

SUSTAINED RELEASE FORMULATIONS OF LOCAL ANESTHETICS

BACKGROUND

Technical Field

This disclosure relates to sustained release formulations of local
5 anesthetics and methods of using the same for managing pain, in particular,
postsurgical pain.

Description of the Related Art

Postsurgical pain is associated with various complications and
can be protracted. The patients typically experience acute pain immediately
10 after surgery and moderate to severe pain during the first 24 hours after
discharge. Thereafter, although the pain decreases over time, it generally
remains severe enough to interfere with daily activities and healing for several
days after surgery.

Conventionally, postsurgical pain may be managed by opioid
15 agents. Opioid agents produce analgesia by interacting with the opioid
receptors in the central nervous system. However, opioids even at low doses
can produce significant adverse events, such as respiratory depression,
drowsiness and sedation.

Unlike the opioids, local anesthetics bind directly and reversibly to
20 the intracellular portion of sodium channels located in the plasma membrane of
nerve cells. Analgesia is produced as the decrease of the influx of sodium ions
prevents the propagation of impulses along the nerve. The degree of nerve
block is governed by the frequency with which the sodium channels are open
and exposed to the drug. Typically, the smaller, pain-transmitting nerve fibers
25 are more sensitive to local anesthetics than the larger nerve fibers that mediate
touch and pressure.

In the immediate postsurgical period, temporary analgesia can be
achieved by infiltration of local anesthetic into the surgical site at closure or
injection of the local anesthetic into an appropriate peripheral nerve fascia or

the surrounding area. However, local anesthetics have analgesic activity for much shorter duration than the duration of postsurgical pain. Thus, patients may experience breakthrough pain that necessitates the use of strong parenteral analgesics such as opioids.

5 Extending the duration of the local analgesic can be effective in managing postsurgical pain while decreasing or eliminating the need for opioids. For instance, a single-dose injection of a sustained release formulation of liposomal bupivacaine (EXPAREL®) reportedly achieves postsurgical pain control of up to 72 hours, about 10 times longer than the duration of action of
10 conventional bupivacaine (7 hours or less). In particular, EXPAREL® provides sustained release of bupivacaine HCl from a multivesicular liposomal drug delivery system. The liposomal delivery system (DepoFoam®) includes microscopic spherical particles composed of hundreds of nonconcentric aqueous chambers encapsulating the drug. Each chamber is separated from
15 its neighboring chambers by a lipid bilayer membrane. Once administered, the liposomal structure progressively erodes, allowing the drug to be released over an extended period of time.

 However, because membranes formed by lipid bi-layers are dynamic, they can be destabilized by a multitude of factors including pH,
20 temperature, high drug loading and the like. Such destabilization can disrupt the desired release profiles by causing leakages or burst release of the encapsulated drug. Moreover, the liposomal delivery system is often constricted in the choice of drugs, because only water-soluble drugs are suitable to be encapsulated in the aqueous chambers.

25 Accordingly, there is a medical need to seek alternative delivery systems for achieving sustained release of local anesthetics.

BRIEF SUMMARY

 Described herein are pharmaceutical formulations, injectable dosage forms and method of using the same for treating or managing pain, in
30 particular, postsurgical pain. More specifically, the present disclosure provides

injectable microparticles, each particle including a crystalline local anesthetic agent substantially encased in a polyvinyl alcohol (PVA) coating. The PVA coating remains substantially intact during the delivery period, while the local anesthetic agent releases by diffusing through the PVA coating. The release
5 rate and duration are controlled by the PVA structure (including molecular weight, level of hydrolysis and crystallinity), the curing process of the PVA coating, and the thickness of the PVA coating, among other parameters.

Thus, one embodiment provides a pharmaceutical composition, comprising: a plurality of microparticles, each microparticle including: (1) one or
10 more crystals of a local anesthetic agent; and (2) a polyvinyl alcohol (PVA) coating fully encapsulating the one or more crystals, wherein the PVA coating is at least 85% hydrolyzed and is about 1-30 wt% of the microparticle, and wherein the one or more crystals of the local anesthetic agent is about 70-99 wt% of the microparticle and each has at least one dimension in a range of 35-
15 500µm.

In a further embodiment, the local anesthetic agent is an aminoamide drug, in particular, ropivacaine.

In additional embodiments, the aminoamide drug or ropivacaine is in a free base form.

20 In further embodiments, the local anesthetic agent comprises more than one crystals bound by a therapeutically inactive agent.

In various embodiments, the PVA coating has a molecular weight (Mn) of 2-200kDa and is at least 85% hydrolyzed. In other embodiments, the PVA coating has a molecular weight (Mn) of 140-190kDa and is at least 99%
25 hydrolyzed.

In a specific embodiment, the PVA coating is thermal cured and physically crosslinked at conditions such as curing at 100-135 °C for 2-8 hours.

In other embodiments, the PVA coating is chemically crosslinked in the presence of a crosslinking agent.

30 In more specific embodiments, the the PVA coating comprises less than 5% by weight of the crosslinking agent.

Advantageously, the pharmaceutical composition described herein show a dissolution rate of the local anesthetic agent at least 5 times slower, or at least 7 times slower, or at least 10 times slower than the dissolution rate of an uncoated local anesthetic agent in the same dissolution medium.

A further embodiment provides a method for managing postsurgical pain at a wound site of a patient in need thereof, comprising either infusing to the wound site a therapeutically effective amount of the coated local anesthetic agent as described herein or injecting the coated local anesthetic agent into an appropriate peripheral nerve fascia or the surrounding area.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

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 1A shows the dissolution behaviors of commercial ropivacaine of finer crystals and the larger, recrystallized ropivacaine.

Figure 1B shows particle size distribution of commercial ropivacaine fine powder.

Figure 1C shows particle size distribution of sieved ropivacaine recrystallized crystals.

Figure 2 shows the intrinsic dissolution of uncoated ropivacaine as compared to ropivacaine coated with PVA membrane.

Figure 3 shows the diffusion rate for the first 5 hours for PVA membranes (146-186kDa, 87% hydrolyzed) at various degrees of crosslinking.

Figure 4 shows the diffusion rate for the first 5 hours for PVA membranes (146-186kDa, 99% hydrolyzed) at various degrees of crosslinking.

Figure 5 shows the diffusion rate for the first 5 hours for PVA membranes (20-220kDa, 87% hydrolyzed) at various degrees of crosslinking.

Figure 6 shows the dissolution rate of ropivacaine from coated microparticles as impacted by the content (e.g., thickness) of the PVA coating (thermally cured).

Figure 7 shows the SEM images of uncoated particles (A and B) and coated particles (C and D) by PVA.

Figures 8A and 8B show the slowed dissolution of coated ropivacaine crystals was proportional to the amount of PVA coating.

Figure 9 shows the DSC curves of commercial PVA, PVA membrane and thermally cured PVA membrane.

Figure 10 shows the FTIR spectra of PVA membrane (uncured) and thermally cured PVA membrane.

DETAILED DESCRIPTION

Described herein are pharmaceutical compositions, injectable dosage forms and method of using the same for treating or managing pain, in particular, postsurgical pain. More specifically, the present disclosure provides injectable microparticles, each particle including a crystalline local anesthetic agent substantially encased in a polyvinyl alcohol (PVA) coating. The PVA coating remains intact during the delivery period, while the local anesthetic agent releases by diffusing through the PVA coating. The release rate and duration are controlled by the curing process of the PVA coating and the thickness of the PVA coating, among other parameters.

As discussed in further detail herein, the injectable microparticles are characterized with high drug-loading, narrow size distribution and a sustained, steady release profile over a certain period within soft tissue (e.g., a wound site following surgery), or subcutaneously, or within a body compartment or a peripheral nerve fascia or the area surrounding a peripheral nerve fascia. In particular, for postsurgical pain management, the steady release may preferably take place over a period of 72 hours, or more preferably 96 hours.

The sustained and steady 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 crystalline drug coated with semi-permeable PVA membrane is injected into the tissue, fluid (water) from the tissue diffuses through the polymeric coating and partially dissolves the crystalline drug core. As a result, a saturated solution of the drug is formed
5 inside the polymeric coating, which remains intact throughout the release period. Since there are essentially sink conditions in the fluid in which the 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
10 solution within the polymeric shell, a constant and steady release of the drug from the coated microparticles is obtained. The release mechanism is described in PCT/US2014/031502, which application is incorporated herein in its entirety.

Microparticles

15 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 local anesthetic agent, in particular, an aminoamide local anesthetic agent, which is in the form of crystals coated with polyvinyl alcohol (PVA).

20 More specifically, each drug-loaded microparticle includes (1) one or more crystals of a local anesthetic agent; and (2) a polyvinyl alcohol (PVA) coating fully encapsulating the one or more crystals, wherein the PVA coating is at least 85% hydrolyzed and is about 1-30 wt% of the microparticle, and wherein the one or more crystals of the local anesthetic agent is about 70-99
25 wt% of the microparticle and each has at least one dimension in a range of 35-500µm.

Local Anesthetic Agent ("Drug")

Two classes of local anesthetic agents are suitable: aminoamide and aminoester local anesthetics.

Aminoamide local anesthetic agents include, without limitation ropivacaine, articaine, bupivacaine (levobupivacaine), dibucaine, etidocaine, lidocaine, mepivacaine, prilocaine, and trimecaine. In a particularly preferred embodiment the local anesthetic agent is ropivacaine.

5 Aminoester local anesthetic agents include, without limitation, benzocaine, chloroprocaine, cocaine, cyclomethycaine, dimethocaine (Larocaine), piperocaine, propoxycaine, procaine (Novocaine), proparacaine, and petracaine (Amethocaine).

It is found that larger crystals of a drug compound have lower rate
10 of dissolution than the amorphous form or fine crystals of the same drug, resulting in a longer dissolution half-life and less initial burst. Larger crystals of the local anesthetic agents can be prepared by recrystallizing the amorphous powder or small fine crystals of the drug (which are the typical commercial forms).

15 Figure 1A shows the dissolution behaviors of commercial ropivacaine as received (in fine powder form) and recrystallized ropivacaine. As shown, the rate of dissolution of the larger, recrystallized ropivacaine crystals is slowed by about 10 times as compared to commercial ropivacaine.

Recrystallization produces large crystal dimensions, which make it
20 possible to resize the drug crystals into substantially uniform dimensions. For example, fine crystals of ropivacaine (in the 100 μ m or lower range) can be recrystallized (e.g., by slow-evaporation) to produce large crystals having dimensions in the millimeter range. The larger crystals can be resized (shortened) and sieved before coating. Figure 1B shows the size distribution of
25 commercial ropivacaine fine powders. As a comparison, Figure 1C shows the size distribution of recrystallized ropivacaine crystals after resizing and sieving. As shown, not only are the recrystallized crystals are larger on average, they may also have narrower particle size distribution than the commercial fine powder.

30 Drug crystals that are recrystallized, resized and sieved can be better controlled to provide drug crystals of uniform size or shapes. In certain

embodiments, the drug crystals have at least two dimensions that are substantially the same in sizes, providing an aspect ratio (*i.e.*, length/diameter) of 1.

The local anesthetic agent thus comprises one or more
 5 recrystallized drug crystals having at least one dimension (*e.g.*, the longest dimension) in the range of 35-500 μ m, and more typically in the range of 75-300 μ m, or more typically, in the range of 50-200 μ m. In various embodiments, the crystals have at least one dimension in the range of 35-200 μ m, or 75-200 μ m, or 100-300 μ m, or 100-200 μ m, or 200-300 μ m, or 200-400 μ m. Larger
 10 crystals (*e.g.*, $\geq 200 \mu$ m) may be coated individually; whereas one or more smaller crystals may be bonded into crystal aggregates or clusters before coating. When in aggregates, drug crystals may be bonded or glued together by a pharmaceutically inactive agent that serves as an adhesive.

In various embodiments, at least 90%, or at least 95% or at least
 15 98%, or 100% of the entire weight of the crystalline drug is the local anesthetic agent. The drug-loading, *i.e.*, the content of pure local anesthetic agent of the entire weight of the microparticle, is in turn about 70-99 wt%.

As used herein, the aminoamide local anesthetic agents are typically in the free base form, which have lower solubility in an aqueous
 20 medium than their salt form (*e.g.*, HCl salt). The low solubility (*e.g.*, less than 1mg/ml) enables a rapid formation of a saturated solution within the PVA coating or shell. Table 1 shows the solubility of ropivacaine in various aqueous media that include PBS buffer (pH 7.4), sodium dodecyl sulfate (SDS), or bovine serum albumin (BSA).

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TABLE 1

Aqueous solutions	Solubility of ropivacaine (μ g/mL)
PBS	254 $\pm$ 13
PBS + 0.05% SDS	254 $\pm$ 14
PBS + 0.1% SDS	306 $\pm$ 18
PBS + 0.2% SDS	350 $\pm$ 12
PBS + 68 mg/mL BSA	792 $\pm$ 111

Because the PVA coating requires curing at elevated temperature (e.g., about 125°C), the aminoamide local anesthetic agents should be heat-stable, at least at the curing temperatures. For example, ropivacaine (commercial or recrystallized) has a peak T_m of about 148-149°C and is shown

5 to be stable below the melting temperature.

PVA Coating/Membrane

One or more crystals of the local anesthetic agent (e.g., recrystallized ropivacaine) are coated with polyvinyl alcohol (PVA). PVA is a water-soluble polymer that forms films easily at above certain molecular weight.

10 The PVA coating substantially encases the crystals. Complete (100%) coverage is preferred but not required.

The PVA coating, also referred to as PVA membrane, is permeable to water and allows the formation of a saturated solution of the encapsulated local anesthetic agent. The dissolved local anesthetic agent then

15 diffuses out of the PVA coating in a sustained and steady manner until the saturated solution can no longer be maintained (i.e., the local anesthetic agent is depleted). For postsurgical pain management, the period of sustained and steady release typically lasts 72 to 96 hours, or 72 to 120 hours (3-5 days) after administration or post-surgery.

20 The permeability of the PVA coating is determined by multiple factors, including the molecular weight, the degree of hydrolysis, the degree of crystallinity, the degree of crosslinking and the thickness of the coating. Without wishing to be bound to any theory, it is believed that as the PVA swells and progressively dissolves in a liquid medium, the permeability increases and

25 drug diffusion occurs.

Suitable PVA has a molecular weight (M_n) in the range of 20-220kDa, or more preferably 140-190kDa. In various embodiments, the PVA has a molecular weight (M_n) in the range of 146-187kDa. In other embodiments, the PVA has a molecular weight (M_n) in the range of 90-120kDa.

Commercial PVA polymers are generally derived from polyvinyl acetate by hydrolysis (*i.e.*, converting the acetate to hydroxy). Thus, PVA polymers are available at different degrees of hydrolysis.

The degree of hydrolysis influences the crystallinity of the PVA coating because the hydroxyl groups can form hydrogen bonds between PVA chains, thereby orienting them in an ordered fashion. Thus, a higher content of hydroxyl group (*i.e.*, high degree of hydrolysis) typically is associated with a higher degree of crystallinity. Higher crystallinity renders the PVA membrane slower to dissolve, resulting in a slower diffusion of the encapsulated drug. Thus, as used herein, the PVA is at least 85% hydrolyzed, or at least 87% hydrolyzed, or preferably at least 98% or at least 99% hydrolyzed.

In order to achieve the desired permeability, the highly hydrolyzed PVA coating may be further thermally cured (physically crosslinked), chemically crosslinked or both.

The degree of the crystallinity of the PVA coating may be controlled by thermal curing at a certain temperature for a certain period of time, provided that the curing temperature is below the melting temperature of the crystalline local anesthetic agent. In various embodiments, suitable curing temperature may be in a range of 100-135°C for 2-8 hours. In certain embodiments, the curing temperature is in the range of 120-135°C for 4-8 hours. In a preferred embodiment, the PVA coating is cured at 125°C for 6 hours. As a result of the thermal curing, the PVA chains may be physically crosslinked.

The degree of the permeability (dissolvability) of the PVA coating may also be controlled by chemically crosslinking between hydroxyl groups. The additional covalent bonding within the polymer structure impedes the dissociation of the polymer chains, thereby slowing down or prevents the dissolution of the PVA. Suitable crosslinkers include organic polyprotic acids, (*i.e.*, acids having two or more carboxylic groups). In various embodiments, the crosslinker may be citric acid, tartaric acid, oxalic acid, succinic acid, gluconic acid and the like. In a preferred embodiment, the crosslinker is citric acid,

which has three carboxylic acid groups. In various embodiments, crosslinking occurs by incorporating a crosslinker in the PVA solution prior to coating. Typically, the amount of crosslinker required depends on the level of hydrolysis of the PVA. For highly hydrolyzed PVA (87% or above) as used herein, less
 5 than 20%, or less than 12%, or less than 8% of the crosslinker is employed.

The degree of crystallinity may be measured by melting enthalpy. A higher degree of crystallinity is associated with a higher melting enthalpy and a higher glass transition temperature. Table 2 shows the effects of the degrees of hydrolysis, thermal curing and crosslinking on the crystallinity of PVA films
 10 (all PVA have $M_n = 146\text{--}186\text{kDa}$, data obtained from first heating cycle).

TABLE 2

Degree of Hydrolysis	Curing	Citric acid (%)	Melting (T_m)			Degradation (T_d)		
			Onset ($^{\circ}\text{C}$)	Peak ($^{\circ}\text{C}$)	Enthalpy (J/g)	Onset ($^{\circ}\text{C}$)	Peak ($^{\circ}\text{C}$)	Enthalpy (J/g)
99%	As received	0	209.69	222.05	55.2	243.93	261.40	501
99%	125 $^{\circ}\text{C}/6\text{h}$	0	215.09	223.63	48.43	228.86	259.18	228.86
99%		4	209.82	216.68	50.77	272.64	303.53	542.6
99%		8	183.00	200.24	47.45	271.79	302.8	451.6
99%		12	179.00	199.48	24.55	299.34	312.12	227.4
87%	As received	0	176.42	189.52	25.45	Out of range		
87%	125 $^{\circ}\text{C}/6\text{h}$	4	161.7	174.95	13.05	269.76	309.24	134.9
87%		8	144.81	158.81	22.46	279.09	317.77	139.6
87%		12	142.83	160.09	24.43	283.04	318.32	70.94

As shown, for highly hydrolyzed PVA (> 99%), exposure to a crosslinking agent does not increase but could decrease crystallinity. It is
 15 believed that chemical crosslinking by a crosslinking agent such as citric acid may have disrupted the hydrogen bonding naturally present in the highly hydrolyzed PVA chains, resulting in a decreased degree of crystallinity.

The PVA coating should remain substantially intact during the sustained release period, though swelling (due to hydration) or minor/partial
 20 dissolution will likely take place concurrently with the drug release. PVA is

water soluble due to the high content of hydroxyl groups. However, highly hydrolyzed PVA or crosslinked PVA have slower dissolution rates because of their highly ordered structure or the additional intrinsic covalent bonds, respectively. Thus, while 87%-hydrolyzed PVA coatings (following curing at 130°C for 6.5 hours) can dissolve in water in one day, 87%-hydrolyzed PVA coatings exposed to 6% citric acid and cured under similar conditions remain intact for up to 158 days.

Compared to chemical crosslinking, physical-crosslinking by heating and curing can be advantageous. By forming physical crosslinking points (e.g., by creating additional hydrogen-bonding) without disrupting the naturally aligned hydrogen bonding in the highly hydrolyzed PVA chains, a physically-crosslinked PVA membrane can be optimized to provide the desired degrees of crosslinking and crystallinity.

Table 3 shows the DSC analysis of commercial PVA, PVA membrane and heat-treated PVA membrane (cured at 125 °C for 6 hrs, data obtained from second heating cycle). All PVA were 99% hydrolyzed with molecular weight of 146-186 kDa. As shown, the cured PVA membrane was physically crosslinked without little or no loss of crystallinity as evidenced by only slight changes in their melting points.

20

TABLE 3

	Glass transition (T _g , °C)	Melting point on set (°C)	Melting point peak (T _m , °C)	Melting enthalpy (Δ, J/g)
PVA	76.80	218.09	225.68	51.26
PVA membrane	71.81	213.48	224.23	48.41
Cured PVA membrane	74.41	212.57	222.20	47.71

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.

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No. 5,639,480), spray-drying techniques (see, e.g., U.S. Pat. No. 5,651,990), air suspension techniques, and dip coating techniques.

Typically, a solution of PVA in water (1-15%) is prepared and spray-coated on the drug crystals, following recrystallization and sizing. One or
5 more crystals may be substantially encased in a continuous membrane of PVA (though 100% coverage is not required). Where crosslinking is required (e.g., PVA less than 99% hydrolyzed), the crosslinker may be dissolved in the PVA solution prior to coating.

The coated particles are subject to thermal curing at a
10 temperature of about 100-135°C for 2-8 hours.

The PVA coating is typically about 1-20%, more typically, about 1-10% of the entire weight of the microparticle. The content of the PVA can be ascertained by NMR quantification by comparing certain selected peak areas (e.g., 3.7-4.0 ppm) with a standardized amount of PVA.

15 In various embodiments, the thickness of PVA coating can be in the range of 5-60µm, or in the range of 10-30µm. The thickness can be directly measured in SEM images. For instance, for coated ropivacaine particles, 10% of PVA (by weight) was shown to be less than 15 µm thick. The thickness of the PVA coating can be controlled by the concentration of the PVA solution for
20 coating and the number of coatings. Thicker coatings result in slower diffusions.

Because the PVA coating is thin compared to the crystalline drug encapsulated, the microparticles formed substantially take the shapes and sizes of the encapsulated crystals. Thus, in various embodiments, the
25 microparticles (when taking into consideration of the coating thickness) have at least one dimension (e.g., the longest) of 35-500 µm, or more typically, 75-300 µm. In certain embodiments, the coated particles have the same aspect ratio as the encapsulated drug crystals. Microparticles of these sizes are large enough for a large payload of the local anesthetic agent, yet small enough to be
30 injected through a needle.

In vitro Dissolution Characteristics

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 factors, the solubility of the local anesthetic agents, and the permeability of the PVA coating.

It is important to recognize that dissolution models are designed to give an approximation of the dissolution as compared to *in vivo* release. 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.

The dissolution characteristics can be measured as the percentage of dissolution over time, and graphed as a dissolution profile. A linear dissolution profile has a constant rate of dissolution as represented by the slope of the linear profile. Constant rate of dissolution is associated with zero-order release, *i.e.*, the rate of release is irrespective of the amount of the drug encapsulated in the PVA coating. 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.

Unless specified otherwise, the dissolution system used for measuring dissolution half-life of the microparticles is USP Type II (paddle). It is important to recognize that dissolution models are designed to give an approximation of the dissolution as compared to *in vivo* release. 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.

A typical dissolution model used herein is USP apparatus I. A typical small capacity apparatus has a 150ml bath. Other parameters include for example, 25-200 rpm, 37°C and 0.1% SDS/PBS.

Compared to the uncoated drug, the coated particles slow the dissolution rate of the encapsulated local anesthetic agent. The dissolution rates of the coated drug crystals are directly related to the permeability of the PVA coating, which is in turned determined by the thickness, molecular weight, 5 degrees of crosslinking, degrees of crystallinity etc. of the PVA coatings. Thus, in certain embodiments, the dissolution characteristics of the coating drug crystals can be defined by the reduction of the dissolution rate of the coated drug crystals as compared to the dissolution rate of the same drug crystals but uncoated, as measured in the same dissolution medium. In various 10 embodiments, the coated microparticles exhibit a dissolution rate of at least 10-fold reduction when compared to the dissolution rate of the uncoated drug crystals of the same dimensions in the same dissolution medium. In other embodiments, the reduction in dissolution rate may be 8 folds, 7 folds, 6 folds, 5 folds, 4 folds or 3 folds when compared to uncoated drug crystals.

15 The reduction in dissolution rate can be modulated by adjusting the degrees of crosslinking (physical or chemical), thickness, crystallinity of the PVA membrane. The dissolution rate is creatable to the in vivo release period. In various embodiments, the coated microparticles are capable of local, sustained release of 3-5 days.

20 Figure 2 shows the intrinsic dissolution of ropivacaine, which is much more rapid than ropivacaine coated with PVA membrane (Mn=20-200kDa, 87% hydrolyzed, crosslinked using 12% citric acid and cured at 125°C for 6 hours).

Figure 6 (see also Example 7) shows that, compared to the 25 dissolution rate of uncoated ropivacaine crystals, coated ropivacaine crystals have much decreased rates of dissolution. More specifically, for 1% PVA (99% hydrolyzed and MW=146-187kDa), the decrease in rate of dissolution is about 3.5 folds; whereas for particles with thicker coatings (9% PVA), the decrease is about 6.5 folds.

In vitro Diffusion Characteristics

When the coated microparticles are administered to a patient, water from the surrounding tissue permeates through the PVA membrane, forming a saturated solution of the encapsulated drug within the membrane. In
 5 a zero-order or pseudo-zero order release, the dissolved drug diffuses through the PVA membrane in a steady and sustained manner.

The diffusion behavior of the encapsulated drug *in vivo* can be predicted based on diffusion coefficient measured in a Franz cell diffusion system. In particular, diffusion coefficient (D) can be quantified according to
 10 Equation 1:

$$D = \frac{L \times J}{\Delta C} \quad \text{Eq. (1)}$$

where:

- D: Diffusion coefficient (cm²/s)
- L: membrane thickness (cm)
- J: flux: (μg×cm⁻²×s⁻¹) = slope (μg/mL/h) × volume (9.8 mL) ÷ (3600 s/h × A cm²)
- A: surface area of the Franz cell (0.650 cm²)
- ΔC: concentration gradient of ropivacaine (μg/mL or μg/cm³) = 339.98 μg/mL (measured receptor fluid concentration) – 0 μg/mL (assumed donor concentration)

Table 4 summarizes diffusion through four polymers prepared as membranes using a range of curing conditions (temperature/time), cross-linking
 15 conditions (with varying amounts of citric acid). Table 3 also compares the values in terms of fold changes (decreases) in ropivacaine diffusion coefficient, relative to buffer with no membrane.

TABLE 4

% Hydrolysis	PVA Mn. (kDa)	Cross-linking Parameters			Polymer Film Properties		Fold Decrease in D
		%	Temp. (°C)	Time (h)	Swelling (%)	D (cm ² /s)	
87	146-186	4	125	6	292	2.32E-07	21
87	146-186	12	125	6	122	2.90E-07	17
87	146-186	4	125	6	318	2.64E-07	19
87	146-186	12	125	6	162	3.85E-07	13
87	146-186	8	125	6	168	2.30E-07	22
87	146-186	8	125	6	167	2.93E-07	17
87	20-220	4	125	6	449	1.94E-07	26
87	20-220	4	125	6	509	2.23E-07	22
87	20-220	8	125	6	255	2.20E-07	23
87	20-220	8	125	6	230	3.01E-07	17
87	20-220	12	125	6	273	4.30E-07	12
87	20-220	12	125	6	285	5.43E-07	9
87	20-220	20	125	6	203	6.26E-07	8
87	20-220	20	125	6	233	3.64E-07	14
87	20-220	30	125	6	148	4.88E-07	10
87	20-220	30	125	6	139	2.82E-07	18
>99	90	8	125	6	183	1.68E-07	30
>99	90	8	125	6	186	1.99E-07	25
>99	90	12	125	6	235	3.59E-07	14
>99	90	12	125	6	245	3.41E-07	15
>99	90	20	125	6	137	2.38E-07	21
>99	90	20	125	6	134	2.01E-07	25
>99	146-186	0	125	6	59	9.09E-08	55
>99	146-186	0	125	6	41	9.21E-08	54
>99	146-186	0	129	3	81	1.47E-07	34
>99	146-186	0	140	6	87	1.33E-07	37
>99	146-186	0	140	6	56	1.19E-07	42
>99	146-186	4	125	6	135	2.40E-07	21
>99	146-186	4	125	6	129	2.15E-07	23
>99	146-186	4	140	6	106	1.97E-07	25
>99	146-186	4	140	6	113	1.44E-07	34
>99	146-186	8	125	6	142	2.02E-07	25
>99	146-186	8	125	6	178	1.91E-07	26
>99	146-186	12	125	6	94	2.41E-07	21
>99	146-186	12	125	6	105	2.18E-07	23

As shown in Table 4, PVA membranes of 146-186kDa and >99% hydrolysis (after thermal curing and physical crosslinking) had the greatest

impact on diffusion, causing a 50-times decrease in diffusion coefficient when compared to the diffusion of ropivacaine in PBS (4.97×10^{-6}).

Pharmaceutical Compositions

The present disclosure provides a pharmaceutical composition comprising a plurality of drug-loaded microparticles, wherein each drug-loaded microparticle includes (1) one or more crystals of a local anesthetic agent; and (2) a polyvinyl alcohol (PVA) coating fully encapsulating the one or more crystals, wherein the PVA coating is at least 85% hydrolyzed and is about 1-30 wt% of the microparticle, and wherein the one or more crystals of the local anesthetic agent is about 70-99 wt% of the microparticle and each has at least one dimension in a range of 35-500 μ m.

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 local anesthetic 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 local anesthetic agent for a specified period.

For postsurgical pain, the quantity of the microparticles in a unit dosage depends upon several factors including the surgical site and the volume required to cover or fill the area. In various embodiments, the unit dosage form comprises 100-3000 mg of local anesthetic agent. In other embodiments, the unit dosage form comprises 500-2000mg of therapeutic agent. For example, in a soft tissue surgery (hemorrhoidectomy), about 1600mg of the local anesthetic agent constituted in a volume of 3ml could be administered. In an orthopedic model (bunionectomy), a dose of about 600 mg in 8ml could be administered.

Other factors include the body weight and the age of the patient, the severity of pain, or the risk of potential side effects considering the general health status of the person to be treated.

Advantageously, because the drug-loaded microparticles
5 described herein are capable of steady release with little initial burst, the initial loading of the drug in the unit dosage form can be rationally designed according to the desired sustained release period. In various embodiments, the sustained release period is 72 hours or 96 hours.

In various embodiments, the unit dosage form may be a syringe
10 pre-filled with the appropriate amount of the microparticles. Immediately prior to infusion, a vehicle may be drawn into the syringe to reconstitute the microparticles. 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-
15 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 can be used for subcutaneous, peripheral nerve blockade, intrathecal,
20 epidural, or intraperitoneal administrations.

The pharmaceutical compositions are particularly suited to be
injected into a body compartment for highly localized, sustained release of local
anesthetic agent. The body compartment typically contains soft tissue and/or
fluid within an enclosure or semi-enclosure. The injection is directed to the soft
25 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.

One embodiment provides a method for reducing or managing
pain, e.g., due to surgical pain, by administering an injectable dosage form to a
30 body wound site before closure. Advantageously, the release is highly
localized within the local tissue or fluid medium of the wound site to ensure a

long-acting local therapeutic level, while maintaining a low or undetectable systemic level of the drug.

In a further embodiment, prior to infusion, the method includes administering a fast-acting local anesthetic agent such as lidocaine or uncoated ropivacaine, may be administered to provide immediate pain relief.

Another embodiment provides a method for reducing or managing pain, *e.g.*, due to surgical pain, by administering an injectable dosage form to a peripheral nerve fascia or the area surrounding a peripheral nerve fascia. Advantageously, the release is highly localized to the particular nerve to ensure a long-acting local therapeutic level, while maintaining a low or undetectable systemic level of the drug.

EXAMPLES:

EXAMPLE 1

RECRYSTALLIZATION OF ROPIVACAINE

Commercial ropivacaine contained a significant portion of fine particles (~ 50%). The presence of very small particles is believed responsible for initially rapid dissolution of ropivacaine particles (Figure 1A). To overcome this problem, commercial ropivacaine was recrystallized and resized using standard sieves.

Ropivacaine was recrystallized by cooling a saturated hot solution of ropivacaine, prepared in methanol, 2-propanol or a mixture of both to room temperature (natural cooling). Crystals were separated by vacuum filtration. Large crystals of up to 2000 μm were obtained.

A specific recrystallization process involved slow evaporation of a sub-saturated methanol solution of ropivacaine. More specifically, 20 g of ropivacaine was dissolved in 165 ml methanol at room temperature under stirring; and the solution was let to evaporate slowly over 5-7 days. The process produced large ropivacaine crystals of several millimeters long.

The large crystals were resized by wet milling using a mortar and pestle in a suitable solution such as 50/50 methanol/water, and passed through standard sieved by squirting a suitable solution such as 50:50 methanol/water. Sieves with a range of mesh size were used: 106, 212, 250 and 300 μm .

- 5 Figure 1C shows the particle size distribution of ropivacaine crystals formed after recrystallization (slow evaporation), wet milling and wet sieving.

Table 5 summarizes the particle sizes of ropivacaine crystals obtained from different recrystallization processes (including different solvent systems). Commercial ropivacaine crystals are also presented as comparison.

10

TABLE 5

Crystallization Solvent	Sieving Fraction	Median size (μm) $d_{(50\%)}$
Commercial	Not sieved	41.9
Methanol	250-300 μm	243.1
Methanol (slow evaporation)	106-300 μm	193.0
Methanol/2-propanol	106-212	240.1
Commercial (sieved)	>212 μm	369.0

The larger, recrystallized particles may have smaller/finer crystals attached to the surface. To remove these finer crystals, the recrystallized particles were suspended in a PVA solution, and washed with water.

- 15 Alternatively, the fine crystals may be removed by washing with a mixture of methanol and water during the wet sieving process.

EXAMPLE 2

QUANTIFICATION OF ROPIVACAINE IN SOLUTION

- 20 A Waters UPLC system equipped with a PDA detector was used for isolating and quantifying ropivacaine in buffer solutions. Separation was performed by reverse phase chromatography using a Waters BEH C18 column of 2.1 x 50 mm dimension and 1.7 μm particle size. An aqueous mobile phase of 10 mM ammonium acetate adjusted to pH 10 combined with acetonitrile were

used in a gradient fashion to retain and elute Ropivacaine. A detection wavelength of 206 nm was used for optimum response.

The method was evaluated over a range of 0.5 – 50 µg/mL ropivacaine in 50/50 water acetonitrile (ACN) and in 0.1%SDS in PBS, using 10 µL injection volumes (full loop). The lowest limit of quantitation was 0.5 µg/mL in both solvent systems with an associated precision of within 2% RSD and an average accuracy (percent deviation from theoretical value) of 1%. The calibration curve displayed some loss of linearity (saturation) at the upper limit (50 µg/mL) but a linear fit with 1/x results in excellent accuracy and precision in the low range. Current experiments are performed over a range of 0.5 – 25 µg/mL in order to avoid saturation effects.

EXAMPLE 3

DISSOLUTION OF ROPIVACAINE

Prior to assessing intrinsic dissolution of ropivacaine, the kinetics of dissolution of crystals in suspension was assessed using a USP I apparatus with either large (1 L capacity, filled to 500 mL) or small (150 mL) dissolution baths. The stir speed was 50 rpm in the large vessel method and 100 rpm in the small vessel method and temperature was 37°C. The media was PBS with 0.1% SDS. The commercial ropivacaine was dissolved rapidly with greater than 60% of the material dissolved within 30 minutes. A 17 mg sample dissolving in the large vessel reached a plateau within 4 hours, although only approximately 80% of the ropivacaine added to the experiment was accounted for.

In contrast, ropivacaine recrystallized from methanol did not exhibit the same burst phase, instead showing gradual dissolution over the first 6 hours, accounting for 60% of the material. Approximately 100-120% of the compound was accounted for in this assay. Regression analysis demonstrates that dissolution in the small vessel apparatus was essentially linear after a “burst phase” of dissolution within the first 30 minutes. The Y-intercept values of the regression is representative of the magnitude of the “burst”, which was

25x higher for the commercial sample compared to the recrystallized sample.
See also Figure 1A.

EXAMPLE 4

DIFFUSION OF ROPIVACAINE CRYSTAL THROUGH PVA MEMBRANES

5 The diffusion of ropivacaine through PVA membranes was measured using a Franz diffusion cell system. The system includes a top donor chamber containing a donor fluid, which is sealed with parafilm during the experiment; and a bottom receptor chamber containing a receptor fluid (9.8 mL of PBS pH 7.3). The donor fluid was prepared in a single batch for use in all
10 diffusion experiments, and consisted of PBS pH 7.3. It was prepared by stirring excess solid ropivacaine in the media for 3 days, and filtering to remove the solids with a 0.22 μ m filter. The assayed content was 339.98 μ g/mL.

 The rate of appearance of ropivacaine in the Franz cell receptor fluid (the slope of the concentration versus time plot of the data multiplied by
15 the receptor cell volume, 9.8 mL), and the measured membrane thickness (after hydration), were used to calculate the ropivacaine diffusion coefficient through the membrane, using the formula for Fick's law (Equation 1).

 The concentration of ropivacaine in the receptor (bottom) chamber was measured at different time points, and the diffusion coefficient
20 was determined from Fick's first law of diffusion. Measured concentrations were converted to total drug transport (μ g) by multiplying by the receptor fluid volume (9.8 mL for all experiments). Figures 3-5 show the diffusion rate for the first 5 hours for three PVA membranes at various degrees of crosslinking induced by various amounts of citric acid. All three PVA membranes exhibited
25 linear rate of ropivacaine diffusion. In particular, Figure 3 shows the diffusion rate for PVA (146-186kDa, 87% hydrolyzed). Figure 4 shows the diffusion rate for PVA (146-186kDa, 99% hydrolyzed). Figure 5 shows the diffusion rate for PVA (20-220kDa, 87% hydrolyzed).

EXAMPLE 5

COATING ROPIVACAINE CRYSTALS

Crystals were coated by spray coating by first preparing a PVA solution, including if needed, a crosslinking agent. One or more crystals of the
5 recrystallized ropivacaine were coated and visualized by SEM to determine the completeness of the coating. Larger crystals may be individually coated; however, more than one crystals could be encapsulated within the coating.

Figure 7 shows the SEM images of uncoated particles (A and B) and coated particles (C and D) by PVA (90kDa, 99% hydrolysis) containing 8%
10 citric acid, following heat treatment 125°C for 6 hours. As shown, the coating appeared complete (qualitatively), with coated crystals having a continuous, striated appearance. The coating also appeared to be thin and conformal. There was no distortion of the shape of the underlying crystal (e.g., edges and discontinuities appeared well defined despite coating).

15

EXAMPLE 6

NMR ANALYSIS FOR DETERMINING PVA CONTENT

NMR analysis was used to determine the amounts of the PVA in microparticles by calibrating with samples of known quantity of PVA. A
standard curve to quantify the amount of PVA in a sample containing PVA and
20 ropivacaine was generated by identifying non-overlapping regions of the proton NMR spectra of the two components (the peak between 3.7-4.0 ppm was selected), and integration of the selected peak in solutions containing a standardized amount of PVA. The concentration dependent peak area provided a linear relationship over the range of 4-20%w/v PVA concentration in
25 solution ($R^2 = 0.999$).

EXAMPLE 7

MICROPARTICLES DISSOLUTION ANALYSIS

Dissolution of ropivacaine microparticles was slowed after PVA coating, compared with uncoated crystals, and the effect was proportional to
5 the amount of PVA coating.

Figure 6 shows the dissolution of ropivacaine as impacted by the content (e.g., thickness) of the PVA coating. As shown, for the highly hydrolyzed PVA coating (Mn=146-187kDa, 99% hydrolysis), a higher content of PVA (9%) markedly slows down the ropivacaine diffusion as compared to the
10 particles of lower content PVA or uncoated particles. In particular, the 9% PVA coated particles showed a dissolution rate (%/hr) that was about 7 folds slower than the uncoated particles.

As shown in Figure 8A, all microparticles exhibited a linear rate of dissolution for at least 6 hours. Microparticles coated with 9% PVA and without
15 crosslinking had a constant rate of dissolution over 29 hours. A 10 folds reduction in rate of dissolution (slopes of the linear dissolution profile, see a/s/o Figure 8B) was observed comparing the uncoated crystals and 1% coated microparticles.

Also shown in Figure 8B, for highly hydrolyzed PVA (99%) at 1%
20 content, mild chemical crosslinking (4% citric acid) appeared to cause a decrease in dissolution rate when compared to thermally cured coated particles (0% citric acid), suggesting that the additional covalent bonds formed by the crosslinking agents reduced the dissociation of polymer chains and membrane permeability. However, an increase in chemical crosslinking (8% citric acid)
25 caused an increase in dissolution rate, suggesting that enhanced chemical crosslinking might have lowered the crystallinity of the PVA membrane, which in turn increased the membrane permeability. Figure 8B shows that thermally curing or physical crosslinking (0% citric acid) at 9% PVA (thicker membrane) had the lowest the dissolution rate.

EXAMPLE 8

PHYSICAL CROSSLINKING PVA MEMBRANE

Thermally cured PVA membranes were physically crosslinked without being chemically altered. PVA membrane (99% hydrolyzed, MW=146-
5 186 kDa) were cured at 125 °C for 6 hrs.

Figure 9 shows the DSC curves (obtained from the second heating cycle) of PVA membrane, cured PVA membrane and commercial PVA. As shown (see also Table 3), the thermally cured, physically crosslinked PVA membrane exhibited similar glass transition temperature, melting point as
10 uncured PVA membrane or commercial PVA.

Figure 10 shows the FTIR spectra of PVA and cured PVA membrane. No formation of new functional groups was observed in FTIR analysis.

The absence of any newly formed chemical bonds in the cured
15 PVA membrane was also confirmed by NMR spectra.

All of the above U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification and/or listed in the Application Data Sheet, including U.S. patent application Serial No. 62/247,159,
20 filed October 27, 2015 are incorporated herein by reference, in their entirety.

CLAIMS

WE CLAIM:

1. A pharmaceutical composition, comprising:
a plurality of microparticles, each microparticle including:
 - (1) one or more crystals of a local anesthetic agent; and
 - (2) a polyvinyl alcohol (PVA) coating fully encapsulating the one or more crystals, wherein the PVA coating is at least 85% hydrolyzed and is 1-30 wt% of the microparticle, and wherein the one or more crystals of the local anesthetic agent is 70-99 wt% of the microparticle and each has at least one dimension in a range of 35-500 μm .
2. The pharmaceutical composition of claim 1 wherein the PVA coating is at least 99% hydrolyzed.
3. The pharmaceutical composition of claim 1 or claim 2 wherein the PVA coating is crosslinked.
4. The pharmaceutical composition of any one of claims 1-3 wherein the PVA coating is thermally cured and physically crosslinked.
5. The pharmaceutical composition of claim 4 wherein the thermal curing takes place at 100-135°C for 2-8 hours.
6. The pharmaceutical composition of any one of claims 1-3 wherein the PVA coating is chemically crosslinked in the presence of a crosslinking agent.
7. The pharmaceutical composition of claim 6 wherein the PVA coating comprises less than 5% by weight of the crosslinking agent.

8. The pharmaceutical composition of claim 6 or claim 7 wherein the crosslinking agent is citric acid.
9. The pharmaceutical composition of any one of claims 1-8 wherein the PVA coating has a molecular weight of 2-200 kDa, or preferably 140-190 kDa.
10. The pharmaceutical composition of any one of claims 1-8 wherein the local anesthetic agent has a dissolution rate of at least 5 times, or 7 times, or 10 times slower than that of the local anesthetic agent, when uncoated, in a same dissolution medium.
11. The pharmaceutical composition of any one of claims 1-10 wherein the local anesthetic agent is an aminoamide drug.
12. The pharmaceutical composition of any one of claims 1-11 wherein the local anesthetic agent comprises more than one crystals bound by a therapeutically inactive agent.
13. The pharmaceutical composition of any one of claims 1-12 wherein the local anesthetic agent is ropivacaine.
14. The pharmaceutical composition of any one of claims 1-13 for use in managing postsurgical pain at a wound site.
15. The pharmaceutical composition for use of claim 14 wherein the local anesthetic agent is sustained released for 3-5 days post-surgery.