounding

fluid. As long as there is some drug core remaining to maintain a saturated solution within the polymeric shell, a constant (*i.e.*, zero order or pseudo-zero order) release of the drug from the coated microparticles is obtained.

Also disclosed herein is a method for reducing or managing pain, *e.g.* due to surgical pain, chronic pain or neuropathic pain, by administering an injectable dosage form to a body compartment. Advantageously, the release is highly localized within the local tissue or fluid medium of the body compartment to ensure a long-acting local therapeutic level, while maintaining a low or undetectable systemic level of the therapeutic agent.

10 Definitions

The articles “a” and “an” are used herein to refer to one or to more than one (*i.e.*, to at least one) of the grammatical object of the article. By way of example, “an element” means one element or more than one element.

The term “plurality” means “two or more”, unless expressly specified otherwise. For example, “plurality” may simply refer to a multiplicity of microparticles (two or more) or an entire population of microparticles in a given composition or dosage form, *e.g.*, for purpose of calculating the size distribution of the microparticles.

As used herein, unless specifically indicated otherwise, the word “or” means “either/or,” but is not limited to “either/or.” Instead, “or” may also mean “and/or.”

As used herein, the term “therapeutic agent” and “drug” are used interchangeable and refer to any agent that can produce a therapeutic effect or benefit. When used with respect to a therapeutic agent or a drug (*e.g.*, a chemotherapy agent), the terms “sustained release” or “extended release” are used interchangeably. Sustained release refers to continuously releasing the therapeutic agent over an extended period of time after administration of a single dose, thus providing a prolonged therapeutic effect throughout the release period.

“Sustained release” is in contrast to a bolus type administration in which the entire amount of the active agent/substance is made biologically

available at one time. Nevertheless, "sustained release" may include an initial faster release followed by a longer, extended period of slower release. As discussed in further detail below, the construction of the microparticles makes it possible to minimize the initial faster release (*e.g.*, a burst release) and prolong
5 the extended release period to achieve a profile of near constant release that is irrespective of the drug concentration (*i.e.*, a zero-order or pseudo zero-order release).

Not all non-zero release is within the meaning of "sustained release." Rather, "sustained release" should provide at least a minimum
10 therapeutically effective amount (as defined herein) of the therapeutic agent during the release period. It should be understood that the minimum therapeutically effective amount of the therapeutic agent depends on the severity of afflictions to be addressed.

"Sustained release period" refers to the entire period of release
15 during which a local concentration of the therapeutic agent is maintained at or above a minimum therapeutically effective amount. The desired sustained-release period can, of course, vary with the disease or condition being treated, the nature of the therapeutic agent, and the condition of the particular patient to be treated. Thus, the desired sustained-release period can be determined by
20 the attending physician.

"Local concentration" refers to the concentration of the drug within a body compartment (as defined herein), including the concentration in the tissue or fluid of the body compartment.

"Plasma concentration" refers to the concentration of the drug in
25 the plasma or serum. The injectable microparticles are capable of hyper-localized release during a prolonged period while maintaining a low plasma concentration, *e.g.*, sufficiently low to minimize undesirable systemic side effects during the sustained release period.

Within the scope of the present disclosure, sustained release of
30 the therapeutic agent is achieved due to the unique structure of the microparticles, which are in core/shell morphology. In particular, a crystalline

drug core of a therapeutic agent is encapsulated by a polymeric shell composed of one or more polymeric coatings, each permeable to the therapeutic agent. In a preferred embodiment, all layers comprise the same polymer. In other embodiments, two to four layers of the polymer are coated on
5 the therapeutic agent, with each layer incrementally slowing the release of the active ingredient and collectively providing the desired sustained release. Furthermore, sustained release of the therapeutic agent is achieved by tailoring this delivery platform to the aqueous or sink environment of the body compartment.

10 As used herein, a “patient,” or “subject,” to be treated by the methods according to various embodiments may mean either a human or a non-human animal, such as primates, mammals, and vertebrates.

The phrase “therapeutically effective amount” refers to an amount of a *therapeutic agent* that, when delivered to a body compartment in the form
15 of the coated microparticles as defined herein, produces a degree of reduced symptoms in the body compartment in a patient (at a reasonable benefit/risk ratio applicable to any medical treatment). The effective amount of the therapeutic agent may vary depending on such factors as the type and severity of arthritis being treated, its advancement, the degree of pain to which patient is
20 subject, the particular microparticle being administered, the active agent and/or the size/age/gender of the subject. One of ordinary skill in the art may empirically determine the effective amount of a particular therapeutic agent according to known methods in the art. Unless specified otherwise, “therapeutically effective amount” refers to the amount of the therapeutic agent
25 localized within the body compartment.

“Minimum therapeutically effective amount” is the least amount of the therapeutic agent that is capable of producing a therapeutic effect (*e.g.*, pain reduction or anti-inflammation).

“EC50” is the concentration of the therapeutic agent that provides
30 50% of the maximal effect, *e.g.*, in reducing pain.

“Unit dosage form” refers to physically discrete units (*e.g.*, loaded syringe cylinders) suitable as unitary dosages for human subjects, each unit containing a predetermined quantity of the therapeutic agent in association with a pharmaceutical acceptable vehicle. The quantity of the therapeutic agent is
5 calculated to produce the desired therapeutic effect for a desired period of time.

The term “treating” is art-recognized and includes treating the disease or condition by ameliorating at least one symptom of the particular disease or condition, even if the underlying pathophysiology is not affected.

“Body compartment” refers to a space or cavity within the body of
10 a vertebrate (including human) that is accessible by injection. Typically, the body compartment is at least semi-enclosed or fully enclosed by hard or soft tissue (*e.g.*, bones, membranes, ligamentous structure) that defines the space. Soft tissue is typically present and may have various degrees of vascularization. The body compartment typically contains a fluid, such as the
15 synovial fluid in the joints, spinal fluid in the epidural and the vitreous humour in the vitreous body of the eye. The fluid may or may not communicate with the outside of the body compartment. More specifically, the body compartment may be naturally occurring anatomical space such as a synovial joint, an epidural space or a vitreous body of an eye. In addition, the body compartment
20 may also be a surgically created space (*e.g.*, a pocket for inserting an implanted device, soft tissue implant such as breast implant, and the like) or any space near the implant that can be accessed through injection. The body compartment may also be a space near a tumor, in particular, a solid tumor. The body compartment may also be an intracranial space. The body
25 compartment may also be a site near or at a surgical site.

The term “synovial joint” refers to a moveable articulation of two or more bones. The articulation is defined by a synovial cavity, which contains a volume of synovial fluid, is lined with a synovial membrane, and is surrounded by a fibrous capsule. The opposing bone surfaces are each covered with a
30 layer of cartilage. The cartilage and synovial fluid reduce friction between the articulating bone surfaces and enable smooth movements. Synovial joints can

be further distinguished by their shape, which controls the movements they allow. For example, hinge joints act like the hinge on a door, allowing flexion and extension in just one plane. An example is the elbow between the humerus and the ulna. Ball and socket joints, such as the hip, allow movement
5 in several planes simultaneously. Condylod (or ellipsoid) joints, such as the knee, permit motion in more than one plane in some positions but not others. For example, no rotation is possible in the extended knee, but some rotation is possible when the knee is flexed. Pivot joints, such as the elbow (between the radius and the ulna), allow one bone to rotate around another. Saddle joints,
10 such as at the thumb (between the metacarpal and carpal) are so named because of their saddle shape, and allow movement in a variety of directions. Finally, gliding joints, such as in the carpals of the wrist, allow a wide variety of movement, but not much distance.

Synovial joints include, but are not limited to, shoulder
15 (glenohumeral and acromioclavicular), elbow (ulno-humeral, radio-capitellar and proximal radioulnar), forearm (radioulnar, radiocarpal, ulnocarpal), wrist (distal radioulnar, radio-carpal, ulno-carpal, mid carpal), hand (carpo-metacarpal, metocarpophalangeal, interphalangeal), spine (intervertebral), hip, knee, ankle (tibiotalar, tibiofibular), and foot (talocalcaneal, talonavicular,
20 intertarsal, tarso-metatarsal, metatarsal-phalangeal, interphalangeal).

“Intra-ocular” and “intravitreous” are used herein interchangeably to mean within the vitreous humour of the eye.

As used herein, the term “microparticle” means a particle having mean dimension less than 1 mm. Although the microparticles are substantially
25 spherical in some embodiments, the microparticles can be any solid geometric shape which is not inconsistent with the principles of the disclosure, including, without limitation, needles, ellipsoids, cylinders, polyhedrons and irregular shapes.

Microparticles are coated drug particles, which may be crystalline,
30 polycrystalline, or amorphous. As used herein, a microparticle has a “core/shell” morphology, shown schematically in Figure 1, in which the drug

core (10) is encapsulated by a polymeric shell (20), the polymeric shell may include one or more thin coatings of the same or different polymers (two coatings, 25 and 30, are shown). Importantly, the polymeric shell (20) is formed of polymer coatings that are not miscible with the drug core, thus, the interface
5 (40) between the drug core and the polymeric shell is sharp with minimal amounts of drug or polymer (e.g., less than 5%, or less than 1% or less than 0.5% of the total weight of either the drug or polymer shall be mixed). If the drug core contains a highly hydrophobic drug, the polymeric shell preferably includes at least one hydrophilic polymer. Conversely, if the drug core contains
10 a highly hydrophilic drug, the polymeric shell preferably includes at least one hydrophobic polymer. Although the polymeric shell may be ultimately degraded, it should maintain its structural integrity throughout the sustained release period, thus retaining an environment for the dissolving drug core to form a saturated solution.

15 As used herein, the terms “core particle,” and “drug core” interchangeably refer to a pre-formed particle that could be a single crystal or multiple crystals, or amorphous particle of the drug. The drug core is encapsulated by a polymeric shell. The core particle can further comprise other compounds, including, without limitation, binders, buffers, antioxidants,
20 excipients, and additional active pharmaceutical ingredients. The core particle can be a single large crystal, a multiplicity of crystals, or mixtures of the above. In a preferred embodiment, the drug core is substantially pure drug (*i.e.*, at least 90%, or at least 95% or at least 98% of the entire weight of the drug core is the drug). In a preferred embodiment, the drug core is 100% crystalline drug.

25 As used herein, “polymeric shell” includes one or more polymeric coatings. “Polymeric coating” means a thin layer of linear, branched or cross-linked macromolecules that has a continuous surface surrounding the crystalline drug core. Referring to Figure 1, the polymeric coatings (25 and 30) are sequentially and concentrically coated on the drug core (20). Although the
30 drug core (20) and the immediate adjacent polymeric coating (25) should be immiscible, the polymeric coatings (25 and 30) themselves may be in intimate

contact with each other, allowing for certain degrees of miscibility at the interface (50) between adjacent coatings in order to form a polymeric shell (20) of a cohesive structure that affords structural integrity during the sustained release period. The polymeric shell must substantially surround or envelope
5 the core particles.

“Coating solution” refers to a solution of pre-formed polymers (e.g., commercially available polymers) and is suitable for coating the drug core according to known methods of the art, e.g. fluidized bed coating.

As used herein, the term “permeable” means allowing the
10 passage of molecules of the therapeutic agent by diffusion but not by fluid flow.

As used herein, the term “semi-permeable” means permeable to some molecules but not to others. As used herein, semi-permeable polymeric shell are permeable to at least water and the therapeutic agent within the coated microparticles of the disclosure.

15 “Dissolution half-life” is an *in vitro* measurement of the dissolution characteristics of the microparticles. Specifically, the dissolution half-life is the amount of time that is taken for half of the original loading of the drug in the microparticles to dissolve and release into a dissolution medium under a specific set of dissolution conditions. Although carried out *in vitro*, the
20 dissolution half-life is nevertheless an art-recognized factor to consider in predicting *in vivo* release characteristics and can represent an accelerated model of the sustained release behavior *in vivo*. In particular, dissolution half-life provides a qualitative tool for predicting *in vivo* behaviors by comparing the dissolutions half-lives of various formulations. For instance, formulations that
25 exhibit a longer dissolution half-life *in vitro* are expected to exhibit a longer sustained release period *in vivo*. Unless specified otherwise, the dissolution system used for measuring dissolution half-life the microparticles is USP Type II (paddle).

“Dissolution profile” is a graphic representation of the percentage
30 dissolution as measured by time. Besides providing quantitatively the dissolution amount as a function of time, the curvature of the profile qualitatively

shows the extent of the initial burst. For example, a sharp rise in the curvature indicates a faster initial release (burst) when compared with a gentler rise.

“Vehicle” refers to a non-toxic carrier, adjuvant, or solvent into which the microparticles are suspended. The vehicle does not alter or destroy the pharmacological activity of the therapeutic agent with which it is formulated. Pharmaceutically acceptable carriers or vehicles that may be used in the compositions include, but are not limited to, water, physiological saline, hyaluronic acid, and the like. As used herein, the term “biocompatible” means characterized by not causing a toxic, injurious or immunological response when brought into contact with living tissue, particularly human or other mammalian tissue.

As used herein, the term “biodegradable” means capable of partially or completely dissolving or decomposing in living tissue, particularly human or other mammalian tissue. Biodegradable compounds can be degraded by any mechanism, including, without limitation, hydrolysis, catalysis and enzymatic action.

As used herein with respect to polymeric coatings, the term “substantially degraded” means degraded to the degree that approximately 50% of the chemical bonds resulting from polymerization of the polymer-forming solution to form the polymeric coating have been broken.

As used herein with respect to the polymeric shell of the disclosure, the term “structural integrity” means retaining a continuous surface which is semi-permeable and permits diffusion, but does not include any discontinuities which permit fluid flow.

As used herein, the term “external environment” means the local area or region of tissue surrounding the coated microparticles of the disclosure after direct injection into the body compartment.

As used herein, the term “saturated” means containing the maximum concentration of a solute (e.g., an active pharmaceutical ingredient) that can be dissolved at a given temperature.

As used herein, the term “substantially insoluble” means having a solubility of less than 1 part solute per 1000 parts solvent by weight.

As used herein, the term “hydrophobic” means having lower affinity for an aqueous solvent than an organic solvent.

5 As used herein, the term “hydrophilic” means having lower affinity for an organic solvent than an aqueous solvent.

As used herein, term “pseudo-zero-order kinetics” means sustained-release of the therapeutic agent which exhibits kinetics which is zero-order (*i.e.*, independent of concentration) or between zero-order and first-order
10 (*i.e.*, proportional to concentration) kinetics over the sustained-release period, where the concentration is based on the total amount of the active pharmaceutical ingredient contained within the coated microparticles. In some embodiments, the release of the active pharmaceutical ingredient exhibits kinetics which more closely approximate zero-order than first-order kinetics.

15 As used herein, the recitation of a numerical range for a variable is intended to convey that the disclosure may be practiced with the variable equal to any of the values within that range. Thus, for a variable which is inherently discrete, the variable can be equal to any integer value within the numerical range, including the end-points of the range. Similarly, for a variable
20 which is inherently continuous, the variable can be equal to any real value within the numerical range, including the end-points of the range. As an example, and without limitation, a variable which is described as having values between 0 and 2 can take the values 0, 1 or 2 if the variable is inherently discrete, and can take the values 0.0, 0.1, 0.01, 0.001, or any other real values
25 ≥ 0 and ≤ 2 if the variable is inherently continuous.

Microparticles

The microparticles of the core/shell morphology described herein are constructed to exhibit a sustained release profile uniquely suited for highly localized, extended delivery of a therapeutic agent within a body compartment.
30 In particular, the microparticle includes (1) a drug core of more than 70% by weight of the microparticle, wherein the drug core includes one or more

therapeutic agent; and (2) a polymeric shell encapsulating the drug core, whereby the polymeric shell is in contact but immiscible with the crystalline drug core.

The *in vivo* sustained release profile is correlatable to the *in vitro* dissolution characteristics of the microparticles, which in turn are determined by, among others, the solubility of the drug core, the permeability, the level of crosslinking and the rate of degradation of the polymeric shell.

Drug Core

The drug core may comprise one or more therapeutic agents in any one of the following classes. In preferred embodiments, the drug core is pure drug, as defined herein.

i. Local Anesthetics

In some embodiments, the therapeutic agent may be one or more local anesthetics (amides) for subarachnoid block (primarily in palliative Cancer pain); extradural blockade (palliative care); and nerve plexus blockade (i.e. Brachial Plexus), or for analgesia, anesthesia, limb and digit grafting to improve blood flow, vascular procedures for same.

Specifically, the therapeutic agent may be Lidocaine, Bupivacaine and Ropivacaine. Other amine-containing "caine" type drugs include, for example, centbucridine, tetracaine, Novocaine® (procaine), ambucaine, amolanone, amylcaine, benoxinate, betoxycaine, carticaine, chloroprocaine, cocaethylene, cyclomethycaine, butethamine, butoxycaine, carticaine, dibucaine, dimethisoquin, dimethocaine, diperodon, dyclonine, ecogonidine, ecognine, euprocin, fenalcomine, formocaine, hexylcaine, hydroxytetracaine, leucinocaine, levoadrol, metabutoxycaine, myrtecaine, butamben, bupivacaine, mepivacaine, beta-adrenoceptor antagonists, opioid analgesics, butanilcaine, ethyl aminobenzoate, fomocine, hydroxyprocaine, isobutyl p-aminobenzoate, naepaine, octacaine, orthocaine, oxethazaine, parenthoxycaine, phenacine, piperocaine, polidocanol, pramoxine, prilocalne, propanocaine, proparacaine, propipocaine, pseudococaine, pyrrocaine, salicyl alcohol, parethyoxycaine,

piridocaine, risocaine, tolycaine, trimecaine, tetracaine, anticonvulsants, antihistamines, articaine, cocaine, procaine, amethocaine, chloroprocaine, marcaine, chloroprocaine, etidocaine, prilocaine, lignocaine, benzocaine, zolamine, ropivacaine, dibucaine, as pharmaceutically acceptable salt thereof,
5 or mixtures thereof.

ii. Central Nerve System (CNS) Agents

CNS medication may be administered locally in the area of nerve damage and possibly also subcutaneously. Suitable CNS agents are CNS modulators focused on GABA receptors. In specific embodiments, the CNS
10 agents may be Gabapentin, Pregabalin (Lyrica), Topiramate (Topamax), Valproic Acid (Valproate) or Oxcarbazepine. The CNS drugs may also be a neurotransmitter, such as dopamine, a dopamine agonist or a dopamine precursor (e.g., L-3,4-dihydroxyphenylalanine).

iii. Antibiotics

15 Antibiotics may be administered systemically (subcutaneously) or locally, for example, bonded to &/or applied with implants such as Pacemakers, Defibrillators, Orthopedic implants, artificial hearts and the like.

Specific antibiotics may be: beta-lactam antibiotics such as cephalosporins, including, first generation cephalosprins such as Cafazolin,
20 Cephalexin; second generation cephalosprins such as Cefuroxime, Cefoxitin, Cefprozil, and third generation cephalosprins such as Cefixime, Ceftazidime, Ceftriaxone and Cefotaxime.

Additional examples of antibiotics include the Penicillin class and combinations including the same, such as Piperacillin and Tazobactam.

25 iv. Chemotherapeutic or Anti-tumor Agents

In some embodiments, the present disclosure provides local delivery of powerful chemotherapeutic agents and hormones given for the treatment of malignancy. The hyper-localized delivery of drug into capsule maximizes effect and minimizes any side effects.

Any existing therapies for the malignancy can be formulated into the drug/shell structures for localized release. The types of tumors and locales for malignancies include, for example, prostate cancer medications (e.g., anti-androgen therapy and chemotherapeutics); brain tumor medications (e.g. 5 steroids and chemotherapeutics particularly for discrete tumours in the brain whether benign or malignant); ovarian cancer medications; spinal tumor medications; and osteosarcoma medication.

The crystalline drug core may also be for example a corticosteroid drug, which is shown to exhibit pseudo-zero order localized release with 10 minimal systemic concentration. The preparation, release behaviors and characteristics are described in PCT/US2014/031502, which application is incorporated herein in its entirety.

As the preferred system is for formulating therapeutic agent, and as this is a "dissolution based delivery system," therapeutic agents of relative 15 low solubility are preferred.

In general, the crystalline form of a given therapeutic agent has even lower solubility than the amorphous form of the same drug, resulting in a longer dissolution half-life and less initial burst. Accordingly, the drug core may be a single large crystal or an aggregation of multiple small crystals. Crystalline 20 drug core coated with a polymeric shell further extends the period of dissolution and further minimizes any initial burst.

The therapeutic agents are used in amounts that are therapeutically effective, which varies widely depending largely on the particular agent being used. The amount of agent incorporated into the composition also 25 depends upon the desired release profile, the concentration of the agent required for a biological effect, and the length of time that the biologically active substance has to be released for treatment.

There is no critical upper limit on the amount of therapeutic agent incorporated except for that of an acceptable solution or dispersion viscosity to 30 maintain the physical characteristics desired for the composition. The lower limit of the agent incorporated into the polymer system is dependent upon the

activity of the therapeutic agent and the length of time needed for treatment. Thus, the amount of the therapeutic agent should not be so small that it fails to produce the desired physiological effect, nor so large that it is released in an uncontrollable manner.

5 A key advantage of the injectable microparticles lies in the much higher drug loading than previously known drug-loaded microparticles. In other words, each microparticle has a comparatively and significantly smaller fraction as the polymeric shell, and a comparatively and significantly greater fraction as the drug core.

10 Moreover, the drug core is substantially pure drug as the drug core is prepared from recrystallized drug in the form of either a single large crystal or an aggregate of smaller crystals. Thus, "substantially pure" means at least 90%, or at least 95% or at least 98%, or 100% of the entire weight of the drug core is the drug in a crystalline form.

15 Thus, in various embodiments, in each microparticle, 70-97% of the total weight of microparticle is the therapeutic agent and 3-30% is polymer. In one embodiment, the drug core is more than 70% of the total weight of the microparticle and less than 30% of the total weight of the microparticle is the polymeric shell. In other embodiments, the drug core is more than 75%, more
20 than 80%, more than 85%, more than 90% or more than 95% of the total weight of the microparticle, with the remainder of the microparticle being the polymeric shell.

Polymeric Shell

 The polymeric shell comprises one or more concentrically or
25 consecutively coated polymeric coatings of the same or different polymers. Standard biocompatible and biodegradable polymeric coatings known in the art can be employed to the extent that they meet the requirements described above with respect to retaining permeability and/or structural integrity during the desired sustained-release period. While the sustained release period is
30 enhanced within the scope of the disclosure via higher drug loading and the beneficial and unexpected interaction of the body compartment and the

dissolution-based delivery system described herein, there are additional factors at play supporting the superior efficacy of the method herein including, but not limited to:

- the degree of solubility of the therapeutic agent
- 5 • the size of the core particle and/or the amount of the therapeutic agent initially present in the core particle
- the presence of other compounds within the core particle that affect the rate of release of the therapeutic agent
- the permeability of the polymeric coating(s) to the therapeutic
- 10 agent
- the rate of degradation of the polymeric coating(s), as well as other factors.

As is known in the art, both the permeability and biodegradability of polymeric coatings can be affected by the choice of polymeric material (*e.g.*,
 15 degree of hydrophobicity or hydrophilicity relative to the therapeutic agent; degree of lability of bonds under physiological conditions), degree of cross-linking and thickness. For co-polymers, the ratio of the different monomers also can be varied to affect permeability and biodegradability.

In preferred embodiments, suitable biocompatible and
 20 biodegradable polymers include polyvinyl alcohol (PVA), poly(p-xylylene) polymers (trademarked as Parylene®), poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(lactic-co-glycolic acid) (PLGA), poly(ϵ -caprolactone) (PCL), poly(valerolactone) (PVL), poly(ϵ -decalactone) (PDL), poly(1,4-dioxane-2,3-dione), poly(1,3-dioxane-2-one), poly(para-dioxanone) (PDS),
 25 poly(hydroxybutyric acid) (PHB), poly(hydroxyvaleric acid) (PHV), ethylene vinyl acetate (EVA) and poly(β -malic acid) (PMLA).

In order to affect permeability and release rates, the polymeric coatings can optionally be covalently or ionically cross-linked. For example, monomers can be chosen which include chemical groups which are capable of
 30 forming additional bonds between monomers, or separate cross-linking agents can be included in the polymer-forming solutions in addition to the monomers.

In some embodiments, the cross-linking groups are thermally activated, whereas in other embodiments they are photoactivated, including photoactivation by visible or ultraviolet radiation. Cross-linking groups include, without limitation, unsaturated groups such as vinyl, allyl, cinnamate, acrylate, diacrylate, oligoacrylate, methacrylate, dimethacrylate, and oligomethoacrylate groups. As many therapeutic agents are hydrophobic, and because it is desirable to reduce or avoid dissolution of the drug core into the polymeric shell in order to maintain a sharp interface between the core and shell, the polymeric shell should include a hydrophilic polymer, particularly in the coating that is most proximate to the crystalline core. Examples of hydrophilic polymeric coatings include, without limitation, poly(vinyl alcohol) (PVA), poly(ethylene glycol) (PEG), poly(ethylene oxide), poly(vinylpyrrolidone), poly(ethyloxazoline), or polysaccharides or carbohydrates such as alkylcelluloses, hydroxyalkylcelluloses, hyaluronic acid, dextran, heparan sulfate, chondroitin sulfate, heparin, or alginate, or proteins such as gelatin, collagen, albumin, ovalbumin, or polyamino acids.

Additional examples of suitable polymers can be prepared from monomers selected from the following group: sugar phosphates, alkylcellulose, hydroxyalkylcelluloses, lactic acid, glycolic acid, β -propiolactone, β -butyrolactone, γ -butyrolactone, pivalolactone, α -hydroxy butyric acid, α -hydroxyethyl butyric acid, α -hydroxy isovaleric acid, α -hydroxy- β -methyl valeric acid, α -hydroxy caproic acid, α -hydroxy isocaproic acid, α -hydroxy heptanic acid, α -hydroxy octanic acid, α -hydroxy decanoic acid, α -hydroxy myristic acid, α -hydroxy stearic acid, α -hydroxy lignoceric acid and β -phenol lactic acid.

Because the drug core is comprised of at least 70% by weight of the microparticles, the overall sizes of the microparticles are largely determined by the size of the drug core. Typically, the polymeric shell has a thickness of about less than 25%, less than 20%, less than 12%, or less than 5% or less than 3% of the total diameter of the microparticle. Likewise, the weight of the microparticle is also predominately the weight of the crystalline core, resulting in

a high drug loading. In preferred embodiments, the microparticle comprises 90-98% w/w of crystalline drug core and 2-10% w/w of polymeric shell.

In various embodiments, the microparticles have a mean diameter of between 50 μm and 800 μm , or a mean diameter of between 60 μm and 250 μm , or a mean diameter of between 80 μm and 150 μm .

In a preferred embodiment, the mean diameter is 150 μm with a standard deviation of less than 50% of the mean diameter. In another preferred embodiment, the mean diameter is 75 μm with a standard deviation of less than 50% of the mean diameter.

10 Methods of Forming Microparticles

Methods of forming polymeric coatings on particles are well known in the art. For example, standard techniques include solvent evaporation/extraction techniques, in-water drying techniques (see, e.g., U.S. Pat. No. 4,994,281), organic phase separation techniques (see, e.g., U.S. Pat. No. 5,639,480), spray-drying techniques (see, e.g., U.S. Pat. No. 5,651,990), air suspension techniques, and dip coating techniques.

In a most preferred form, the method of forming microparticles as described in U.S. Patent Publication 2007/003619, which is fully incorporated herein by reference. The crystalline drug core is coated with one or more layers of polymeric coatings, which together form the polymeric shell. For example, in one aspect, a PVA polymeric coating can be applied using a dip coating technique. In brief, a 1% coating solution of PVA in water can be formed by dissolving excess PVA in water at 60° C. for 2 h (see, e.g., Byron and Dalby (1987), J. Pharm. Sci. 76(1):65-67). Alternatively, a higher concentration PVA solution (e.g., 3-4%) can be prepared in a reflux with heating to approximately 90-100° C. After cooling, the microparticles can be added to the PVA solution and agitated by, for example, swirling or stirring. The microparticles are then removed from the solution by, for example, filtration on filter paper with a mesh size appropriate to the microparticles. Optionally, vacuum-filtration can be employed to assist in drying. Untreated, PVA polymeric coatings or films are readily permeable to water and hydrophilic

drugs. Heating of PVA, however, causes an increase in crystallinity and decrease of permeability of up to 500-fold with increasing temperatures in the range of 100-250° C. for periods of 0-160 hours (Byron and Dalby (1987), supra). Thus, in some embodiments, PVA polymeric coatings can be heated to
5 temperatures between 100° C. and 250° C., between 125° C. and 175° C., or between 155° C. and 170° C. for periods between 1 sec. and 160 hours, between 1 min. and 10 hours, or between 5 minutes and 2 hours. Most preferably, heating is to 220°C for one hour, or 90% or more, depending on the degree of permeation needed. Optionally, the coating process can be repeated
10 several times to build-up a thicker polymeric coating. Most preferably, 2-5 coatings are applied to achieve a 5% thickness of coating.

In one embodiment, the microparticles undergo a precision heat treatment step at a temperature within the range of 210-230°C for at least one hour. It is unexpectedly discovered that the level of crosslinking, and hence
15 permeability, can be precision controlled by heating the microparticles within this temperature range. More preferably, the heat treatment step is carried out at 220°C for one hour. As discussed in further detail below in connection with the dissolution characteristics and Example 6, heat-treated microparticles at a particular temperature range (210-230°C) surprisingly attain a level of
20 crosslinking and permeability that are capable of significantly enhancing the dissolution half-life.

In vitro Dissolution Characteristics

The structure of the microparticles makes it possible for a highly localized delivery system based on dissolution. Accordingly, *in vitro* dissolution
25 characteristics, such as dissolution half-life are correlatable to the sustained release period *in vivo*.

It is important to recognize that dissolutions models are designed to give an accelerated dissolution as compared to *in vivo* release. An IVIVC that mirrored the actual *in vivo* dissolution could take months to complete.
30 Nevertheless, an accelerated USP type II standard dissolution is useful to

provide a qualitative comparison among various formulations and to offer a predictor for the *in vivo* release behaviors.

PCT/US2014/031502 demonstrates methods for quantifying *in vitro* dissolution characteristics in the context of a corticosteroid drug, which methods may also be extended to quantifying the dissolution characteristics of the microparticles described herein.

Figure 2 shows the effect of the microparticle structures on dissolution rates. More specifically, Figure 2 shows the *in vitro* release profiles of uncoated fluticasone propionate powder (amorphous or very small crystals), uncoated fluticasone propionate crystals and coated fluticasone propionate crystals. The dissolution profiles clearly show a trend of longer dissolution half-life and less initial burst in the crystalline drug as compared to amorphous drug. The trend is more pronounced for the coated crystalline drug compared to the uncoated crystalline drug. Additional details of the dissolution conditions are described in the Example sections.

The process of forming the microparticles also has a profound impact on the dissolution characteristics. In particular, a precision heat-treatment within a narrow temperature range (e.g., 210-230°C) unexpectedly provides a significantly enhanced dissolution half-life when compared to those of microparticles having undergone heat treatment at temperatures outside of this range. In a dissolution test using United States Pharmacopoeia Type II apparatus, wherein the dissolution conditions are 3 milligrams of microparticles in 200 milliliters of dissolution medium of 70% methanol and 30% of water at 25°C, the dissolution profiles of microparticles that have undergone heat treatments at 160°C, 190°C, 220°C and 250°C are shown in Figure 3A. Microparticles heat-treated at 220°C have the slowest and gentlest initial release, as compared to those of microparticles treated at temperature above or below 220°C. Figure 3B shows the dissolution half-lives of the microparticles of Figure 3A. As shown, microparticles heat-treated at 220°C have a significantly longer dissolution half-life (12-20 hours) than those of the other microparticles (all less than 8 hours).

The result indicates that precision thermal processing (*i.e.*, heating within a narrow range of temperature for a specific period of time) afford certain structural characteristics (including, *e.g.*, degrees of crosslinking, crystallinity, porosity and/or permeability) that are most effective in enhancing the dissolution half-life, and by extension, the sustained release period.

In vivo Release Characteristics

PCT/US2014/031502 demonstrates that corticosteroid microparticles are capable of highly localized sustained releasing of the corticosteroid drug within a body compartment (*e.g.*, an intra-articular space) for 2- 12 months after a single injection, or more typically, for 2-9 months, or for 3-6 months after a single injection. The results are discussed in more detail in Examples 10-13.

Even as the local concentrations exceed the EC50 of corticosteroid, the plasma concentration of the corticosteroid drug unexpectedly remains much lower than the local concentrations at any given time during the sustained release period and can be below quantifiable limit after 7 days. The low plasma concentration minimizes any clinically significant HPA axis suppression.

Moreover, the corticosteroid microparticles do not exhibit any significant initial burst (locally or systemically), unlike known drug-loaded microparticles.

The methods described in PCT/US2014/031502 for quantifying *in vivo* release characteristics in the context of the corticosteroid drug may also be extended to quantifying the dissolution characteristics of the microparticles described herein.

The *in vivo* release characteristics confirm the release mechanism of pseudo-zero order of the drug-loaded microparticles described herein, by which mechanism a therapeutic agent is released at a nearly constant rate so long as a saturated solution can be maintained within the polymeric shell (*e.g.*, for more than 60 days or for more than 90 days, or for more than 180 days), irrespective of the original drug loading. See *also* Examples 10-13.

Further, the *in vivo* release behaviors are correlatable to the *in vitro* dissolution behaviors. In particular, microparticles that have undergone heat-treatments at different temperatures (220°C vs. 130°C) exhibited *in vivo* release behaviors that are consistent with their *in vitro* dissolutions. See also, 5 Examples 8 and 11.

Pharmaceutical Composition

One embodiment provides a pharmaceutical composition comprising: a plurality of microparticles, the microparticle including 1) a crystalline drug core of more than 70% by weight of the microparticle, wherein 10 the crystalline drug core includes one or more crystals of a therapeutic agent; and (2) a polymeric shell encapsulating the crystalline drug core, wherein the polymeric shell is in contact but immiscible with the crystalline drug core, wherein said composition when dissolution tested using United States Pharmacopoeia Type II apparatus exhibits a dissolution half-life of 12-20 hours, 15 wherein the dissolution conditions are 3 milligrams of microparticles in 200 milliliters of dissolution medium of 70% methanol and 30% of water at 25°C.

In a preferred embodiment, the crystalline drug core comprises a therapeutic agent such as an anesthetic agent, a central nerve system agent, an antibiotic, or a chemotherapeutic agent.

20 In certain embodiments, the microparticles have undergone a heat-treatment step within a temperature range of 210-230°C.

In various embodiments, the mean diameters of the microparticles are in the range between 50 µm and 800 µm, or in the range between 60 µm and 250 µm, or in the range between 80 µm and 150 µm.

25 In further embodiments, the crystalline drug core is more than 75%, more than 80%, more than 85%, more than 90% or more than 95% of the total weight of the microparticle, with the remainder of the microparticles being the polymeric shell.

In various embodiments, at least 90%, at least 95%, at least 98%, 30 or 100% of the entire weight of the drug core is the drug in a crystalline form.

In preferred embodiments, the diameters of the microparticles in a given pharmaceutical composition may be tailored or selected to suit a particular route of administration. Thus, one embodiment provides an injectable composition, in which more than 90% of the microparticles have diameters in the range of 100-300 μm , which are particularly suitable for an epidural injection. Another embodiment provides an injectable composition comprising microparticles in which more than 90% of the microparticles have diameters in the range of 50-100 μm , which are particularly suitable for intra-articular or intra-ocular injection.

Because the dissolution rate of the crystalline drug is related to the size of the crystals, *i.e.*, the smaller the crystals, the higher the initial burst rate (see Figure 2), it is preferred that the population of microparticles in a pharmaceutical composition has a narrow size distribution. Thus, in one embodiment, the plurality of microparticles in the pharmaceutical composition have a mean diameter in the range of 50 μm to 300 μm and a standard deviation of less than 50% of the mean diameter.

In a preferred embodiment, the mean diameter is 150 μm with a standard deviation of less than 50% of the mean diameter (*e.g.*, for epidural injections). In another preferred embodiment, the mean diameter is 75 μm with a standard deviation of less than 50% of the mean diameter (*e.g.*, for intra-articular or intra-ocular injections).

In a further embodiment, the pharmaceutical composition further comprises a pharmaceutically acceptable vehicle, in which the plurality of microparticles is suspended. It is preferred that the microparticles of therapeutic agent are mixed with the vehicle immediately prior to injection, so there is no time for the therapeutic agent to dissolve into the vehicle and there is no or substantially no initial burst of drug prior to injection.

Unit Dosage Form

A unit dosage form is a pharmaceutical composition (including all the embodiments as described above) having a predetermined quantity of the drug-loaded microparticles which, after a single injection, provides sustained

release of the therapeutic agent for a specified period. The quantity of the microparticles in a unit dosage will depend upon several factors including the routes of administration (intra-articular, intra-epidural, or intra-ocular), the body weight and the age of the patient, the severity of pain or infection, or the risk of potential side effects considering the general health status of the person to be treated.

Advantageously, because the drug-loaded microparticles described herein are capable of near zero-order release with little initial burst, the initial loading the drug in the unit dosage form can be rationally designed according to the desired sustained release period.

Thus, one embodiment provides an injectable unit dosage form of a therapeutic agent for injecting into a body compartment, the injectable unit dosage form comprising: a plurality of microparticles, the microparticle including (1) a crystalline drug core of more than 70% by weight of the microparticle; and (2) a polymeric shell encapsulating the crystalline drug core, wherein the crystalline drug core includes one or more therapeutic agent, and the polymeric shell is in contact but immiscible with the crystalline drug core, wherein the injectable dosage form is capable of sustained-release of the therapeutic agent for a period of 2-20 months while maintaining a minimum therapeutically effective concentration of the therapeutic agent within the body compartment.

In a further embodiment, the sustained release period is 2-9 months.

In a further embodiment, the sustained release period is 3-6 months.

In other embodiment, the plasma concentration of the therapeutic agent is below quantifiable level after 7 days.

In various embodiments, the unit dosage form comprises 0.5-500 mg of therapeutic agent. In other embodiments, the unit dosage form comprises 3-500mg of therapeutic agent.

In various embodiments, the unit dosage form further comprises a pharmaceutically acceptable vehicle. Preferably, the vehicle is combined with

the drug-loaded microparticles immediately before injection to avoid dissolution of the drug into the vehicle. Advantageously, because of the lack of initial burst, any dissolution of the drug into the vehicle during normal handling time in preparation for an injection is insignificant. In contrast, many known drug-

5 loaded sustained release formulations are capable of saturating the vehicle during handling time due to an initial burst.

Methods of Using and Routes of Administration

The pharmaceutical compositions and dosage forms described herein are particularly suited to be injected into a body compartment for highly

10 localized, sustained release of therapeutic agent. The body compartment typically contains soft tissue and/or fluid within an enclosure or semi-enclosure. The injection is directed to the soft tissue or the fluid, into which the drug-loaded microparticles are released. When needed, the injection can be guided by an imaging system such as an ultrasonic or X-ray device.

15 In one embodiment, the injection is administered intra-articularly for sustained-release of a therapeutic agent in the synovium or synovial fluid.

In another embodiment, the injection is administered into an epidural space for sustained-release of a therapeutic agent.

In a further embodiment, the injection is administered intra-

20 ocularly, or intra-vitreously for sustained-release of a therapeutic agent in the vitreous humour.

In a further embodiment, the injection is administered to a surgically created pocket or a natural space near an implant for sustained-release of a therapeutic agent therein for reducing pain (e.g., anesthetics),

25 infection (antibiotics) or solid tumor (chemotherapeutic agents).

In other embodiments, the pharmaceutical compositions and dosage forms may be suitable for systemic administration for sustained release of a therapeutic agent, in particular, a chemotherapeutic agent.

As an alternative to injection, the drug-loaded microparticles may

30 also be first affixed to an implant such as pacemakers, defibrillators, orthopedic

implants, artificial hearts prior to implantation for reducing infection or surgical adhesion.

The drug-loaded microparticles may also be combined with mesh, film or membrane (e.g., a surgical mesh) by coating, adhesion or soaking. The mesh, film or membrane incorporating the microparticles may be placed in a body compartment or surgical site. This route of administration is particularly suited for antibiotics-loaded microparticles.

Diseases that May be Treated Using the Formulations of this Disclosure

Various embodiments provide long-acting treatments or therapies for reducing pain or infection, CNS disorders or treating cancer/tumors.

Thus, one embodiment provides a method of managing pain in a body compartment of a patient in need thereof, comprising injecting to the body compartment a therapeutically effective amount of pharmaceutical composition having a plurality of microparticles, the microparticle including 1) a crystalline drug core of more than 70% (preferably more than 90%) by weight of the microparticle, wherein the crystalline drug core includes an anesthetic agent; and (2) a polymeric shell encapsulating the crystalline drug core, wherein the polymeric shell is in contact but immiscible with the crystalline drug core.

In various embodiments, the microparticles have undergone a heat-treatment step within a temperature range of 210-230°C.

In various embodiments, the mean diameters of the microparticles are in the range between 50 µm and 800 µm, or in the range between 60 µm and 250 µm, or in the range between 80 µm and 150 µm.

In preferred embodiments, the diameters of the microparticles in a given pharmaceutical composition may be tailored or selected to suit a particular route of administration. Thus, one embodiment provides an injectable composition, in which more than 90% of the microparticles have diameters in the range of 100-300 µm, which are particularly suitable for an epidural injection. Another embodiment provides an injectable composition comprising microparticles in which more than 90% of the microparticles have diameters in the range of 50-100 µm.

In further embodiments, the crystalline drug core is comprised of more than 75%, more than 80%, more than 85%, more than 90% or more than 95% of the total weight of the microparticle, while the remainder being the polymeric shell.

5 In various embodiments, at least 90%, at least 95%, at least 98%, or 100% of the entire weight of the drug core is the drug in a crystalline form.

 In certain embodiments, said composition when dissolution tested using United States Pharmacopoeia Type II apparatus exhibits a dissolution half-life of 12-20 hours, wherein the dissolution conditions are 3 milligrams of
10 microparticles in 200 milliliters of dissolution medium of 70% methanol and 30% of water at 25°C.

 In other embodiments, said composition when dissolution tested using United States Pharmacopoeia Type II apparatus exhibits a dissolution half-life of 12-20 hours, wherein the dissolution conditions are 3 milligrams of
15 microparticles in 200 milliliters of dissolution medium of 70% methanol and 30% of water at 25°C.

 Another embodiment provides a method of treating central nerve system disorder a patient in need thereof, comprising injecting to the patient a unit dosage form having a plurality of microparticles, the microparticle including
20 (1) a crystalline drug core of more than 70% (preferably more than 90%) by weight of the microparticle; and (2) a polymeric shell encapsulating the crystalline drug core, wherein the crystalline drug core includes a central nerve system (CNS) drug, and the polymeric shell is in contact but immiscible with the crystalline drug core.

25 In further embodiments, the injectable dosage form is capable of sustained-release of the CNS drug for a period of 2-12 months while maintaining a minimum therapeutically effective concentration of the CNS drug within the body compartment.

 A further embodiment provides a method of treating infection in a
30 body compartment of a patient in need thereof, comprising injecting to the body compartment a single injection of a unit dosage form having a plurality of

microparticles, the microparticle including (1) a crystalline drug core of more than 70% (preferably more than 90%) by weight of the microparticle; and (2) a polymeric shell encapsulating the crystalline drug core, wherein the crystalline drug core includes an antibiotic agent, and the polymeric shell is in contact but
5 immiscible with the crystalline drug core.

In further embodiments, the injectable dosage form is capable of sustained-release of the antibiotic agent, for a period of 1-7 days while maintaining a minimum therapeutically effective concentration of the antibiotic agent within the body compartment.

10 A further embodiment provides a method of treating cancer or solid tumor in a patient in need thereof, comprising injecting (e.g. to a body compartment or systemically) a unit dosage form having a plurality of microparticles, the microparticle including (1) a crystalline drug core of more than 70% (preferably more than 90%) by weight of the microparticle; and (2) a
15 polymeric shell encapsulating the crystalline drug core, wherein the crystalline drug core includes a chemotherapeutic agent, and the polymeric shell is in contact but immiscible with the crystalline drug core.

In further embodiments, the injectable dosage form is capable of sustained-release of the chemotherapeutic agent for a period of 2-12 months
20 while maintaining a minimum therapeutically effective concentration of the chemotherapeutic agent within the body compartment or systemically.

Additional specific embodiments include:

- said microparticles have a mean diameter of between 50 μm and 800 μm .
- 25 • said microparticles have a mean diameter of between 60 μm and 250 μm .
- said microparticles have a mean diameter of between 80 μm and 150 μm .
- sustained release refers to at least three months.

- wherein said pharmaceutical preparation for sustained release comprises large particles of substantially pure therapeutic agent coated with at least one biocompatible or bio-erodible polymer.
 - which reduces or eliminates an initial drug burst.
- 5 • the polymer comprises at least one of polylactic acid, polyvinyl alcohol and Parylene™
 - the disease progression is slowed or halted due to the maintenance of the constant low level of drug in the body compartment.
 - the particles of drug are mixed with the vehicle immediately
 - 10 prior to injection, so there is no time for the drug to dissolve into the vehicle and there is no or substantially no initial burst of drug.
 - the present method has fewer systemic side effects than other therapies
 - diffusion of said therapeutic agent across said first polymeric
 - 15 coating exhibits pseudo-zero-order kinetics during said sustained-release period.
 - said first polymeric coating is not degraded until AFTER a sustained release period (which is a point of differentiation as compared to other sustained release formulations)
 - 20 • said first polymeric coating maintains structural integrity during said sustained-release period.
 - said microparticles have a maximum dimension between 50 μm and 250 μm .
 - said microparticles have a maximum dimension between 50
 - 25 μm and 150 μm .
 - said therapeutic agent is hydrophobic and said first coating solution is hydrophilic.
 - The polymeric shell comprises one or more polymeric coatings that are the same or different and may comprise a polymer or co-polymer
 - 30 including at least one monomer selected from the group consisting of sugar phosphates, alkylcellulose, hydroxyalkylcelluloses, lactic acid, glycolic acid, β -

propiolactone, β -butyrolactone, γ -butyrolactone, pivalolactone, α -hydroxy butyric acid, α -hydroxyethyl butyric acid, α -hydroxy isovaleric acid, α -hydroxy- β -methyl valeric acid, α -hydroxy caproic acid, α -hydroxy isocaproic acid, α -hydroxy heptanic acid, α -hydroxy octanic acid, α -hydroxy decanoic acid, α -hydroxy myristic acid, α -hydroxy stearic acid, α -hydroxy lignoceric acid, β -phenol lactic acid, ethylene vinyl acetate, and vinyl alcohol.

- the polymeric coating is applied to said core particles by an air suspension technique.
- said polymeric coating is applied to said core particles by a dip coating technique.

These and other changes can be made to the present systems, methods and articles in light of the above description. In general, in the following claims, the terms used should not be construed to limit the disclosure to the specific embodiments disclosed in the specification and the claims, but should be construed to include all possible embodiments along with the full scope of equivalents to which such claims are entitled. Accordingly, the disclosure is not limited by the disclosure, but instead its scope is to be determined entirely by the following claims.

EXAMPLES:

EXAMPLE 1

GENERAL PROCEDURE FOR PREPARING CRYSTALLINE DRUG CORE

To fluticasone propionate (FP) powder (1 g), methanol (100 mL) is added and the suspension heated with stirring until a clear solution is obtained. The flask is left at room temperature over-night resulting in the formation of needle-shaped crystals. The crystals are collected using a Buchner funnel and thoroughly oven-dried at 40-50°C for 2 h. The dry FP particles are added to an 80-170 μ m mesh sieve along with a monolayer of glass beads. A 30-60 μ m mesh sieve is added below the sieve containing the FP particles and beads, followed by shaking for 3-4 min. The 80-170 μ m mesh sieve is replaced with a clean 80-170 μ m mesh sieve, a 2000 μ m mesh sieve added to the top

(optional), and the sieve stack attached to a Buchner funnel. The content of the 80-170 μm mesh sieve containing the FP particles and beads is gently poured into the 2000 μm mesh sieve to collect the glass beads and washed with deionized water ($\text{DI-H}_2\text{O}$) under suction. The 2000 μm mesh sieve is removed
5 and the content of the 80-150 μm mesh sieve washed with $\text{DI-H}_2\text{O}$ under suction. A total of 200-300 mL of $\text{DI-H}_2\text{O}$ typically is used. Alternatively, the content of the sieves may be washed with TWEEN-80 (0.1% w/v) before washing with water, or the glass beads are replaced by gentle grinding using a glass rod in a 212 μm mesh sieve. The content of the 80-170 μm and 30-60
10 μm mesh sieves is separately dried at 40°C and the dry material combined for polymer coating.

EXAMPLE 2

SIZE DISTRIBUTION OF CRYSTALLINE DRUG CORE

1 gram of fluticasone propionate (FP) powder (CAS 80474-14-2)
15 was dissolved in 100mL of ACS-grade methanol over a hot plate. The final solution was clear. This solution was cooled and allowed to rest for 24 h at room temperature. The resulting crystals were filtered, sieved and collected below 180 μm screens ($\sim 180 \mu\text{m}$), cleaned with 0.1% TWEEN-80 aqueous solution, and washed twice with distilled water and dried at 40°C for 3h. 940
20 mg of fluticasone propionate crystals (94% yield) were obtained using this procedure. Figure 4A and 4B show the mean particle sizes obtained and size distributions.

Figure 4A is a graph representing the particle size distribution of fluticasone propionate monodisperse distribution with mean particle size of ca.
25 110 μm , and the standard deviation is ca. 41 μm . Particles of these sizes can be injected easily through 23g needle (internal diameter 320 μm)

As a comparison, Figure 4B is a graph representing the particle size distribution of Traimcinolone Acetonide (KenalogTM). The mean particle size is ca. 20 μm . There is a relatively wide distribution with a second peak at
30 ca. 1 μm . The standard deviation is about 13 μm . These small particles

contribute to the burst effect seen with this type of formulation common in the prior art. See also Figure 6.

EXAMPLE 3

GENERAL PROCEDURE FOR COATING CRYSTALLINE DRUG CORE

5 The dry FP crystals prepared according Example 1 are coated with polyvinyl alcohol (PVA, 2% w/v in 25% v/v isopropyl alcohol in DI-H₂O) in a model VFC-LAB Micro benchtop fluidized bed coater system (Vector Corporation) using the following range of parameters:

air flow, 50-60 L min⁻¹;
10 nozzle air, 5.0-25 psi;
pump speed, 10-35 rpm;
inlet temperature, 99°C;
exhaust temperature, 35-40°C;
spray on/off cycle: 0.1/0.3 min.

15 The PVA content is periodically measured by quantitative ¹H nuclear magnetic resonance (NMR) spectroscopy by comparing the relative signal intensities of the FP and PVA resonances in the drug product to corresponding signals from calibration standards (See Example 3). A target final PVA concentration in the drug product is in the range of 0.1-20% w/w, or
20 preferably 2-10% w/w. Coating of the particles is continued until the desired amount of PVA has been achieved. The coated particles are then dried in an oven at 40°C for 1 h. The dry, coated particles are sieved in a sieve stack defined by 150 µm mesh and 53 µm mesh sieves.

EXAMPLE 4

25 NMR ANALYSIS FOR DETERMINING DRUG CONTENT IN MICROPARTICLES

NMR analysis was used to determine the amounts of the drug core and the polymeric shell in microparticles by calibrating with samples of known quantity of the pure drug.

The NMR system includes a Bruker Spectrospin 300 MHz magnet, Bruker B-ACS 120 autosampler, Bruker Avance II 300 console, and a Bruker BBO 300 MHz S1 5mm with Z gradient probe. A calibration curve was prepared using five samples of known fluticasone propionate, and PVA concentrations made in NMR grade d6-DMSO. Proton (1H) NMR was run on two samples: the first containing only pure fluticasone propionate and the second containing PVA-coated fluticasone. Each sample was loaded manually and spun at 20 Hz inside the magnet. The probe was tuned and matched for proton (1H) NMR. The magnet was shimmed manually with the first sample in the magnet. Each sample was integrated for 1.5 hours with 1024 scans. Fluticasone peaks were integrated from 5.5 to 6.35 ppm, and the PVA peak was integrated from 4.15 to 4.7 ppm (see Figure 5). Using this method, the finished coated fluticasone particles were determined to contain 2.1% PVA total weight of coated particles. Assuming spherical particle shape and mean particle diameter of 100 μm , this represents a coating thickness of ca. 7 μm .

EXAMPLE 5

IN VITRO DISSOLUTION ANALYSIS

To each vessel (1000 mL capacity) of a USP Type II dissolution system is added the dissolution medium and 3 mg of PVA-coated FP particles. The dissolution medium typically consists of 5-90% v/v of an alcohol-water mixture, where the alcohol can be methanol, ethanol, and isopropanol. The volume of dissolution medium used is in the 50-750 mL range. The temperature of the dissolution medium is maintained either at room temperature or at a temperature in the 5-45°C range. Aliquots are removed from the dissolution medium at regular, predetermined time points and the samples are stored for subsequent analysis, such as with UV-visible absorption spectroscopy or high performance liquid chromatography.

A specific set of dissolution conditions is as follows:
drug for dissolution: 3 mg PVA-coated FP particles;

dissolution medium: 200 ml of 70% v/v ethanol and 30% v/v water;

dissolution temperature: 25°C.

EXAMPLE 6

5 THERMAL PROCESSING AND EFFECTS ON DISSOLUTIONS

The coated microparticles prepared according to Example 2 were thermal processed, *i.e.*, heat treated for a specific period of time. Specifically, the interior of a borosilicate Petri dish was lined with aluminum foil and a monolayer of PVA-coated FP particles was spread. The dish was covered with
10 perforated aluminum foil. An oven was pre-heated to the desired set-point and the samples were heat-treated for a pre-determined amount of time. The temperature set-point were 160°C, 190°C, 220°C and 250°C.

Figure 3A shows the dissolution profiles of microparticles having undergone heat treatments at the above temperatures. The dissolution
15 conditions are as follows: 3 mg of PVA-coated FP microparticles were dissolved in a dissolution medium of 200 ml of 70% v/v ethanol and 30% v/v water at 25°C. The resulting concentration-time data are analyzed (*e.g.*, one phase decay model) to afford the dissolution half-life (shown in Figure 3B).

As shown in Figure 3A, microparticles heat-treated at 220°C have
20 the slowest and gentlest initial release, as compared to those of microparticles treated at temperature above or below 220°C.

Figure 3B shows that the dissolution half-lives of the microparticles of Figure 3A. As shown, microparticles heat-treated at 220°C have a significant longer dissolution half-life (12-20 hours) that those of the
25 other microparticles (all less than 8 hours).

EXAMPLE 7

SUSTAINED RELEASE (SR) FORMULATIONS FOR ANIMAL STUDY (SHEEP)

Dry FP crystals were prepared according to Example 1 and were coated with polyvinyl alcohol (PVA, 2% w/v in 25% v/v isopropyl alcohol in DI-

H₂O) in a model VFC-LAB Micro bench top fluidized bed coater system (Vector Corporation) using the following range of parameters: air flow, 50-60 L/min; nozzle air, 23 psi; pump speed, 15 rpm; inlet temperature, 99°C; exhaust temperature, 35-40°C; spray on/off cycle: 0.1/0.3 min.

5 The resulting microparticles were then heat-treated at 130 °C for 3 hours.

The microparticles have mean diameters in the range of 60-150 μm . The PVA content of the resulting microparticles was 2.4% as analyzed by NMR analysis according to the method described in Example 4.

10 EXAMPLE 8

SUSTAINED RELEASE (SR) FORMULATIONS FOR ANIMAL STUDY (DOG)

Dry FP crystals were prepared according to the above procedures and were coated with polyvinyl alcohol (PVA, 2% w/v in 25% v/v isopropyl alcohol in DI-H₂O) in a model VFC-LAB Micro benchtop fluidized bed coater system (Vector Corporation) using the following range of parameters: air flow, 50-60 L/min; nozzle air, 8.0 psi; pump speed, 25 rpm; inlet temperature, 99°C; exhaust temperature, 35-40°C; spray on/off cycle: 0.1/0.3 min.

The resulting microparticles were then heat-treated at 220°C for 1.5 hours.

20 The microparticles have mean diameters in the range of 60-150
µm. The PVA content of the resulting microparticles was 4.6% as analyzed by
NMR analysis according to the method described in Example 4.

Figure 6 shows the dissolutions profiles of the microparticles prepared by Example 8 compared to the microparticles prepared by Example 7. In addition, Figure 6 further shows the dissolution profiles of another corticosteroid (triamcinolone acetonide) and fluticasone propionate powder (uncoated, non-crystalline or very small, less than 10µm crystals). Both coated FP microparticles (Examples 7 and 8) exhibit much longer dissolution half-lives and less initial bursts than the FP powder and triamcinolone acetonide. In addition, microparticles that have been heat-treated at 220°C are shown to

have even longer dissolution half-life than microparticles similarly prepared but heat-treated at 130°C (Example 7).

The dissolution conditions were as follows:

drug for dissolution: 3 mg PVA-coated FP particles

5 dissolution medium: 200 ml of 70% v/v ethanol and 30% v/v
water;

dissolution temperature: 25°C.

EXAMPLE 9

FORMULATION OF SUSPENSION / INJECTABILITY.

10 Optimized suspension formulations of coated particles were
obtained using an iterative process, whereby different suspension solutions at
varying concentrations were assessed for their ability to keep coated particles
in suspension. The most homogeneously distributed formulations were then
injected through needle sizes ranging from 18 to 25 gauge. Particle transfer
15 efficiency was measured by HPLC. A 1% CMC solution provided the maximum
suspension and a 23 gauge needle provided adequate injection efficiency.

Sterility. Polymer-coated fluticasone particles were steam-
sterilized (122°C, 16 psi, 30 min) in amber vials. The sterilization process did
not affect the chemical composition of the formulation according to ¹H NMR
20 spectroscopy and HPLC analysis. See Figure 5. *In vitro* studies in 500 mL
USP Type II systems confirmed that the sterile material had the same
fluticasone release profile as the same material prior to autoclaving.

EXAMPLE 10

IN VIVO PHARMACOKINETIC (PK) STUDIES (SHEEP)

25 In a non-GLP exploratory study, the local toxicity and drug
concentration levels were evaluated for 3 months in sheep (n=4) after a single
intra-articular injection into the left stifle joint using a 23G needle of a tuberculin
syringe. The injectable dosage form was 0.5mL of 20 mg extended release
fluticasone propionate (EP-104) prepared according to Example 7.

Clinical observations were performed throughout the study, and histopathology was performed at the end of the study to evaluate local toxicity. To evaluate fluticasone propionate concentration levels in treated knees, synovial fluid samples were collected at designated time points. Blood was
5 collected throughout the study to determine plasma concentration levels. Plasma fluticasone levels were measured by HPLC-MS. Mistry N, et al. Characterisation of impurities in bulk drug batches of fluticasone propionate using directly coupled HPLC-NMR spectroscopy and HPLC-MS. *Journal of Pharmaceutical and Biomedical Analysis* 16(4):697-705, 1997. Mortality,
10 morbidity, and body weights were also evaluated.

There were no changes during clinical observations, and no histopathologic changes occurred in any of the knees after 3 months. There was no mortality or morbidity, and sheep gained weight throughout the study.

Fluticasone propionate concentrations were detected in synovial
15 fluid at 3 months (n=4; 11.51, 9.39, 13.22, and 18.89 ng/mL). Plasma concentration levels were less and declined at a greater rate than those of synovial fluid. Fluticasone propionate concentrations in plasma were below quantifiable limits (BQL) at 0 or below 0.3 ng/mL beginning at Day 70. Plasma and synovial fluid concentrations throughout the study are provided in Figure 7.

20 Of note is an absence of burst and sustained local concentrations achieved for the duration of the experiment. The reported EC₅₀ for fluticasone propionate is 7 -30 pg/ml. Möllmann H, et al. Pharmacokinetic and pharmacodynamic evaluation of fluticasone propionate after inhaled administration, *European journal of clinical pharmacology* Feb; 53(6):459-67,
25 1998. Significantly, after 90 days, the local concentration of FP in the synovial fluid remained considerable amount (n=4; 11.51, 9.39, 13.22, and 18.89 ng/mL) and above the EC₅₀ level, while the plasma concentration was no longer detectable (the plasma concentration became BQL at day 70).

As a comparison, the release of triamcinolone hexacetonide
30 (40mg) from human subjects is also plotted in Figure 7. Derendorf H, et al. Pharmacokinetics and pharmacodynamics of glucocorticoid suspensions after

intra-articular administration. *Clinical Pharmacology and Therapeutics* Mar; 39(3):313-7 (1986). As shown, triamcinolone hexacetonide release shows a significant initial burst followed by rapid decline. The duration of release is significant shorter than that of the coated FP microparticles described herein, 5 despite having a much higher initial dose.

The shape of the PK curve of the corticosteroid microparticles is substantially different from that of the triamcinolone hexacetonide. The slow rise and near constant release over a period of 60 days confirms the release mechanism of pseudo-zero order, by which the corticosteroid drug is released 10 at a nearly constant rate so long as a saturated solution can be maintained within the polymeric shell (e.g., for 60 days), irrespective of the original drug loading.

The animals were euthanized on day 90 and the joints excised and sent for histology. There were no safety or toxicity issues noted on clinical 15 examination. Histological examination of the injected joints showed no abnormalities (Figures 8A, 8B, and 8C).

EXAMPLE 11

IN VIVO PHARMACOKINETIC (PK) STUDIES (DOGS)

Extended release fluticasone propionate formulation (EP-104IAR) 20 was prepared according to Example 8. The *in vivo* release characteristics were evaluated in the knee of Beagle dogs (n=32) during a 60-day study. Two groups of 16 male and female dogs were evaluated. Group 1 (n=8 males and 8 females) were administered a target dose of 0.6 mg EP-104IAR by intra-articular injection (the low dose group). Group 2 was administered a target 25 dose of 12 mg EP-104IAR by intra-articular injection (the high dose group).

Synovial fluid and plasma were collected at 7, 29, 46, and 60 days after injection, and cartilage tissue drug concentrations and microscopic changes were also evaluated at these time points. Mortality checks, clinical observations, and body weight measurements were performed. Blood was 30 collected for plasma bioanalysis from all surviving animals at pre-dose, and on

Days 3, 5, and 7; and twice weekly thereafter until necropsy (including the day of necropsy). Two animals/sex from each group were euthanized on Day 7, 29, 46 or 60. Prior to necropsy, synovial fluid was collected for bioanalysis.

Results:

5 In the low dose group, there were no measurable concentrations of free fluticasone propionate in plasma at any of the sampling time points, indicating the drug remained in the joint. See Figure 9.

 In the high dose group, measurable but low plasma concentrations occurred on Day 3 after injection and ranged from 0.2 to
10 0.5 ng/mL. On the other hand, local concentrations of the drug in the synovial fluid and tissue were significantly higher throughout the entire period of the study. See Figure 10.

 The highest concentrations of fluticasone propionate in synovial fluid generally occurred on Day 7 in both dose groups and ranged from 3 to
15 25 ng/mL in the low dose group (Figure 9) and 179 to 855 ng/mL in the high dose group (Figure 10). In the low dose group, measurable fluticasone propionate concentrations in synovial fluid were detected at Day 60, but concentrations were below the limit of quantification (1.0 ng/mL) at this collection time point. Fluticasone propionate concentrations in synovial fluid of
20 high dose animals at Day 60 were 97 to 209 ng/mL.

EXAMPLE 12

COMPARATIVE RESULTS – SHEEP VS. DOG STUDIES

 Figure 6 demonstrates the impact on dissolution characteristics by a thermal processing step during the microparticle formation. In particular,
25 microparticles that have undergone a precision thermal processing step (220°C for 1.5 hours) exhibited a significantly longer dissolution half-life than that of microparticles that have undergone a thermal processing step at a much lower temperature (130°C for 3 hours). The result indicates that the precision thermal processing step at 220°C has caused certain structural changes in the
30 polymeric shell that in turn altered its permeation characteristics.

5 Microparticles that have undergone different thermal processing steps were used in the sheep study (heat-treated at 130°C) and dog study (heat-treated at 220°C) and their *in vivo* sustained release behaviors were discussed in Examples 9 and 10, respectively.

- 5 Figure 11 shows the plasma concentrations measured in the sheep study as compared to those in the dog study. As shown, the plasma concentrations in the sheep study exhibited much higher concentrations after 3 days, when compared to those in the dog study, despite the fact that the sheep received a substantially lower dose (0.25mg/kg) than the dogs (1.2mg/kg).
- 10 Moreover, the plasma concentrations in the dogs were largely constant before they became undetectable. In contrast, the plasma concentrations in the sheep exhibited more variations over the release period. The results indicate that the thermal processing step during the microparticle formation had a significantly impact on the release behaviors *in vivo*, much like it did on the dissolution
- 15 behaviors *in vitro* (See Example 8).

EXAMPLE 13

LACK OF INITIAL BURST

- Fluticasone propionate microparticles were prepared according to Example 8. Microparticles having mean diameters in the range of 50-100 µm
- 20 were used to study the plasma pharmacokinetic (PK) in the first two days following injection. Two groups of dogs (n=3 per group) were injected with a 2mg dose (low dose) and a 60mg dose (high dose), respectively.

- Most sustained release formulations are expected to exhibit an initial burst or a peak in the plasma within the first 48 hours following dosing.
- 25 Unexpectedly, however, the FP sustained release formulation according to an embodiment of this disclosure shows no initial burst. Figure 12 shows a complete absence of initial burst or peak in the first 2 days in the high dose group and all samples were below limit of quantification (albeit detectable). In the low dose group only a single sample was detectable, but was below
- 30 quantification. Accordingly, the sustained release formulations described

herein are capable of highly localized delivery of a corticosteroid (e.g., fluticasone propionate) while keeping the systemic corticosteroid below the level that may result in any clinically significant HPA axis suppression. Significantly, the complete absence of an initial burst in even the high dose
5 group indicates that the *in vivo* release is following a zero-order or pseudo-zero order pattern.

All of the above U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-
10 patent publications referred to in this specification and/or listed in the Application Data Sheet, are incorporated herein by reference, in their entirety.

CLAIMS

WE CLAIM:

1. A pharmaceutical composition, comprising:
a plurality of microparticles, the microparticle including:
 - (1) a drug core of more than 90% by weight of the microparticle, the drug core including one or more therapeutic agents selected from an anesthetic, an antibiotic agent, a central nerve system (CNS) agent, or a chemotherapeutic agent; and
 - (2) a polymeric shell encapsulating the drug core, the polymeric shell being in contact but immiscible with the drug core,wherein the plurality of microparticles have a mean diameter in the range of 80 μm to 150 μm and a standard deviation of less than 50% of the mean diameter.
2. The pharmaceutical composition of claim 1 wherein the plurality of microparticles have a mean diameter of 75 μm and a standard deviation of less than 50% of the mean diameter.
3. The pharmaceutical composition of claim 2 wherein the plurality of microparticles have a mean diameter of 150 μm and a standard deviation of less than 50% of the mean diameter.
4. The pharmaceutical composition of any one of claims 1-3 wherein more than 90% of the microparticles have diameters in the range of 100-300 μm .
5. The pharmaceutical composition of any one of claims 1-3 wherein more than 90% of the microparticles have diameters in the range of 50-100 μm .

6. The pharmaceutical composition of any one claims 1-5 wherein the therapeutic agent is an anesthetic agent.

7. The pharmaceutical composition of any one claims 1-5 wherein the therapeutic agent is a central nerve system agent.

8. The pharmaceutical composition of any one claims 1-5 wherein the therapeutic agent is an antibiotic agent.

9. The pharmaceutical composition of any one claims 1-5 wherein the therapeutic agent is a chemotherapeutic agent.

10. A method of managing pain in a body compartment of a patient in need thereof, comprising injecting to the body compartment a therapeutically effective amount of pharmaceutical composition of claim 6.

11. A method of treating central nerve system disorder in a patient in need thereof, comprising injecting to the patient a therapeutically effective amount of pharmaceutical composition of claim 7.

12. The method of claim 11 wherein pharmaceutical composition is capable of sustained-release of the CNS drug for a period of 2-12 months while maintaining a minimum therapeutically effective concentration of the CNS drug within the patient.

13. A method of treating infection in a body compartment of a patient in need thereof, comprising administering to body compartment of the patient the pharmaceutical composition of claim 8.

14. The method of claim 13 wherein the pharmaceutical composition is administered by injection.

15. The method of claim 13 wherein the pharmaceutical composition is combined with an implant, a surgical mesh, surgical film or surgical membrane.

16. The method of claims 13-15 wherein pharmaceutical composition administered is capable of sustained-release of the antibiotic agent, for a period of 1-7 days while maintaining a minimum therapeutically effective concentration of the antibiotic agent within the body compartment.

17. A method of treating cancer or tumor in a patient in need thereof, comprising administering to the patient a pharmaceutical composition of claim 9.

18. The method of claim 17 wherein the pharmaceutical composition is administered by injecting systemically or into a body compartment adjacent to a solid tumor.

19. The method of claim 17 or claim 18 wherein the pharmaceutical composition is capable of sustained-release of the chemotherapeutic agent for a period of 2-12 months while maintaining a minimum therapeutically effective concentration of the chemotherapeutic agent within the body compartment.